

A STUDY IN PHARMACY.\*<sup>1,2</sup>

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Let us now consider some of the characteristics of the fourteen solvents classified on page 137, JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 1918.

## GLYCERIN.

This odorless alcohol possesses valuable characters as a solvent, but has been largely misused in pharmaceutical directions. For this error the Pharmacopœia of 1860 seems to a considerable extent responsible, because in that publication glycerin was given an undeserved conspicuity in connection with many galenical preparations in which its presence was undesirable, or at least unnecessary.

Glycerin serves a useful purpose for abstracting and holding tannates or near-tannates. It is a good solvent for a few alkaloids and neutral principles, but for the natural alkaloidal structures that exist in plants it is generally inferior to either water or alcohol. It is of no value in abstracting resins, fats, wax and oil, and should never be employed for this purpose. In many respects glycerin resembles water as a menstruum more nearly than it does either ethyl or methyl alcohol. One advantage it possesses over water is that, like alcohol, it does not expand ligneous fibre or other plant structures. For this reason it is sometimes desirable to substitute glycerin in moderate amount for water, where its solvent power as regards the desirable constituents of the drug may be no greater than that of water, or even inferior. Exceedingly gummy drugs, for example buchu, may be studied advantageously in connection with glycerin. By so doing it is possible to prevent the objectionable expansion of this as well as other glutinous drugs. Glycerin as a menstruum for plant extraction has, for some purposes, the disadvantage of not being volatile. For this reason, in making fluid plant products, care must be taken not to use more glycerin than the final standard will admit, as the excess cannot be evaporated. This is important in the direction of such substances as fluidextracts, where low grade percolates are to be evaporated. Nor can the difficulty be overcome in the preparation of solid extracts. Often glycerin is desirable in such preparations (solid extracts) as a final addition, in order to prevent subsequent drying.

Glycerin mixes with water in all proportions, and neither ferments, evaporates nor freezes at ordinary temperatures. Thus as a pharmaceutical solvent it presents characters possessed by no other feasible, neutral solvent. For this reason it is often desirable to substitute a portion of glycerin for water where alcohol is

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<sup>1</sup> Scientific Section, Portland meeting, 1928.

<sup>2</sup> This article, written between the years 1879 and 1885, is naturally defective in many directions as contrasted with the researches made since that date. Appreciating this fact the author ventured to place the manuscript in the hands of Dr. Wolfgang Ostwald of Leipzig, with the request that he comment thereon in directions where, in his opinion, his comments could be serviceable. These comments will be found as footnotes under the respective page locations. Unquestionably the readers of the article as well as myself must gratefully accept his thoughtful contributions.

inadmissible. In many instances it may thus be used to advantage even where glycerin possesses no solvent superiority. Pure glycerin is not always a "non-irritant" as seems to be generally accepted. It has a strong affinity for water and abstracts it with avidity from mucous and abraded surfaces, producing a sensation of warmth when applied to the skin. When concentrated glycerin is injected into the tissues, often great pain follows. Hence it should be diluted with water or some bland liquid when designed as a solvent for drug principles that are to be employed hypodermically or applied externally.

Glycerin is the most feasible of all neutral solvents for the red tannates and astringent plant constituents. In the writer's experience it should constitute a good part of the menstruum used in making (or in finishing) fluid preparations of such substances as oak bark, gossypium, sassafras bark, stillingia, geranium and similar vegetable bodies, which we hope to study hereafter separately.

#### WATER.

This agent is the most important of all solvents, being abundant, and used from time immemorial. And yet, in legitimate pharmacy, water has a circumscribed application, notwithstanding its great value as a cosmopolitan extractor and solvent. This is owing to the fact that an aqueous solution of plant constituents is prone to subsequent decomposition and fermentation. Water is an excellent solvent of mucilaginous, albuminous and saccharine substances. It also abstracts natural tannates, or plant astringents, more or less freely, many plant coloring matters; some alkaloids and most if not all natural alkaloidal salts; most glucosides (perhaps the term "many" is better) all the sour vegetable acids and many other substances that are obtained from plants and are classed as vegetable acids. Boiling water bursts the corpuscles and then dissolves starch and likewise disintegrates other vegetable tissues that are scarcely affected by cold water, thus forming liquids (by reason of the pressure of the dissolved materials) of different solvent power from cold water. In this way it is found that water solutions of plant constituents may produce important menstrooms, quite different from water alone.

It may thus be made to dissolve water-insoluble substances that from their characters, at the first glance, would appear not to be soluble in a menstruum in which the only added liquid present is water.<sup>1</sup>

Under such circumstances water may become a solvent or at least an abstractor of resins, oils, glucosides and other plant constituents that, in a purified condition are insoluble or nearly so in water. This character (alteration in the solvent power of water by reason of substances dissolved) is advantageously employed in directions that may properly be mentioned as methods of comparison. These examples also show how its solvent power is affected by the presence of other substances, thus, although water alone is used, the solution really forms menstrooms different from water. Familiar illustrations, from the inorganic field, may be cited as follows:<sup>2</sup>

Iodide of lead is soluble in about 2000 parts of water, and yet is freely soluble in aqueous solution of chloride of ammonium. In ordinary conditions it is a citron

<sup>1</sup> See "Precipitates in Fluidextracts," PROCEEDINGS A. PH. A., current issues (1879-1885).

