9. Every item should show date of purchase, price paid and the source of the purchase.

10. It may be wiser to refuse some prescriptions for certain specialties than to suffer a loss when the demand ceases. If more pharmacists were to do this, the physician would find that prescribing them is of little avail, due to the difficulty in securing them; this would cause a demand for the better known standard ones.

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## THE PHARMACIST AND PARENTERAL SOLUTIONS.*

BY SISTER CRESCENTIA WISE.[1]

The rapid development of parenteral medication has brought about numerous problems. While manufacturing pharmacists have done much to render this form of medication safer and more convenient, most pharmacists outside the manufacturing field have been slow to accept responsibility for extemporaneous preparations of parenteral solutions. Since the need for much of this medication is of an emergency nature there seems no valid reason why the trained pharmacist, in either the hospital or retail field, should consider this work to be the sole responsibility of pharmacists in the commercial field.

If local irritation is to be avoided some attention must be paid to the tonicity of the solution.

Since all fluids and secretions of the body contain dissolved substances, in definite proportions, these solutions will exert a certain definite osmotic pressure which is uniform for each fluid. (Since this paper deals with parenteral solutions only, we will confine our attention to blood and lymph, though isotonicity is of equal or greater importance in solutions intended for use in the eye or nose.) If a solution is introduced into the circulation it may contain dissolved substances in a different proportion or of a different character from those of natural body fluids, hence it will have a different osmotic pressure. When a liquid has a lower osmotic pressure than the body fluid with which it is mixed it is hypotonic; when it has a higher osmotic pressure it is hypertonic; when it has the same osmotic pressure it is isotonic. Whether any given solution is isotonic depends upon (1) the proportion of dissolved substances which it contains and (2) upon the character of those substances. Salts which dissociate freely exert a greater osmotic pressure than those which dissociate slightly or organic non-dissociating substances. Therefore the type of dissolved substance is of more importance from osmotic pressure standpoint than the amount in solution.

The practical value of this subject lies in the fact that hypotonic or hypertonic liquids when injected into the circulation in considerable amounts, may cause pain until equilibrium is established between the osmotic pressure of the fluid within the tissue cells and that of the injected fluid. When only a small amount of solution is injected into the blood stream it is quickly diluted so that the difference is not felt.

Often a hypertonic solution is desired for therapeutic purposes but as a rule an isotonic solution is more satisfactory. If given subcutaneously any solution that is not isotonic will cause temporary local irritation.

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Systemic reactions do occur, unavoidably, occasionally. In our hospital, over a period of a month, there were slight reactions following 4% of the injections. This compares favorably with reports from other hospitals.

A survey of the literature reveals five main causes for systemic reactions.

1. Foreign protein.
2. Speed of injection.
3. Temperature of the solution.
4. Individual susceptibility and disease.
5. $p_H$ of the solution.

Speed of injection, temperature of solution, individual susceptibility and disease are scarcely within the scope of this paper but it would be well to mention that numerous investigators have found that the more acutely ill the patient, the more likely is a reaction to follow an intravenous injection, and that in septicemia a reaction is a rule rather than an exception.

Foreign protein may come from water which complies with all the requirements for Aqua Distillata, U. S. P. Much stress has been placed upon double and triple distilled water. If these are available, well and good, but they are not important. One large eastern hospital has been using single distilled water for more than four years and has not had a single reaction that was not traceable to sources other than water. It is of vital importance that the still be in good condition and that the water be exposed to the bacteria-loaded air, as short a time as possible, and be sterilized at once after it is distilled. The bacteria, pathogenic or non-pathogenic, are killed by sterilization but the protein matter from their dead bodies remains in solution and causes at times very severe reactions. One writer has stated that it is not advisable to inject into the circulation a floating bacterial graveyard.

The $p_H$ of the water should be very close to 7. Theoretically, water is neutral but in practice it is rare to find it absolutely so. A small percentage of $CO_2$ dissolved in it as the water condenses will cause slight acidity but this is not sufficient to cause any difficulty. If it is permitted to remain in contact with the air, it will absorb additional $CO_2$ besides becoming saturated with bacteria. These bacteria during sterilization break up and increase acidity. It is a good practice to have the inlet tube to the receiving flask pass through a plug of cotton so as to filter the air during the period of distillation.

The degree of acidity or alkalinity of the finished solutions is often of vital importance, and while the total acidity or alkalinity may be determined by titration, the true acidity should be ascertained by determining the $p_H$ concentration. This may be very satisfactorily accomplished by the colorimetric method and in many cases by the use of nitrazine paper.

