duction of untoward reactions. Only specially selected pure gum rubber tubing should be used for setting up the infusion apparatus. This tubing should be prepared for use, when new, by thoroughly washing in running tap water. Then soak, or better autoclave, in a 5% solution of sodium carbonate. Finally a rinse in running distilled water for another thirty minutes will provide a suitable tubing. After this preparation it may be wrapped in a towel and sterilized by autoclaving in the approved manner. It is further suggested that after the apparatus has been set up for an infusion it is always best to discard the first fraction of solution being administered that will completely fill the length of tubing used.

Solutions of dextrose in the distilled water should be brought about with all the pharmaceutical skill at one's command. We prefer to pass this solution through a Berkefeld filter, under pressure, more with the thought of clarifying the solution than of obtaining a sterile product. This solution is transferred into the containers described, capped and hooded with a parchment paper cap that protects the lip and neck of the bottle. This hermetically sealed package is placed in the autoclave and processed as described for Aqua Destillata Sterilisata, that is, sterilization is to be preferably accomplished under steam pressure giving a temperature of 115° C. and maintained for thirty minutes. It should be reiterated that a common fault of "soft" glassware, if not properly prepared, is that at this temperature discoloration as by caramelization may develop. Sample bottles are selected from each lot and tested chemically and bacteriologically. The finished solution for parenteral use is a clear, colorless, sterile, physiologically compatible solution. A printed label describing the solution as to composition and character, together with a control number identifying the batch, is then attached. Such solutions remain stable for a considerable time.

THE EXTEMPORANEOUS PREPARATION OF SALINE AND GLUCOSE SOLUTIONS FOR INTRAVENOUS USE.*

BY ROBERT S. FUQUA.[1]

The use of intravenous therapy by physicians and surgeons has been constantly increasing in late years, especially in hospital practice. While manufacturing pharmacists have done much to make intravenous medication safer and more convenient for the physician, it appears that most pharmacists outside the manufacturing field have been slow to accept responsibility for the extemporaneous preparation of suitable solutions for this form of medication. Since the need for much of the intravenous medication is largely of an emergency nature, the writer can think of no valid reason why the trained pharmacist, in either the hospital or retail field, should consider this work to be the sole responsibility of the large manufacturing laboratories.

As indicated in the title, this paper will discuss the preparation of only the two most frequently used solutions of this type—that of Physiological Saline Solution, or "Normal Salt," and the intravenous solutions of Dextrose. Such information regarding these as the writer has been able to obtain, has been gained

* Section on Practical Pharmacy and Dispensing, A. PH. A., Washington meeting, 1934.

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over a period of years in the pharmacy department of one of the larger eastern hospitals, where large volumes of such solutions are prepared. This experience has shown that with proper care, close attention to details and a supply of pure materials, the well-trained pharmacist can, with a little practice, soon become proficient in the preparation of satisfactory intravenous solutions.

Regarding the materials required, it should be remembered that the standards of purity set up in our Pharmacopœia for some of these items are not established on the theory that all U. S. P. chemicals, and the distilled water used for pharmaceutical compounding, must be of sufficient purity for intravenous therapy. No super-judgment is required to determine those instances in which materials of a higher standard of purity than is necessary for oral medication should be used for this purpose. In the case of dextrose, it is perhaps unfortunate that we must have in the Pharmacopœia the impure mixture of dextrins, dextrose and levulose recognized under the title "Glucosum;" when physicans assume that medicinally the name Glucose applies only to the U. S. P. Dextrose, or D—Glucose. At this time however, it seems rather unlikely that any pharmacist would dispense the impure syrupy product when glucose is ordered by a physician for medicinal uses. For making intravenous solutions, the U. S. P. Dextrose, which usually contains traces of dextrin, and possibly sulphur dioxide, should not be used. Only the variety of glucose marketed by standard chemical manufacturers as "C.P. Anhydrous Dextrose" should be used. The processes employed in the dehydration and recrystallization of the latter product remove practically all traces of the above-named impurities, which may be present in the hydrated material.