<sup>2</sup> The problem of double salts, even physical chemistry, intrudes in this field.

yellow powder, but may be easily obtained in crystals from a hot solution of water and ammonium chloride. In the manufacture of potassium ferrocyanide (from leather and potash) considerable amounts of sulphate, sulpho-cyanides and the sulphides of potassium result as admixtures. In order to manufacture the substance economically, the sulphate, sulphocyanide and sulphides must be separated both from the excess of potash of the "liquor," as well as from the ferrocyanide of potassium. This is readily accomplished under a careful study of the value of water, both pure and saline, as illustrated by its foreign content. By the use of the proper proportions of alkali (potash) these substances can be successively expunged or even crystallized, although it is impractical to obtain definite crystals of the sulphides of potassium from pure aqueous solution. Examples such as these, or others more familiar perhaps, might be multiplied to illustrate the fact that, even in pure chemistry, water as a solvent is altered in value by the presence of indifferent substances.

The phenomenon is very much more important in galenical pharmacy where our plant tissues are made up of associations of complex bodies. Here it should be accepted that the solution of the indifferent substance in water produces new menstrooms which act as new mediums, and that water is not then the sole menstruum that finally effects the solution of the class of substances referred to. It is only a part thereof.<sup>1</sup> It may be shown by experimentation that when water is employed as a menstruum with various proportions of some definite chemical substances that are indifferent to each other, the solvent power of the medium changes in accordance with its composition, either increasingly or decreasingly as proportions and materials vary. The value (influence) of water as a galenic solvent is thus largely governed by the substances it holds in solution, even though they are chemically indifferent to each other. These conditions are often so obscure as to promise to become an object of advanced detail study.

Having introduced the foregoing as an illustration of the principle involved, the relationship in pharmacy between such examples and the use of water as a menstruum naturally follows. The difference between the making of a menstruum by dissolving isolated substances in water and the consideration of water in its action on complex plant structures, where in the crude drug many substances are physically associated or united in adhesion complexities, is markedly important. We then find that water may become a solvent for modicums of such constituents as resins, oils and the indifferent bodies before alluded to.

It is impossible to infuse a crude vegetable drug in water without dissolving such constituents as gums, sugar, some coloring matters and mineral salts, that are in themselves water-soluble and are blanketed together by writers as "the usual constituents of plants." These produce, when dissolved in the water, especially when heat is employed, a new menstruum that bears quite different relationships to other bodies present in the plant, from that which pure water bears toward the same substances after their isolation. In some cases the solvent action increases, in others it diminishes in accordance with the substance (drug) operated upon, as well as by variations in the proportions of the dissolved ingredients.

It is not unusual to find during the act of maceration changes, such as have

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<sup>1</sup> This rule applies to the other solvents, but having been considered here need not again be mentioned.

been described, that insensibly grade into each other and produce several distinct solvent reactions. In the first series of such manipulation processes, substances may dissolve that are afterward thrown out of solution by subsequent menstrua thus produced. Such precipitates may even, after a period, again dissolve. Thus at first the decoction of a drug is a solution of some of its constituents in water, finally to become, at a point of concentration, a solution of water in the extract. In such cases a transparent liquid extract made of water as the solvent precipitates on the addition of water. I have met instances where a thick mush immediately resulted.

Precipitates of plant structures that flow and ebb into solution and out again have been noticed by me, although as a rule a precipitate cast down by a change in solvent power of a solution remains a precipitate unless the temperature changes. It is a well-known fact that aqueous infusions and decoctions of drugs in which isolated "active" principles of these drugs are scarcely soluble may be therapeutically energetic. While it is true that in many instances these preparations depend upon mechanically suspended, finely-divided suspensions of proximate principles (emulsion-like), it is no less evident that when first made the constituents approach true solution. For such substances in the borderland between precipitates and solutions, I use the term *near-solutions*, considering them as a class to themselves. Cathartic solutions may thus be made by percolating resinous drugs, as jalap or podophyllum<sup>1</sup> with cold or hot water and filtering the percolate. This especially applies to green, undried drugs. Fixed oils and fatty and waxy bodies practically insoluble in water may be abstracted from water-filtered solutions of these drugs by chloroformic rotations, thus showing they have passed into solution.<sup>2</sup> After separation they refuse to re-dissolve in water. Under these conditions as already stated the plant constituents that are dissolved first in the water serve to form solvents of different powers than those possessed by water.

In further studying the nature of water as a solvent for galenicals in pharmacy, we are led to conditions that seem even more opposed to our understanding of the solvent power of a purely aqueous menstruum, but which are perfectly rational when considered in the foregoing relationship. By way of example, if an ounce of a given chemical be dissolved in enough water to produce a saturated solution, the evaporation of a part of the water of such solution reduces the capacity of the residue as a solvent and, when the remainder of the solution cools, precipitation or crystallization of the superfluous salt usually results rapidly (excluding so-called supersaturations).