In regard to solvents, distilled water and physiological sodium chloride solution only, need be considered here.

The glassware used, flasks or containers, graduates, graduated pipettes or burettes, etc., should be of insoluble glass. An intermediate grade termed "harder than soft" has been used satisfactorily by one large hospital. It is advisable to treat all new containers, especially if made from the "harder than soft" variety of glass, by first sterilizing in them, Boric Acid Solution. This fixes the alkali in the glass.

The style of containers will depend upon individual preference. Hard glass bottles with skirted rubber stoppers are satisfactory for quantities up to 100 cc.

For quantities over 100 cc. convenient containers are bottles graduated from bottom to top and from top to bottom, closed with two-holed rubber stoppers. In one hole is a piece of glass tubing reaching nearly to the bottom of the bottle, an air inlet. The other hole is free to receive the glass connector and rubber tubing. A round piece of pure rubber is fitted over the stopper and over all is a metal screw cap. This provides a hermetic seal. Another advantage of these containers is that the danger of accidental contamination in transferring the solution from one container to another is avoided. Pyrex Erlenmeyer flasks may be used for any quantities. These should be closed with non-absorbent cotton wrapped in close mesh gauze which has been flamed to rid it of shreds and capped with cellophane paper which should come well down over the neck of the flask.

All new rubber parts should be given preliminary treatment before use. It is the practice in our hospital to allow new rubber to stand twenty-four hours in 2% NaOH. It is then thoroughly washed in running tap water and placed in distilled water where it remains another twenty-four hours, after which it is sterilized.

Filtration can be accomplished much more efficiently and rapidly if a little thought is given to the filtering media. The creped paper shreds, and, frequently, repeated filtration through the same paper only adds to the number of shreds in the filtrate and has the disadvantage of exposing the solution to the bacteria and $CO_2$ of the air over an unjustifiable period of time. Much less annoyance will be experienced if a hard smooth-surfaced filter paper such as Reeve Angel Close Texture Filter Paper (Reeve Angel Co.) or Whatman Filter Paper (Coleman Bell Co.) is used. A little difficulty may be encountered with viscid solutions. These may be filtered through a bed of siliceous earth in a Büchner funnel using suction, or a "fritted" glass filter may be employed. The latter has been satisfactorily used for some time at a certain University Hospital.

Many factors influence the stability of parenteral solutions. Reference has been made to $p_H$ concentration as affecting systemic reactions. It also materially affects stability of solutions. Nearly every solution has its optimum $p_H$.

Solutions should be sterilized immediately after preparation. It is preferable to make the solutions from water distilled during the working hours of the morning rather than from sterilized distilled water. One filtration is avoided in this way and the water is fresher. All the solutions under consideration at this time can be sterilized in an autoclave at 15 or 20 pounds pressure for 15 minutes. A hypodermic needle may be inserted in the rubber caps, but if they fit tightly and the bottles are not more than two-thirds full this will not be necessary.

The hermetically sealed solutions have been proven to remain stable over a long period of time, but generally it is not necessary to use solutions which have been prepared longer than a week. Though the demand for parenteral solutions fluctuates it should be comparatively easy to keep sufficient solutions on hand without becoming overstocked.

Obviously not all solutions are suitable for preparation by the hospital or retail pharmacist, but there can hardly be any reasonable excuse for his feeling incompetent to prepare such simple solutions as Solutions of Sodium Chloride, Dextrose, Magnesium Sulfate, Physiological Buffer Salts and Fischer's Solution.

Sodium Chloride Solutions present no particular problem except freeing them from filter shreds and by observing what has been said above, this problem is easily

solved. As a rule chemically pure Sodium Chloride, reagent quality, should be used, but there is no objection to the use of Sodium Chloride U. S. P.

Physiological Solution of Sodium Chloride U. S. P. contains 8.5 Gm. NaCl dissolved in enough freshly distilled water to make 1000 cc. The U. S. P. directs that this be used within 24 hours unless hermetically sealed (rendered impervious to air or other fluids) in which case it shall respond to certain tests for sterility.

A hypertonic solution of Sodium Chloride between 5% and 10% is frequently called for and should be available. It would be practical to prepare a 10% solution in units of 300 cc. This could easily be diluted to any concentration less than 10% by introducing directly into the container through a sterile glass funnel the proper proportion of sterile distilled water. Then the solution may be administered from the original container, clamping off the rubber tubing when the desired amount has been given.