In making Normal Salt Solution, I would not hesitate to use sodium chloride of U. S. P. purity specifications when a purer salt was not immediately available. However, we may, and do, use a C.P. or Reagent grade of sodium chloride to insure maximum purity in saline solution for intravenous administration. A point which I would like to stress here is that no chemical which has been freely exposed to contamination by dust and other atmospheric impurities should be used in solutions which are to be injected into the blood stream, regardless of indicated purity on label of container. This applies with even more force to the distilled water which is to be used as a solvent. The Pharmacopœia lists certain tests to which distilled water must conform to be satisfactory for ordinary pharmaceutical purposes. Here again, water which conforms to these mandatory requirements as to purity may fall short of that degree of purity needed to produce satisfactory intravenous solutions. Distilled water may pass all standard tests for chemical purity, and be more nearly neutral in reaction to hydrogen-ion indicators than is necessary to come within the p_H range of those specified in the U. S. P., and still be totally unfit for intravenous injection, because of bacterial contamination. The specifications set up for the "Sterilized Distilled Water" of the U. S. P. are in line with those generally held necessary for a suitable diluent for the sterile concentrated solutions supplied in ampuls by manufacturing laboratories, and for general hypodermic use. For the extemporaneous preparation of these solutions, which must be filtered and sterilized as final steps, we need freshly distilled water, which has been exposed to bacterial or other contamination as little as possible, but not necessarily sterilized before use. All distilled water contains traces of carbon dioxide and oxygen, which are absorbed when steam is condensed; and usually will

absorb more on standing in contact with air. We have found however, that the usual slight acidity in distilled water, when due entirely to small quantities of CO_2 in solution, is of small consequence as compared to the dangers incident to undue exposure of the fresh distillate to contaminated atmosphere.

Sterilization of solutions will kill all living bacteria which they contain, but will not remove the bacterial proteins and other related impurities which remain in the finished product. This fact is well known to all interested persons, but seems to be frequently overlooked. Perhaps we sometimes forget that the atmosphere in most places is loaded with bacteria and organisms of various sorts and that these furnish the proteins and other substances which produce most of the toxic symptoms observed when carelessly prepared intravenous solutions are used. Under no circumstances should distilled water which has been purchased in bulk containers, commercially, be used in preparing intravenous solutions, unless same has been redistilled immediately before use, and according to the Pharmacopœial process. Normal Salt Solution which has not been freshly prepared should likewise not be used as a solvent.

I would like to depart from subject in hand momentarily, to say that Normal Salt solution should never be kept on hand in pharmacies for use when same is ordered as a solvent in any preparation. We have had bacteriological tests made on such solutions which were made under aseptic conditions and stored in partly filled, cork-stoppered bottles, on prescription-counter shelves. After two weeks many colonies of bacteria appear in cultures; and after one month such solutions are dangerous to use in preparations for local use on membranous surfaces, or in the eye if same has been injured.

Regarding the process of making Normal Salt Solution for intravenous use, little need be said here. Our procedure calls for the use of water which has been distilled the same day as used, and protected as far as possible from atmospheric or other contamination before use. Solutions are now being filtered through a hard smooth-surfaced filter paper, in covered glass funnels, into a well-covered, glass-lined receptacle. When filtration is completed the finished solution is placed in flasks of suitable size, stoppered with a plug of non-absorbent cotton wrapped in close-meshed gauze, which has been previously flamed to remove adhering lint, capped with a strong paper cap which extends well down the neck of the flasks, and then sterilized. Our sterilizing technique calls for autoclaving this solution at 125° C. for a period of thirty minutes. In the retail establishment not having facilities for autoclaving, sterilization may be accomplished for immediate use by boiling the solution for an equal length of time, providing an excess of water sufficient to take care of evaporation is added when solution is made. Proper filtration of this solution appears to be the greatest problem encountered. A complete absence of filter shred in filtrate is impossible to obtain with the standard grades of pharmaceutical filter paper, especially those with creped surfaces. After a number of experiments we selected an extra-hard grade of smooth-surfaced paper as offering the most practical solution. Suction filtration through candle filters will give better results for a time, but on extended use these are not wholly satisfactory. For large-scale production we keep a battery of these on hand for use in case a faulty lot of filter paper is encountered.