The *opposite* is possible in many conditions where water is used as a solvent in plant pharmacy. Although the writer has never seen the statement made, all who have been concerned in the practical manipulation of pharmaceutical preparations may readily recall experiences where water has been used as a plant extractor,

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<sup>1</sup> The writer is aware that resin of podophyllum is not a true resin, but is slightly soluble in water, not, however, to the extent it is under the conditions named.

<sup>2</sup> Let us reserve the coined term *near-solutions* in which molecular dispersion seems to form a borderland of much interest.

Ostwald: Francesco Seleni (the discoverer of the cadaver alkaloids, *i. e.*, ptomaines) called those systems "pseudo-solutions" in about 1840-1850.

in which the filtered concentrated solution precipitated at once on the addition of water. This apparently paradoxical phenomenon may also be easily exhibited in another way. In many aqueous solutions that contain precipitates and are turbid therefrom, the undissolved matter gradually disappears *as the mixture is concentrated by evaporation*; finally at a given point forming a transparent solution which will become turbid when water is added thereto, but which re-precipitates when water is added in amount sufficient to reproduce the original bulk. Manufacturers of aqueous solid extracts are familiar with the fact that the turbid percolate of many drugs becomes clear when the evaporated percolate approaches the consistency of syrup, forming then, when in thin layer, a transparent ruby extract, which as a rule, although clearly a perfectly homogeneous mass, is only partially re-soluble in water.

This phenomenon results from the fact before stated that the water forms a part only of the menstruum in which, when the proportion of water is increased sufficiently to disturb the equilibrium of the compound, the result is the exclusion of one or more of the constituents. Sometimes successive precipitations of several substances follow in a manner that will be more fully considered in another place.

Temperature must not be overlooked in this connection, where ebullition is employed, for, when an infusion or decoction is being evaporated by boiling, the temperature increases as the water disappears, which increase of temperature induces the liquid gradually to increase in solvent power as well as to produce alteration of content. The increased solvent capacity induced by the successively rising temperature may even render the remaining liquid (notwithstanding loss by evaporation) a better solvent for certain substances than was the original at the lower temperature.<sup>1</sup>

A vital point in this connection is that continued application of heat, either high or low temperature, dissociates some of the constituents operated upon, forming others of different nature, as well as solvent power. Such decomposition products are as likely to be less as more soluble in water.

After a dry vegetable powder is moistened with water it expands considerably, and this is true to a modified degree of diluted alcohol. In working large amounts of powdered drugs, after moistening them with water it is best to permit them to expand before packing them for percolation. The writer has known large glass percolators to be burst into fragments by expanding drugs, and it is not unusual for such expansion to render powders so compact that percolation is suspended. With buchu, comfrey, sassafras and similar mucilaginous drugs, the act of percolation by aqueous liquids is also arrested because the powders not only expand, but become slimy, coalescing into a viscid mass, from the mucilage produced.

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<sup>1</sup> In my opinion the term "water as a solvent" becomes in these directions reversed to *water dissolved by the water-made solvent*. A time comes when the concentrate is dominated by the solids, then the water is dissolved by the mass, a transparent liquid resulting.

Ostwald: Good examples of a new solvent power by only mixing water and alcohol are seen with plant albumins, resp., globulins, for instance, zein, the globulin of corn flour (*Zea Mays*). This albumin is only soluble in mixtures of about 70-80% alcohol. It precipitates *as well* by pouring the water-alcohol solution into pure water or into absolute alcohol.<sup>2</sup>

<sup>2</sup> You obtain a solution of this globulin only by digesting corn flour with this mixture.

The solubility of nitrocellulose (collodium) is, of course, well known, only in mixtures of alcohol-ether, etc.

As a rule, substances are more soluble in hot than in cold water, but there are exceptions even with a few of the mineral salts, as for example, citrate and hypophosphite of calcium, in which a cold saturated solution becomes turbid on heating, to precipitate at a boiling temperature and re-clarify on cooling. It is not impossible for organic bodies to act in the same manner, but the writer knows of none so constituted.<sup>1</sup> In the case of sodium sulphate, that at successive temperatures precipitates by reason of molecular rearrangements in which successive degrees of dehydration at increasing temperatures are followed by the formation of less soluble salts, another cause of greater solubility at low temperatures is exemplified, but no similar example (hydration differences) presents itself to the writer in the consideration of plant products.

Aqueous solutions of dried plants when filtered are usually dark brown. They are often syrupy or even "ropy" by reason of the burden of the gum, mucilage, plant sugars mostly uncrystallizable and "extractive matters" that dissolve easily in water. The addition of alcohol causes precipitation of all or part of these bodies. By alcoholic additions such substances as inorganic salts may also be more or less excluded, and by adhesions thereto alkaloidal salts, or even very soluble substances, may follow as precipitates. By the proper manipulation of neutral menstrua, such as water and alcohol mixtures, dissociations of plant conglomerates can be accomplished without the destructive application of heroic chemistry.

