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In the work of compiling formulæ for the use of medical practitioners and pharmacists, care is necessary to test the keeping properties of the various solutions and preparations, and having prepared and kept a number of these preparations, I thought a few notes on them might prove interesting. They are purely pharmaceutical, and must not be considered as having bacteriological importance.

The vehicle mostly used for the internal administration of medicines, of course, is water in some form or other, but distilled water alone is recognised by the Pharmacopœia, and probably this, as frequently met with, is more defective from a standard of purity than most preparations in the Pharmacopœia. It is even more prone to develop minute organisms than many of the spring waters that are to be met with, although these may contain inorganic salts, which render them unsuitable as solvents and vehicles in which to administer medicinal preparations. So much has distilled water obtained this evil reputation that a bacteriologist of eminence is reported to have said that one of the best incubating fluids was a certain manufacturer's distilled water.

Various means have, therefore, been adopted for sterilising it and rendering it aseptic for pharmaceutical use, such as keeping it in a cool place, and of course free from dust, and having it recently well boiled and cooled. The best and only method to be depended upon, however, care having been taken to select a good

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water for distillation, as well as to refuse the first and last products, and to ensure freedom from contamination afterwards, is to have it freshly distilled ; in fact as regards the whole of the preparations of the Pharmacopœia, they should be as freshly prepared as possible, and the use of preservatives should be avoided unless absolutely necessary, but from a practical point of view we cannot do without them. For example, the public demand for pills is now that they must be well preserved and look nice, although they may be nsoluble.

Alcohol.—The most common preservative used officially is alcohol in one form or another ; it is true it is not used solely as a preservative but as a solvent ; it enters more or less into the composition of nearly all our tinctures, liquid extracts, wines, and many of our official solutions. The germination of most of the micro-organisms occurring in aqueous solutions of vegetable and animal substances is inhibited by the presence of 20 per cent. by volume of absolute alcohol, but it is inhibitory only, and in this proportion or upwards; it is in no way germicidal, as on evaporation the anæsthetised germs, if I may so term them, readily take up life and propagate. This applies to most of the volatile antiseptics, in fact, few antiseptics are germicidal except those that are destructive to organic tissues, such as strong mineral acids, alkalies, and halogens. Exceptions to this are carbolic acid, creasote, and weak solutions of corrosive sublimate, which act probably by coagulating the albuminous substance of the microbe. Wines I have mentioned ; unless fortified, from their very origin, that of fermentation, they are too weak to prove of useful service in pharmacy, and in fact medical wines are anachronisms.

Glycerin.—The abuse of alcohol has led those who take extreme views on this subject to endeavour to use other solvents and preservatives for pharmaceutical preparations. Among these, avoiding ethylic alcohol, whose physiological properties are too well known, they have selected glycerin, which is but another alcohol whose action physiologically is not so well ascertained, nor is it so inhibitory to the development of micro-organisms. Its strong solvent action on vegetable extractives, its non-volatility, and its stability in other respects would have rendered glycerin a useful pharmacopœial solvent, but although it has been tried again and again and was made official, more especially in preparing some of

the liquid extracts of the United States Pharmacopœia, it has not met with general acceptance. It nevertheless has a curious preservative action over some inorganic compounds in preventing oxidation. For example, black mercurial lotion can be preserved in its normal black colour by the addition of 5 per cent. by volume of glycerin, but I find that 10 per cent. of mucilage of tragacanth will produce the same result, and have the advantage, from its viscosity, of holding the mercurous oxide well suspended; the addition of both these to this preparation would be an advantage. It has further been suggested that glycerin should be used to preserve sublimate solution, especially the official liquor hydrargyri perchloridi, as it has been thought necessary that this solution requires preserving, from the chemical, not, of course, from the biological point of view. But both glycerin and alcohol added to this solution, especially if exposed to light, cause a reduction of the salt and deposition of mercurous chloride, as in the official solution of the Codex, which contains 10 per cent. of alcohol. Notwithstanding statements to the contrary, I find that a simple solution of mercuric chloride in distilled water, or even in spring waters containing supercarbonate of lime in solution, is more stable than it is with a preservative added, especially one of such a nature as chloride of ammonium in the official solution. This, as I showed so long ago as 1870,* instead of being a preservative, forms a double salt in solution (sal alembroth *plus* an excess of chloride of ammonium), and the solution, if prepared with common water in place of distilled water, or even if prepared with distilled water and diluted, throws down a quantity of one of the white precipitates of mercury. To such an extent is this the case that I found in preparing a pint of the official solution with New River water in place of distilled water, that 2·7 grains of this precipitate was deposited, thus about one-fourth of the mercurial salt was rendered insoluble in preparing the solution, and more deposited on further dilution with the water. In fact, a time arrived when there was scarcely a trace of mercury salt in solution, and as this preparation is most largely used in hospitals where common water is always used to dilute the medicines, it leads to very discrepant results therapeutically.