In making intravenous glucose solutions we use freshly distilled water, col-

lected directly from the still in large glass flasks. The glucose is dissolved in this immediately, without heat, and solutions are filtered at once through chemically hardened filter paper, in Büchner type porcelain funnels, by means of vacuum suction, into flasks which have been thoroughly cleaned and rinsed. Solutions are refiltered if necessary to secure a properly cleaned filtrate. Filtered solutions which show only occasional isolated paper shreds are strained through sterile fine-meshed silk cloth to remove same, rather than risk further contamination in repeated filtrations. Small squares of silk cloth are kept on hand for this purpose, immersed in 70% alcohol. Filtration of solutions of dextrose is not difficult and vacuum-suction is not necessary when the softer grades of filter paper are used. It should be noted, however, that only those grades of filter paper which are free from starch and chlorine should be employed in the filtration of solutions for either hypodermic or intravenous use. More shreds will usually be found in filtrates when non-parchmentized papers are used, but these shreds can be removed if a silk cloth of very fine mesh is available for straining. Silk bolting cloth (200 mesh per inch) is very satisfactory for this purpose, but is rather expensive. These solutions are placed in flasks of proper size, stoppered and capped in the same manner as described for saline solution, and sterilized the same day as made. After cooling, the flasks of sterile glucose solution are placed in low-temperature refrigerators to prevent possible fermentation before use. Our routine age limit for the use of these sterile solutions, prepared and stored as indicated, is five days. Bacteriological tests have shown them to remain sterile in the flasks for a much longer period, but the shorter time limit is placed as a safety precaution. Sterilization of glucose solutions is accomplished by autoclaving at 120° C. for fifteen minutes, with volume per flask being limited to not more than 600 cc. Flasks are placed on hardwood boards in sterilizers to protect bottoms of flasks from overheating on metal shelves. Solutions of 5 and 10 per cent strengths are turned out sterile and crystal clear under this treatment. If an autoclave is not available, glucose solutions may be rendered sterile for immediate use by heating on a water-bath, partially immersed in boiling water, for one hour. Depending on filtration through the usual type of candle filter to render glucose solutions sterile is not a safe procedure to follow.

Questions regarding the advisability of buffering solutions of dextrose which are to be administered intravenously are frequently brought up, and considerable disagreement exists among physicians on this point. At present the apparent consensus of opinion appears to regard the addition of buffer salts necessary in only a small percentage of cases. Under other methods of preparing and preserving solutions, or for prolonged continuous administration, buffering might render these solutions safer to use. In our institution several thousand gallons of intravenous glucose solutions are being used each year, and we seldom find it necessary to use buffer salts in same in order to secure satisfactory clinical results.

A second question, on which there appears to be no consensus of medical opinion, pertains to the necessity of using double or triple distilled water in intravenous solutions in order to obtain satisfactory results. No answer to this question which did not take into consideration the quality of raw water supply, type of distilling apparatus and other factors involved in individual cases, would be proper. With a raw water supply of good quality, and with efficient automatic distilling

apparatus, to the operation of which we devote some care, we have found multiple distillations unnecessary.

To sum up, I would say that if reactions are to be avoided in the use of these intravenous solutions, cleanliness and care in the preparation are necessary from start to finish. The chemicals used must be of a proper degree of purity, and must be kept free from contamination by dust and moisture. All utensils and apparatus used must be thoroughly cleaned, and then rinsed with freshly distilled water before being used. The distilled water and finished solutions must not be contaminated by undue exposure to dust and bacteria in the air. Sterilization will kill bacteria but does not remove them from solutions. The presence of excessive numbers of killed bacteria in solutions may cause reactions. Filtration and sterilization methods employed must be adapted to the particular product being handled; and suitable methods of preservation must be employed to protect unstable solutions packaged in containers which are not sealed. The use of chemical preservatives, in sufficient quantities to keep solutions sterile, is not permissible where large volumes of dilute solutions are to be administered intravenously.

STUDIES ON BISMUTH SUBSALICYLATE PREPARATIONS.*

BY WILLAIM F. REINDOLLAR.

One of the important recent developments in syphilotherapy is the treatment of that disease by intramuscular injections of suspensions of insoluble bismuth compounds in oil. This drug is alternated with the arsenicals in a course of treatment, thereby reducing the toxic effects, caused by prolonged administration of the latter, and at the same time preventing the spirochete from adjusting itself to the environment produced by either drug. The serious consequences that may follow injections beneath the skin of any product of inferior quality, together with the toxic effects that follow an overdose, make the control both of the qualitative and quantitative aspects of the product a matter of paramount importance.

Bismuth as a spirillicide has been said to be second to arsphenamine and superior to mercury. It is less toxic than either arsenic or mercury, dose for dose, and apparently exhibits no predilection for any particular organ. It is slowly absorbed and probably cumulative. Although numerous forms of this drug are employed we are concerned only with the official product, bismuth subsalicylate. This is described in the U. S. P. X as "a basic salt of varying chemical composition, which, when dried to constant weight at 100° C. yields upon ignition not less than 62% and not more than 66% of bismuth oxide."

In the venereal clinics of the Maryland State Health Department bismuth is administered as the subsalicylate in suspension in olive oil, the concentration being so adjusted that 0.1 Gm. metallic bismuth is received in 1 cc. of oil. The injection is made deep into the gluteal muscles of the upper outer quadrant of the buttock, alternating the right and left sides. For administrations of this type it is evident that a drug must not only contain the correct amount of active ingredient, but must exhibit certain physical and chemical properties, if it is to produce an opti-

* Section on Practical Pharmacy and Dispensing, A. PH. A., Washington meeting, 1934.