#### ALCOHOL.

This menstruum mixes with water in all proportions and equals water in importance as a solvent, being in pharmacy indispensable and irreplaceable. It is particularly applicable to the abstraction of resins, fats, most neutral principles, natural alkaloidal salts, chlorophyll and chlorophyll wax or tallow,<sup>2</sup> most coloring matters, amorphous plant sugars, and nearly all the acrid and bitter constituents of plants. It refuses to dissolve gum, mucilages, starch, albuminates and many mineral compounds, but yet it extracts most mineral organics. It does not dissolve any considerable amount of crystallized cane sugar.<sup>3</sup>

Alcoholic solutions neither ferment nor putrefy, in consequence of which alcohol more or less diluted has long been employed as a solvent in the making of tinctures, which are the offspring of mediæval elixirs, or at least contemporaneous with them. These were followed by fluidextracts or "concentrated tinctures," as well as solid extracts.

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<sup>1</sup> Since the above was written the solution of an alkaloid from *Veratrum* has, in the writer's hands, proved to precipitate on warming, to re-dissolve on cooling.—J. U. L.

Ostwald:           Water + diethylamine  
                          Water +  $\beta$ -collidine  
                          Water + nicotine (C. S. Hudson, *Z. physik. Chem.*, 47 (1904), 113)

are organic substances which have a *decrease* in solubility at certain higher temperatures.

<sup>2</sup> Chlorophyll in vegetation is so closely connected with plant wax, grease and fat as to be nearly inseparable therefrom. They go together into solution and out again. I have coined the term "chlorophyll wax or tallow" for such adhering educts.

<sup>3</sup> In vegetation, sugars in an uncrystallized condition are soluble in alcohol. After crystallization they may become practically insoluble.

Alcohol is an important *excluder*, as well as solvent, and this property gives it a special value, in many instances scarcely less prominent in pharmacy than are its dissolving and anti-fermentative qualities. By this term, *excluder*, which is herein perhaps first used in pharmacy in the sense employed, should be understood its power of throwing out of solution such bodies as gums, albumen, mucilage, most cane sugar and the mineral salts which, intimately associated with medicinal constituents, are usually present in roots in considerable amounts.

For example, although water is a solvent for the desirable constituents of squill, it is scarcely practical to make a concentrated liquid representative of that drug by using water as the menstruum, because of the abundance of mucilage abstracted by it. Although acidulated water, on account of the preservative action of acetic acid (as well as solvent service), is probably the rational solvent for the therapeutic constituents of that drug, its use is precluded other than in making of comparatively dilute solutions as for example, vinegar of squill or syrup of squill. Perhaps one of the most familiar examples in illustration of the excluding value of alcohol is exhibited with *nux vomica*, in which, although acidulated water is unequalled as a solvent of the textural alkaloids, we are forced in manipulative pharmacy to employ nearly strong (U. S. P.) alcohol in order to avoid the loads of mucilage that are also abstracted by water.<sup>1</sup> Accordingly, if the water be increased beyond a certain proportion, the liquid becomes syrupy, opalescent and refuses to filter, the drug swells to an enormous degree, and neither percolation nor maceration is practical in pharmaceutical directions. By taking advantage of the quality of alcohol as a solvent of textural alkaloids, and conversely as an *excluder* of this class of gummy and mucilaginous substances, the alkaloidal content can be fairly abstracted. Alcohol is not, as is generally accepted, superior to water as a solvent of the majority of natural active principles, but actually inferior thereto, were the undesirable neighbors not disturbers.

This is true of many similar preparations that pharmacists find necessary to prepare, but it must be remembered that sometimes the mucilaginous principles of a drug are those desired. Among such substances may be named, comfrey, elm bark, quince seed, althea, chestnut and similar vegetable productions, in which the less alcohol employed the better. But as a preservative, we are forced even with these to use some alcohol, either as a part of the menstruum or as a later addition. In our experience eighteen per cent alcohol is needed.

Thus it will be seen that when we study alcohol as a menstruum we have to consider its excluding power from two aspects. It may improve one class of preparations by excluding inert substances and it may injure another class by excluding those desirable.<sup>2</sup>

One of the advantages alcohol enjoys over water in the abstraction of spongy vegetable tissues is the fact that woody materials, alike insoluble in both menstrooms, are penetrated (swollen) by water and not by alcohol. Such substances absorb water freely, expand, often enormously, and cannot be abstracted by percolation if water is employed as a menstruum, even though the active principles

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<sup>1</sup> Various aqueous menstrooms can be employed in the preparation of alkaloids.

<sup>2</sup> These remarks regarding *excluders* are not limited to alcohol. Any antipode of this solvent throws out of alcoholic solution materials held therein. Thus *water* becomes an *excluder* where resins and fats are dissolved in alcohol.

of the drug are perfectly soluble in water. Of this class, arnica, chionanthus and collinsonia may be mentioned as illustrations. Other substances deficient in ligneous material absorb water, soften, agglutinate and at the same time often expand in bulk, then become slimy or pasty, thus preventing satisfactory percolation or abstraction by maceration. Of this class buchu, senna, sassafras and squill are familiar types. In such instances the use of water alone as a percolating menstruum is out of the question and, although alcohol is inferior as a solvent for the desired constituents of the majority of such bodies, we are compelled to give preference to mixtures of alcohol and water in order to overcome these obstacles. The foregoing points embrace the important features concerning alcohol as a pharmaceutical menstruum in contra-distinction to water, with which, from its importance in pharmacy, it naturally should be classified.