According to most writers Glucose Solutions require the use of chemically pure dextrose, though one very good authority uses Dextrose U. S. P. The concentrations in use at the present time are 5% and 10% dissolved in either distilled water or physiological salt solution and 50% dissolved in distilled water.

There is a great deal of discussion about the advisability of buffering dextrose solutions. Dextrose is normally acid and will deteriorate in alkaline solution. Unbuffered, it may have a $p_H$ as low as 5.0 after sterilization, but this represents all available acidity. The buffer power of the blood is such that this degree of acidity can be handled, except in case of excessive depletion of alkaline reserve, in which case extemporaneous addition of alkali (buffer salts) is advisable. One reliable authority advises the routine use of Sodium Biphosphate U. S. P. ($NaH_2PO_4$) as a buffer. It is used in the proportion of 2 Gm. per 1000 cc. of solution and should be dissolved in the distilled water before the Dextrose is added. This maintains a $p_H$ of 6.5 to 6.7. The literature lists no disadvantages in the use of buffers and its routine use seems logical until some practical reason for not using it is revealed.

The only problem in connection with the preparation of Magnesium Sulfate Solutions is the preservation of the chemical. The formulas are for the crystallized salt ($MgSO_4.7H_2O$). Either the C.P. or reagent grade should be used and should be purchased in glass containers to prevent loss of water of crystallization.

It is used in 50% and 25% solutions. The dosage is usually 2 cc. of 50% or 10 cc. of the 25%. These may be put up in convenient sized vials with skirted rubber closures. Care should be taken that the containers are not more than one-half or two-thirds full to allow for expansion in the sterilizer.

Physiological Buffer Salts may be prepared ready for use or in the concentrated form and diluted when ready for use. The formula for the concentrated solution is as follows:

| | |
|---|---|
| Lactic acid 85% | 1.2 cc. |
| NaCl | 3.0 Gm. |
| KCl | 0.2 Gm. |
| $CaCl_2$ | 0.1 Gm. |
| Distilled water *q. s.* | 20.0 cc. |

This must be diluted to 25 times its volume (500 cc.) before use.

In the preparation of Fischer's Solution the first step is to select a formula. Quite a number exist, each claiming to be the original. The following formula was supplied by Merck and Company:

| | |
|---|---|
| NaCl | 14.00 Gm. |
| $Na_2CO_3.H_2O$ | 4.33 Gm. |
| Distilled water *q. s.* | 1000.00 cc. |

Anhydrous or Crystalline Sodium Carbonate may be substituted for the monohydrated provided the weight is adjusted according to their molecular weights. C.P. salts should be used and it is essential that only *hard* glass be used on account of the alkalinity of this solution.

This solution presents some as yet unsolved problems. After 24 hours a precipitate forms so that the solution must be absolutely fresh. There could be no chemical reaction to explain the precipitate. It would be convenient to have a concentrated solution which could be diluted when needed, but a concentrated solution (the amounts in the formula in 100 cc.) yields a floating precipitate resembling a white membrane. Only a clear solution may be used.

The economy of preparing these solutions is shown by the following tabulations which are taken from a report of a North Carolina Hospital with the exception of the "units used" column in which is substituted the figures from the records of our own hospital.

TABLE I.—COST OF COMMERCIAL PRODUCTS.

| Solution. | Cost per Unit. | Units Used. | Cost. |
|---|---|---|---|
| 1000 cc. 5% dextrose in normal saline | $0.79 | 1325 | $1046.75 |
| 1000 cc. 10% dextrose in normal saline | 1.05 | 1325 | 1391.25 |
| 100 cc. ampul dextrose 50% | 0.40 | 1200 | 480.00 |
| 50 cc. ampul dextrose 50% | 0.23 | 1200 | 276.00 |
| 500 cc. physiological NaCl solution | 0.32 | 7935 | 2539.20 |
| | | | $5733.20 |

TABLE II.—COST OF SOLUTIONS PREPARED IN HOSPITAL PHARMACY.

| Solution. | Cost per Unit. | Units Used. | Cost. |
|---|---|---|---|
| 1000 cc. 5% dextrose in normal saline | $0.1823 | 1325 | $241.5475 |
| 1000 cc. 10% dextrose in normal saline | 0.2187 | 1325 | 289.7775 |
| 100 cc. ampul dextrose 5% | 0.0505 | 1200 | 60.6000 |
| 50 cc. ampul dextrose 10% | 0.0323 | 1200 | 38.7600 |
| 500 cc. physiological NaCl solution | 0.0963 | 7935 | 764.1405 |
| | | | $1394.8255 |

Cost of solutions prepared as above, includes cost of (1) chemicals, (2) water, distillation, depreciation of apparatus (still, etc.), (3) capping and (4) sterilization, depreciation of sterilizers and breakage of containers.