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* *Pharmaceutical Journal* [2], vol. xi., p. 544.

It has also been suggested that chloride of sodium should replace chloride of ammonium in the official solution, as this salt is largely used in making the sublimate tablets for the convenience of surgeons' use, but I have found that although sodium chloride helps these tablets to disintegrate readily it has no advantage, in fact it is detrimental to the keeping properties of the solution. I have here two specimens prepared in November, 1895, with water from the Brighton constant supply, which is a very calcareous water ; one is a simple solution of the perchloride, and the other has an equal weight of pure chloride of sodium added. The latter you will observe has deposited much more than the former, in which there is hardly a trace of deposit. This strongly illustrates the undesirability of tampering with solutions in order to make them, as we consider, more stable, in fact, with few exceptions no preservative should be added to a pharmacopœial preparation unless the label indicates boldly that it is there. While on the subject of mercuric salts, I should like to illustrate the importance of having our lime water of full strength, and well preserved.

In making the yellow mercurial lotion of the B.P., which has 18 grains of sublimate to 10 ounces of lime water ; if the lime water be only three-fourths, or from keeping, so low as one-half the pharmacopœial strength, a brick-red preparation, an oxychloride, is produced, rather than the yellow mercuric oxide.

Acetic Acid.—Of other preservatives, which are also solvents used officially, acetic acid of varying strengths is employed, as in acetum cantharidis and acetum scillæ. This, as I notice Professor Remington recently points out,* was much employed in the pharmacy of the ancients, sometimes combined with honey to form oxymels, of which we have inherited both the vinegar and oxymel of squill. Acetic acid has the disadvantage, however, unless in a very concentrated form, of growing micro-organisms abundantly, and the fungi and animalculæ developed in brown vinegar must be well known to all of you. Acetic acid, therefore, besides being incompatible with alkalies, is not a good preservative, although in some cases it may be a useful solvent.

Sugar.—Of the preservatives used officially which are not solvents,

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* *American Journal of Pharmacy*, March, 1897, p. 121.

this is employed most extensively, not only with us, but in France and in the United States; in fact, so much is this the case in France, that Mr. Ince once remarked in this room that French pharmacy might be summed up in the one word, "sugar." On account of its palatability it of course meets with favour, especially among children. It enters into the composition of all the syrups and lozenges, and most of the confections and powders, and is a useful preservative from oxidation of the ferrous preparations, such as the saccharated carbonate of iron, mixture of iron, Blaud's pill, and iodide of iron pill. It also preserves lime in solution, as in the well-known liquor calcis saccharatus, of a strength about sixteen times that of the official lime water; if a pure marble lime be used, I find as much as 1·77 per cent. is dissolved, or 8·16 grains in a fluid ounce. This preparation is more conveniently made by using an equivalent weight of syrup, *i.e.*, three ounces in place of two of sugar, and adding it to nineteen ounces of distilled water containing the lime in suspension. The "caking" which is apt to occur is thus avoided.

Salicylic Acid.—The well-known uses antiseptically of this for surgical purposes, although prohibited from being used for preserving wines in France, have rendered it serviceable in preserving the official solution of hydrochlorate of cocaine, which contains $1\frac{1}{2}$ per mille of the acid, with 10 per cent. of the cocaine salt. I find that this solution, even if diluted with four times its volume of water, still keeps free from fungoid growths. The use of this acid might be objected to in the solution, because salicylic acid forms with cocaine an indefinite compound rather than a salt, the so-called salicylate of cocaine; but it appears not to throw the hydrochloric acid out of combination, and has proved very serviceable in preserving the solution of this cocaine salt, which has a great tendency to develop fungoid growths. The salicylic compound appears to be allied to the benzoic compound, benzoyl-ecgonine. It forms a pasty mass which has not, that I am aware of, been studied. If any defence were needed for using a preservative, perhaps this official solution of cocaine is a typical case. The use of this solution of salicylic acid, $1\frac{1}{2}$ per mille, which is nearly saturated, as a vehicle, might be extended to other solutions, for example, the official solution of sulphate of atropine, but I have not found this solution, if made with a well-crystallised salt, prone to

grow fungi. Its use, however, cannot be extended to the hypodermic injection of morphine ; if a solution of tartrate of morphine, 1 in 12, or even 1 in 20, be prepared in it, a crystallised salicylate of morphine separates. 16½ tartrate keeps well alone.