Alcoholic percolates or filtrates of dry plant remedies are often brown or brown-red (tinctured) from the presence of resinous or tannin-like plant constituents, as well as their load of flavone derivatives and glucosides. They are usually mobile and easily filtered. As a rule they precipitate or lose their transparency on the addition of water, by reason of precipitation of these and allied substances.

#### METHYL ALCOHOL (WOOD ALCOHOL).

This liquid can be used as a vegetable solvent in some instances instead of ethyl or ordinary alcohol, providing it is not retained as a part of the finished preparation.<sup>1</sup> It has a solvent action on resins, oils, fats and many plant constituents such as chlorophyll, alkaloids, alkaloidal salts and neutral principles. It will not dissolve gum, starch, inorganic salts, albumen and mucilage. It is very volatile and much loss is experienced in handling it in ordinary manipulative processes, so much so that the difference in price in its favor as compared with ethyl alcohol is often more than balanced by the increased loss. Another factor that operates against commercial methyl or wood spirit is the irritating action of its vapor in the eyes of the workmen, a factor that must be considered in manipulating on a large scale. Besides this, its complexity of by-products make commercial "wood alcohol" a forbidding conundrum so far as internal medicine is concerned.

#### ACETONE.

This cosmopolitan solvent presents perplexing qualities when employed as a solvent in plant pharmacy. Whereas it is an immediate solvent for a great list of plant structures and products, it seems at once to begin both to dissociate as

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<sup>1</sup> Most tenaciously do some vegetable structures hold very volatile liquids. For example, benzol (and commercial benzine) long adhere to ligneous bodies if they be in a finely divided condition. Seemingly, a form of attraction similar to *catalytic* is involved. A parallel seems to be in solution precipitates whereby a precipitate thrown out in colloidal (see Graham's work) form, carries with it other materials very soluble in the liquid of which it is a part. This interesting phenomenon is very important. It should be studied scientifically and it should not be accepted that a material is not affected by adhering materials theoretically inactive.

Ostwald: To-day we call this binding capacity of finely divided substances "adsorption capacity." It is used in recovering, for instance, the vapors of benzol, etc., in the manufacture of rubber goods.

acetone and also to dissociate the material dissolved. In this way new products continuously arise, often very soon, of varied undefined compositions. To such a degree is this true as, even within a short period, practically to decompose textural alkaloids and alkaloidal salts even of most pronounced characteristics.

The rhizome of *Sanguinaria* may be mentioned as an example, the changes being easily manifest to the sight. If slices of the fresh rhizome, dripping with blood-red juice, be submerged in acetone, the change to yellow is immediate. In twelve hours the color disappears, excepting some of the pockets of red, resinous saturated cells in the drug's structure. In forty-eight hours the section becomes grey, practically no red cells remaining. The original alkaloidal structure has completely disappeared. The writer of this paper touches acetone very lightly in manipulative plant processes.<sup>1</sup>

#### CHLOROFORM.

This liquid stands unique in the fact that of all the volatile solvents of fat and oils herein considered, it is not inflammable, nor is its vapor combustible. When mixed with air its vapor is not explosive. Thus it stands alone, and separated from sulphuric and acetic ether, benzol, benzin, carbon disulphide, methyl and ethyl alcohols, acetone and essential oils. Its nearest friend in this regard is amylic alcohol, with which it may be classed in some respects as a solvent. For this reason, whenever it is necessary to employ a volatile fat abstractor near a flame, the writer naturally selects chloroform, if it has no immediate destructive influence on the material manipulated.

Chloroform mixes in all proportions with members of the second, third, fourth, fifth and sixth classes. (See "Solvents in Pharmacy," *JOUR. A. PH. A.*, 6 (1917), 940-949.) It dissolves in about two hundred volumes of water, but does not take up an appreciable amount of that liquid when shaken with it. Chloroform dissolves chlorophyll, wax, oils and fats, many resins as well as caoutchouc-like bodies, many structural alkaloids and glucosides and flavone derivatives. Mineral salts, gum, starch, sugar, glucose, most colored tannates and alkaloidal salts are when pure insoluble or only slightly soluble in chloroform. When mixed with alcohol and then with water it separates largely from solution, carrying with it much alcohol, together with many water-insoluble substances that we often find desirable to separate from hydro-alcoholic solution. An example of the application of this principle may be made by dissolving one part of sugar in ten parts of diluted alcohol and then adding a solution of one part of resin in ten parts of chloroform. After shaking together the lower or chloroformic solution will be found to contain practically all the resin and the upper solution nearly all the sugar. The principle may be more pointedly illustrated by adding one part of syrup to one part of tincture of iodine and mixing with the product one part of chloroform. On separation of the liquids the iodine will be found to be mostly transferred to the chloroform, while the water above contains most of the sugar. This principle applied to galenic pharmacy becomes of great service in accom-

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<sup>1</sup> Do not accept that acetone stands alone in producing inter-structural alterations. Other solvents possess both extractive and destructive qualities. For example, chloroform may prove very destructive, the by-products having peculiar qualities. In many cases water begins at once to react disastrously, and in nineteen days a mixture (infusion) is generally putrid.

plishing separations of substances that are abstracted together by hydro-alcoholic percolates, although to this date (1885) advantage is not taken of it in the making of any official galenical preparation.