A glance at the figures shows that it costs less than one-fourth as much to make the solutions as it does to buy them from a commercial laboratory.

While the cost of ingredients is often passed on to the patient and therefore does not immediately concern the hospital, both physicians and laymen are taking notice of increasing cost of illness, and whatever is done to lessen the cost without lessening the efficacy of the treatment will be of direct benefit to the patient and indirectly will benefit the physician and the hospital. When nearly one-third of the total number of patients are either charity or only part-pay patients, as was the case in our hospital for the year 1936, the saving to the hospital would go far toward extending the works of charity in which those in charge of the hospital are intensely interested.

Even though intelligent and conscientious attention must be given to every detail from the time the preparation of parenteral solutions is begun until they are administered, still there is no reason why the trained pharmacist in the hospital dispensary or in a retail pharmacy should not be competent and willing to assume this responsibility.

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## WHY SIMPLE OINTMENT, U. S. P.?*

BY WILLIAM A. PROUT[1] AND JAMES R. ADAMS.[2]

Dispensing pharmacists are asking why we have Simple Ointment as it now appears in the pharmacopœia, when apparently it cannot be employed as a base in any of the official ointments, therefore why include it? With this question in mind, we began a study and comparison of the pharmacopœial ointments with regard to the constituents of their bases and the proportion in which they are combined. As a result we find a group of ten ointments, three of which have a base composed of constituents identical with those of Simple Ointment, six of which use yellow petrolatum in place of white, and seven of which use yellow wax in place of white. In none of the bases did the percentage strengths of the constituents in the bases vary more than one and one-half per cent in the case of wool fat and wax and not more than three per cent in the case of petrolatum, as is shown by the table following.

TABLE I.

| Pharmacopœial Ointments. | Per Cent of Active Constituent. | Per Cent of Constituents Other Than Those in the Base. | Per Cent of Petrolatum. | Per Cent of White Petrolatum. | Per Cent of White Petrolatum if Simple Ointment Was Used. | Per Cent of Wool Fat. | Per Cent of Wool Fat if Simple Ointment Was Used. | Per Cent of Yellow Wax. | Per Cent of White Wax. | Per Cent of White Wax if Simple Ointment Was Used. |
|---|---|---|---|---|---|---|---|---|---|---|
| Boric acid | 10 | .... | .. | 80 | 81.0 | 5 | 4.5 | . | 5 | 4.5 |
| Tannic acid | 20 | Glycerin 20 | 54 | .. | 54.0 | 3 | 3.0 | 3 | . | 3.0 |
| Belladonna | 10 | Dil. alcohol 5 | 75 | .. | 76.5 | 5 | 4.25 | 5 | . | 4.25 |
| Chrysarobin | 6 | Chloroform 4 | 74 | .. | 75.6 | 5 | 4.2 | 5 | . | 4.2 |
| | | Liq. petrol. 6 | .. | .. | .... | . | .. | . | . | .. |
| Nutgall | 20 | .... | 70 | .. | 72.0 | 5 | 4.0 | 5 | . | 4.0 |
| Ammoniated mercury | 10 | .... | .. | 80 | 81.0 | 5 | 4.5 | | 5 | 4.5 |
| Yellow mercuric oxide | 1 | Liquid petrolatum 1 | 88 | .. | 88.2 | 5 | 4.9 | 5 | . | 4.9 |
| Iodine | 4 | KI 4 | 70 | .. | 72.0 | 5 | 4.0 | 5 | . | 4.0 |
| | | Glycerin 12 | .. | .. | .... | . | .. | . | . | .. |
| Sulfur | 15 | . .. | | 75 | 76.5 | 5 | 4.25 | 5 | . | 4.25 |
| Zinc oxide | 20 | Liquid petrolatum 10 | .. | 60 | 63.0 | 5 | 3.5 | . | 5 | 3.5 |

Aside from the difference in the color of the finished product, bases made with yellow wax and yellow petrolatum in place of white wax and white petrolatum seem to be equally satisfactory in consistency.

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