Of the salts of morphine suitable for hypodermic injection, the tartrate seems to be now favoured ; the acetate solution, prepared by dissolving pure morphine in just enough acetic acid, has till lately been mostly used, but it has the objection of possessing a tendency to decomposition and becoming muddy and dark-coloured. Still I have two solutions here over 18 years old, no extra sterilising precautions were taken when made ; they are well preserved and are perfectly transparent, although they have slightly changed colour. One is of the strength of 1 grain in 6 minims, which I advocated in a paper in 1870,* the other is 1 grain in 12 minims. A small dose is generally preferred for hypodermic injection, but the strength of 1 grain in 6 minims is considered now to be dangerously strong in the hands of an unskilled operator. The more nearly saturated, however, the aqueous solution of any salt or crystalline principle is, the better it will keep ; in fact, it was a curious argument of an advocate for spontaneous generation that there was a debatable land between that of crystallisation and the germination of organisms in these solutions—that is, between the growth of crystals and of organisms ; this applies widely in pharmacy, as we well know, in keeping syrups for example. A nearly perfect syrup consists of two parts of sugar and one of distilled water ; kept at a uniform temperate heat, this neither crystallises nor grows fungi ; and our solid medicinal extracts are preserved if they contain no excess of moisture.

Further, these remarks especially apply to the official solutions of acetate and citrate of ammonium, which are much better kept in a concentrated form.

The salicylic acid solution cannot either be used for preparing the hypodermic injection of apomorphine ; a 1 per cent. solution of the hydrochlorate of apomorphine prepared in it gives a quantity of a crystalline deposit.

Hydrochlorate of apomorphine in aqueous solution rapidly

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* *Pharmaceutical Journal* [2], vol. xi., p. 480.

develops a green colour; this has been attributed to the influence of ammonia in the atmosphere, but although a drop of solution of ammonia does develop the green colour immediately, it is apparently not due to this alone. This salt is now prepared much purer than formerly, and it is also not so soluble. The official strength of the hypodermic injection, 1 grain in 50 minims, *i.e.*, 1 in 45·5 parts, of camphor water is not held in solution at 60° F. Dott gives the solubility in water as 1 in 50·89, Squire as 1 in 56 to 60. I find 1 part in 60 of boiled and cooled distilled water dissolves, but turns green within a few hours, but if acidulated with a trace of hydrochloric acid, say an equal weight of the official diluted hydrochloric acid, the colour is preserved, but it is rendered less soluble. More than a 1 per cent. solution, if acidulated, is not certain to keep free from crystals at the variable temperatures to which it may be exposed, and less than the quantity of acid I have named does not keep it free from colour.

Sulphurous Acid.—A trace of sulphurous acid, say one-quarter per cent., added to a 2 per cent. solution of the apomorphine salt keeps the solution for a moderate time, but not indefinitely, and the use of such a deoxidising agent is not desirable, as its action on the apomorphine salt is not clearly understood. Nevertheless, sulphurous acid is largely used as a preservative of such preparations as orange wine.

Boric Acid.—Of the preservatives suggested for keeping apomorphine injection, boric acid has been mentioned, but this I find, in a solution containing 2 per cent. of each, boric acid and hydrochlorate of apomorphine, forms an opaque white jelly, and even with 1 per cent. of each a curious translucent jelly is formed, quite unsuitable for hypodermic injection. Boric acid has been recommended and is used largely for preserving solutions for hypodermic injection, but as a solution of it, 1 in 30 parts of water, which is nearly saturated, will itself develop some peculiar fungi, I can see little advantage in employing such a preservative pharmaceutically. Mr. Lee has mounted a specimen of a *torula* which has been grown in a saturated solution of boric acid in distilled water.

Camphor Water.—The same remarks apply to camphor water, the favourite of Raspail, as to boric acid. It is a weak inhibitor, and it further has the disadvantage of the camphor being volatile.