When chloroform is studied systematically in its various relationships and attributes, it will doubtless serve as an important agent in developing the better plant preparations that are sure some day to supplant the present crudities in official galenical pharmacy. In this connection it must be repeated that chloroform *alters* many delicate plant structures if allowed to stand in contact therewith. Chloroform water is thus very inadequate as a preservative of plant ultimates, as experience has taught the writer of these comments.

#### AMYLIC ALCOHOL.

This solvent is of importance because of its usefulness in extracting some alkaloids from plant solutions after they are made alkaline, quinine being an example. Its irrespirable vapor renders it very disagreeable to manipulate, but a product of such extraction may be readily freed of the solvent and need have no odor. Its solvent power on alkaloids and natural structures is shown by the fact that fresh *Sanguinaria* at once yields to it its red salt.<sup>1</sup> That it is preferable as a solvent to some other liquids that are equally good solvents is shown by the fact that no change in *Sanguinaria* extractive occurs in twenty days. (See Acetone.)

#### ACETIC ETHER.

This solvent is never found in commerce free from (either or both) water and alcohol. It has been entirely overlooked in galenic pharmacy, possibly being displaced by its co-laborer, sulphuric ether. It unquestionably possesses attributes that render such neglect inexcusable. While the Pharmacopœia of the United States wisely gives place to and describes it, there is no official preparation in that work that either contains or uses it in the process of manipulation. It possesses nearly all the serviceable qualities of sulphuric ether and is less objectionable in many regards. In many places where sulphuric ether is employed in pharmacy, acetic ether might be substituted to advantage.

Acetic ether mixes freely with members of the second and third classes of solvents,<sup>2</sup> and with most volatile oils. For example, one part of turpentine and three parts of acetic ether mix transparent, but upon further addition of turpentine become milky. In this reaction the moisture of alcohol that is present in commercial acetic ether possibly accounts for the milkiessness when the proportions are reversed. It freely dissolves about half its bulk of liquid petrolatum, becoming milky when the proportions are increased to equal amounts. The liquid part of petrolatum is naturally quite soluble in acetic ether, the paraffin dissolving more slowly. Acetic ether boils at about 76° C. (169° F.), a fact that in many cases gives to it a great advantage over sulphuric ether which is extremely volatile.

<sup>1</sup> Sanguinarine is often given as an example in these notes. This is because the color is so marked. Other alkaloids and alkaloidal structures require detailed chemical tests for identification. Some of these in textural form seem even more evanescent than are the alkaloids of *Sanguinaria*. There are, however, exceedingly stable alkaloids, strychnine for example.

<sup>2</sup> See *JOUR. A. PH. A.*, 6 (1917), 940-949. This article was written in 1885.

The odor is pleasant which cannot be said of sulphuric ether. The inhalation of the vapor does not seem to produce the unpleasant symptoms that follow inhalation of the vapor of sulphuric ether, thus adding further to its favor.

Acetic ether dissolves fat, oils, wax-and-fat-bound chlorophyll, many resins and alkaloids, vegetable acids and glucosides. Ammoniacal acetic ether is an excellent abstractor of many alkaloidal drugs, so far as the alkaloidal products are concerned, first breaking them out, and next carrying them away.

It dissolves in about eight parts of water, but does not reciprocate, for water is taken up by it very sparingly. This is a very important quality as contrasted with sulphuric ether. For example, with sulphuric ether solutions of alkaloids, by rotation with acidulated water, the sulphuric ether disappears by solution in the water, while acetic ether very much more slowly wears out. Should acetic ether come into use in regular pharmacy,<sup>1</sup> and be allowed to remain in any pharmaceutical preparation whatever, even in small amount, the medical profession would necessarily have to be educated concerning its character. The general impression would be that such a preparation had *soured*, few modern physicians being sufficiently familiar with the nature of menstrua of drugs to distinguish between the fragrance of acetic ether and the "sour" odor of acetic acid. Naturally, at this date, acetic ether may only be employed as an aid to systematic plant studies where as a final result the menstruum will be totally dissipated.