Camphor water is official as the solvent of atropine in the solution of sulphate of atropine, but oculists complain of the irritating action of camphor on the eye.

Chloroform.—The addition of chloroform to vegetable infusions and other aqueous preparations of vegetable and animal substances was recommended by Mr. J. B. Barnes* in the proportion of from one-eighth to one-half per cent. by volume. The addition of chloroform as an inhibitory in suspended pharmaceutical operations is of great service, and it has the advantage that by gently warming the solution for a short time it can be easily dissipated, but it has also the disadvantage that the chloroform evaporates too easily for prolonged preservation, yet I have tried the experiment of preserving fruit (damsons) in stoppered bottles, adding about one three-hundredth part of their weight of chloroform to them. The preservation was complete, but the flavour of the chloroform was not dissipated by even baking the fruit in pies.

Hydrate of Chloral has been used as possessing similar properties to chloroform, being more readily soluble and less volatile, but its taste is nauseous.

Carbolic Acid.—The odour and flavour of this most powerful antiseptic is against its use for internal administration, excepting for hypodermic injections; it is the best preservative of ergotin in aqueous solution. Boric acid in this solution fails; Mr. Severn kindly infected for me three solutions of ergotin with *Penicillium glaucum*; No. 1, without preservative added, developed in forty-eight hours; No. 2, with 1 per cent. of phenol added, is undeveloped yet, after five days; No. 3, with 2 per cent. of boric acid, developed on the side of the bottle, just above the surface of the liquid, in seventy-two hours. Creosote also, although one of the best preservatives, as its name indicates, is not admissible, on account of its odour.

Cherry Laurel Water.—This is recommended in France for preserving hypodermic injections. So, also, are the distilled waters of meadow sweet and eucalyptus. I am not aware that

Formaldehyde has been much used pharmaceutically, although it has, I understand, been used for milk preserving for some time. Its peculiar action on gelatin in rendering it insoluble would tend

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* *Pharmaceutical Journal* [3], vol. v., p. 441

to prove that it was not desirable for internal administration, as it might seriously interfere with digestion.

Hypophosphorous Acid.—This and *citric acid* are employed commercially to prevent the change of colour of the ferrous syrups; as traces only are needed, it may be considered a venial offence. But preservatives are sometimes used, or are added even officially, which are often disadvantageous. For example we have two arsenical solutions official, one acid and the other alkaline. A simple solution of arsenious anhydride in water of the same strength, coloured if desired, is perfectly stable. It would be compatible with both acids and alkalies, and might take the place of both the official solutions.

Carbonic Acid.—This in solution in water is inhibitory to organic growths, and is largely used in preparing carbonated waters and "Fluid Magnesia," but otherwise it is not of much service.

Benzoic Acid.—For preserving lard and some official ointments the melted fats are macerated with powdered benzoin, by which means they obtain an agreeable odour and become impregnated with benzoic acid. Both these tend to preserve the fats from becoming rancid. But in using these fats for preparing the ointments of the alkaloids, apparently some change takes place; they become discoloured, and in the case of cocaine we know, as I have before mentioned, a comparatively inert compound of benzoylecgonine, etc., is formed, so that the use of benzoated lard is to be avoided for preparing these ointments.

Paraffin Basis.—Where quick absorption is not required, the preservative action of the soft paraffins renders them all that can be desired, as also is oil of theobroma for suppositories.

Aromatic Waters and Essential Oils.—The oils of clove, cinnamon, peppermint, and many others are preservatives; so are their aqueous solutions, but I can only mention them.

Heat and Cold.—A gentle heat assists the incubation of nearly all micro-organisms; a greater heat, that of boiling water for example, is a steriliser; whereas a still higher temperature is a disorganiser, and is destructive to all organic growths. Cold, on the contrary, the freezing point of water and below, as a rule, is only inhibitory to the development of the lower organisms, their vitality is but suspended, and they spring into life again with the first application of a gentle warmth. It may appear irrelevant to my subject, but

the important bearing preservatives have on our food supplies, including frozen meat, makes them of great importance commercially. In fact, in viewing the pharmaceutical aspect of preservatives, I have but touched the fringe of the subject of their utility. Without the aid of boric acid and other preservatives, many of our articles of daily food would be at famine prices. In such a condensed population as that of London, it would now be almost impossible to supply the necessary quantities of butter, milk and fish in a fresh condition. We have long been dependent to a great extent on the importation of flour and corn. The same has now become the case in regard to our animal food products.

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