#### SULPHURIC ETHER.

This is an excellent menstruum for the abstraction of fats, fat-bound chlorophyll and associates, balsams, waxes, some resins, many alkaloids, vegetable acids and glucosides. It also dissolves many neutral principles, resinous bodies and a few acrid constituents of plants, as for example, the acrid constituent of Indian turnip (probably of other species of *Arum*) which is practically insoluble in both alcohol and water. Alkaloidal salts are mostly insoluble in ether, although, as aforesaid, many alkaloids in a free state readily dissolve in it. In this way ammoniacal sulphuric ether serves as a breaker of natural alkaloidal structures and as an abstractor of alkaloids from natural combinations, in some plants where neutral ether is valueless. As an *excluder* of undesirable extractives sulphuric ether is often even more valuable than alcohol. In many cases, such as fatty, alkaloidal drugs, preliminary percolation with sulphuric ether can be resorted to without fear of disturbing the desirable alkaloidal textures of the plant, a manipulative feature we cannot often indulge with alcohol. Thus powdered ergot can be extracted by means of ether, then dried and next percolated with dilute alcohol, when it will be found that the hydro-alcoholic menstruum, minus the fat, will contain all the desirable constituents of ergot, but also it yet contains mineral salts objectionable for hypodermic use. The preparation is still crude but much better than the official fluidextract and can next by neutral liquid precipitants be depleted of its earthy salts, leaving the desirable constituents intact. Many seeds may be treated in the same way with advantage. It may be repeated that

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<sup>1</sup> I here use the term "regular" as applied in medicine. An "irregular" is he who seeks in the outside for opportunities which the inside (regular) authorities have not recorded. To me the term has no terrors.—J. U. L.

sulphuric ether does not dissolve gums, starch, sugar, glucose, albumen or mucilage, but is the rational solvent for wax, fat-bound chlorophyll and all volatile oils. It should be remembered that commercial sulphuric ether (Pharmacopœia, 1880) contains alcohol enough to become a modifying factor in many cases, and thus these remarks must be considered as being applied to concentrated or stronger ether of the Pharmacopœia of 1880.

In some respects ether occupies a position different from that of any other menstruum, including its near companion, acetic ether. Thus carbon disulphide, benzol and benzin will neither dissolve in nor dissolve water, while chloroform to saturation is taken up by water to the extent only of about one-half per cent. Sulphuric ether, upon the contrary, dissolves water largely, and in turn is dissolved by about ten volumes of water. This character is of great value in galenic pharmacy, as by taking advantage thereof it is possible to abstract the ether from solutions it has made of desirable substances, and by introducing water (repeated shaking with water) in its stead, obtain the desired material as a precipitate. This method can be adapted (without heat) to the breaking up, disintegrating of associations of natural plant adhesion constituents in which ether is primarily employed as a solvent, and water is used next as a precipitant.

The inflammable and volatile nature of ether renders it necessary to exercise manipulative care, especially in laboratory work on a large scale, while the fact that its vapor is heavier than air must not be overlooked. In this connection consider the remarks on acetic ether.

#### BENZIN AND BENZOL.<sup>1</sup>

These rationally follow sulphuric ether, the remarks concerning that substance applying in many respects to these liquids. They are excellent solvents for fats and some resins, benzol especially being a solvent for balsams. They do not dissolve alkaloidal salts in either the natural plant textures or the artificial compounds. They refuse to soften or abstract in the least albuminates, sugar, gum, starch, woody fibre and the usual plant coloring matters, excepting wax-or-fat-bound chlorophyll. Some alkaloids and neutral principles are dissolved by them but the list is not extensive. In some aspects they are superior to any of the solvents previously mentioned for water-free, fatty drugs. As a rule fatty tissue may be percolated with them until the fat is practically abstracted without disturbing associated constituents, provided the tissues are water-free and porous. Neither of them will dissolve in or be dissolved by water, a property that renders them superior to sulphuric ether for some purposes, inasmuch as the moisture abstracted from a drug by sulphuric ether is often considerable, producing therewith a menstruum that will dissolve bodies that are insoluble in pure sulphuric ether. Both benzol and benzin have great penetrating qualities and do not in the least expand any vegetable structure known to this writer. For this reason a powder in a percolator may be more tightly pressed (compact), for their use than for most solvents, providing the powder is dry and porous. One unfortunate condition concerning commercial benzin is the contamination therewith of offensive hydrocarbons and unknown mixtures that do not readily evaporate from drug textures. They

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<sup>1</sup> The scientific and commercial terms applied to these substances are perplexing as a study of their histories demonstrates.

remain often tenaciously adhering to the substance that has been operated upon, even a temperature of 100° C. being insufficient to expel them. In this connection, *adhesion* plays a prominent part. Very volatile substances may remain most tenaciously attached to vegetable powders, the final portions often refusing to be dissipated under temperatures far above the boiling point of the adsorbed liquid. This problem, already mentioned, we consider in our remarks on "Physics in Pharmacy," or mass action of materials.

For many purposes in applied pharmacy, such liquids as these (benzol and benzine) are irreplaceable. The writer believes that in time to come they will occupy important authoritative positions in the preparation of perfected galenical products.

#### CARBON DISULPHIDE (BISULPHIDE).

This highly refractive liquid possesses strong solvent properties for fat-bound chlorophyll, fats, balsams, wax, some resins, a few alkaloids, a few glucosides and other neutral principles. It does not dissolve alkaloidal salts, gums, albumen, glucose, sugar, mineral salts, the brown coloring matter of dried plants and substances generally which, by reason of our ignorance of their structures, we denominate "the usual constituents of plants."<sup>1</sup> It may best be classed (see Class 3, *JOUR. A. PH. A.*, 7 (1917), 137) with benzol and benzin, as its solvent properties resemble those liquids. For the purpose of abstracting fats and oils from aqueous plant liquids, it is equal to chloroform, and may afterward be separated from the liquid as readily, owing to its great specific gravity. It is cheaper than chloroform, thus favoring its use in manufacturing on a large scale, but it possesses the disadvantage of being inflammable and volatile, the mixture of its vapor and air forming an explosive compound. Indeed, it has been asserted that spontaneous explosions have resulted in its manipulation. The odor of the commercial liquid is more offensive than that of benzin, although the Pharmacopœia described it as a liquid that should have "a strong, characteristic, but not fetid odor."

It has been stated that odorless carbon disulphide is a commercial possibility and that, were the demand to arise, such a desirable condition of the substance would probably appear in our market, the offensive odor being ascribed to foreign bodies and not to CS<sub>2</sub>. Carbon disulphide does not expand cellular matter. Drugs abstracted by it should therefore be perfectly dry and porous, as this liquid has no affiliation for water. It is impractical to use carbon disulphide as a menstruum should it remain even in traces in the finished plant pharmaceutical preparation, owing to its rank odor and poisonous nature. Hence it should be employed only as a preliminary menstruum in removing objectionable substances such as fat and oil, or in making separations of plant constituents, from which it is afterward freed by distillation.

#### OIL OF TURPENTINE (TURPENTINE).

Fats, oils, many resins and some coloring matters dissolve in this liquid. The fact that it is cheap and separates so sharply from water renders it desirable

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<sup>1</sup> Let me repeat that traces of most vegetable materials are likely to be taken by any liquid if one is inclined to demand the preciseness of exactness. This is not essential in a general sense.

in some forms of plant manipulation. Turpentine emulsions are difficult to make permanent, which theoretically indicates its desirable employment where emulsions disturb analytical processes. However, in practice, the reverse is true. If a mixture of turpentine and water be well shaken together, the lower, aqueous liquid becomes milky, the white emulsion remaining for months, probably permanently. This is true of no other mixture of liquids named in this series.

#### PETROLATUM AND LIQUID PETROLATUM.

Soft Petrolatum, U. S. P., 1880. This unctuous substance is increasing in pharmaceutical use, but chiefly as a carrier of remedies to be employed for inunction rather than as an abstractor and solvent. Plants yield their fats, oils and many resinous and balsamic constituents to hot petrolatum, which agent can thus be used as an extractor for this purpose. It is, however, as before stated, chiefly employed as an excipient, although occasionally it is desirable as an abstractor. It is a poor solvent for most energetic plant constituents, even when hot, although when melted it will abstract and purify alkaloids that have been liberated from acidulous combinations by an alkali. If, for example, an impure alkaloid, the alkaloidal constituent being soluble therein, be digested and agitated in hot petrolatum, it will generally be found that although the alkaloid is dissolved, most coloring matters will remain undissolved. By rotating the alkaloidal petrolatum saturated with acidulated hot water, the alkaloid is quickly removed in a very pure condition. This method of purifying alkaloids can be made of great practical utility in cases where the alkaloid is soluble in petrolatum. Since (unlike most menstruums) petrolatum has no affinity, or very little, for the extractive coloring matters of plants, it may be perceived that a consideration of this agent in the light herein indicated is not unwarranted. It is probable that in a time to come, it will be a useful factor in making the perfected pharmaceutical preparations of plants yet to be developed, provided pharmaceutical thought and action are not paralyzed by some unforeseen intrusion.

*Liquid Petrolatum.*—This substance possesses an advantage over petrolatum in that it is fluid at ordinary temperatures and yet possesses to a degree the solvent power and other characters of melted petrolatum. That which has been recorded in the preceding paragraph concerning petrolatum may be applied to this substance. Notwithstanding its fluidity, the penetrating and abstracting action of liquid petrolatum is much enhanced by a high temperature.

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The Medicinal Plant Garden, which is maintained by the College of Pharmacy of the University of Florida at Gainesville, will prove of interest to the pharmacists who will attend the Convention at Miami next year.

The perennial group of plants in the Garden is perhaps the most interesting because its numbers have been assembled from so many parts of the world. Thus, for example, we find here the West African tree which yields Acacia; the Russian turpentine pine; the Spanish Cork Oak which produces cork for stoppers, linoleum, life preservers, etc.; the East Indian Nux-vomica tree; Ginger plants from Jamaica and China; the Japanese mulberry, the leaves of which feed the silk worm; the Central American Logwood tree which produces a violet dye as well as an astringent drug; the South Asiatic Turmeric plant. These are only a few of the many interesting plant immigrants to be found in the Medicinal Plant Garden. It is learned that there are now over one hundred and fifty different species under cultivation in the garden.