► ACUTE KIDNEY FAILURE HAS PROVED A SERIOUS AND sometimes fatal complication of certain kinds of surgery. An exhaustive search for a means of preventing this kidney failure during surgery was carried out by a research team in the Eldridge H. Campbell Surgical Research Laboratory at the Albany Medical College. This team found that mannitol was remarkably effective in preventing kidney failure. As a result of their work, the Department of Surgery of the Albany Medical Center Hospital began administering mannitol to patients undergoing operations where the risk of kidney shutdown was high. In the past, it was not uncommon to find that 20 to 25 surgical patients each year would require artificial kidney treatment because their kidneys stopped functioning. In 1961, thanks to mannitol, there were no cases of acute kidney failures following surgery at this Hospital.[1]

Background

At the time this procedure was being instituted the Department of Pharmacy was carrying in stock mannitol injection,[2] commercially available as a 25 percent solution packaged in a 50 ml. ampul. This was acceptable for most cases since mannitol is administered intravenously in doses as high as 100 grams or more. In using this concentration undiluted, the fluid volume is kept to a minimum, which has a distinct advantage. There are occasions when this product is added to an intravenous solution, such as dextrose injection 5 percent. This could be done without significantly affecting the pharmacological aspects of either the mannitol or the large volume parenteral solution. This is one advantage of the high concentration of mannitol in mannitol injection.

The injection can be administered, undiluted or directly intravenously. Large doses can be given in a short time with a minimum fluid volume introduced.

Mannitol is also used as a diagnostic agent for kidney function.[3]

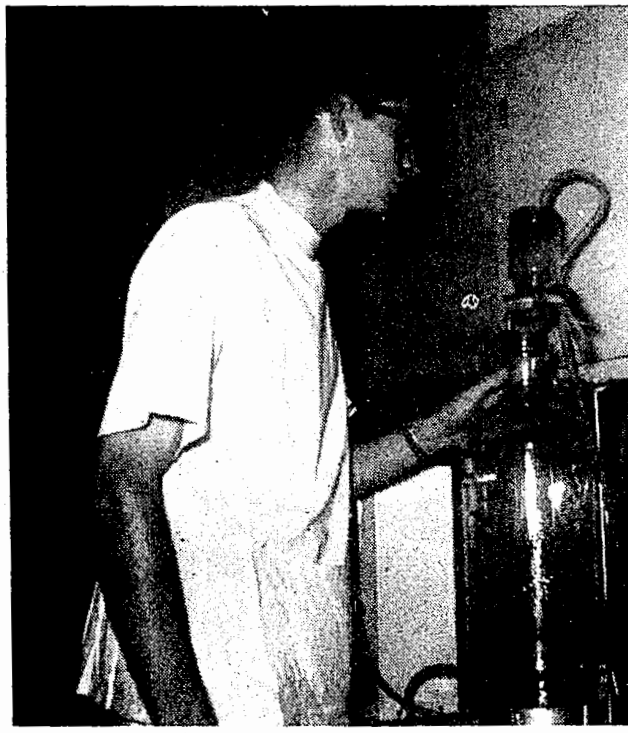
Physical Characteristics

Mannitol, official in *N.F.* XI, is a hexahydric alcohol which is rather widely distributed in the tissue fluids of various plants. It is obtained from manna and natural sources by means of hot alcohol extract purified form, it is a white, crystalline powder, and having a sweetish taste. It melts between 1 167°C. One gram dissolves in about 5.5 ml. of (18 percent solubility). It is obvious that a 25 solution is a supersaturated one.

Under certain conditions it is possible to pre solution containing a larger amount of solute necessary to form a saturated solution. This ma when a solution is saturated at one temperatu excess solid solute removed, and the solution The solute present in solution, even though it less soluble at the lower temperature, does not separate from the solution and there is prod supersaturated solution. Such solutions may be to deposit their excess of solute in one of the ing ways: by vigorous shaking; by scratching t of the vessel in contact with the solution; by ducing into the solution a small crystal of the so by reducing the temperature of the solution to extent.

This information gives us some idea of the characteristics of mannitol injection 25 percent. normal conditions, it is a stable solution. But shipping, handling, and storage of the injecti treme temperatures and conditions may prev

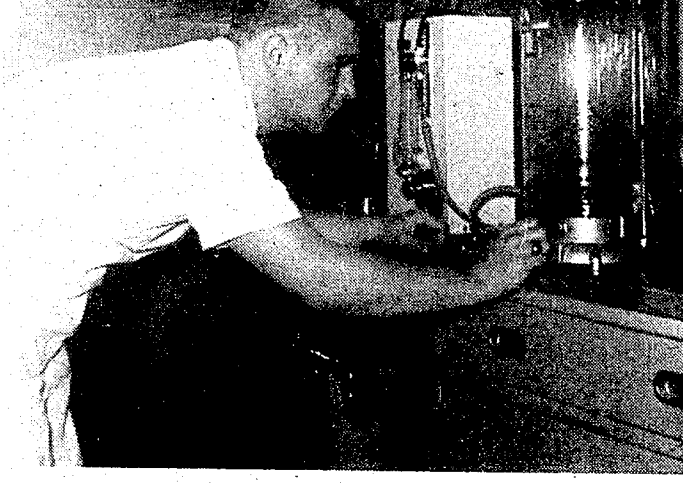
Kenneth H. Fish, Jr. prep equipment for the process of mannitol



LOUIS P. JEFFREY, M.S., is Director of Pharmacy and Central Supply, Albany Medical Center Hospital, Albany, New York. KENNETH H. FISH, JR., B.S., is Supervisor, Division of Bulk Pharmaceutical Development, Department of Pharmacy, Albany Medical Center Hospital, Albany, New York.

each case and each box to visually inspect the ampuls. The ampuls which contained crystals were set aside for return. The greatest problem arose in the late fall and during the winter months, when practically every ampul received contained large clumped crystals of mannitol.

We decided to follow the recommendation of the manufacturer who suggested that ampuls, in which crystals were evident, be warmed to body temperature in water. We found that if the crystals were large and formed a solid mass at the base of the ampul, it was impossible to redissolve them using this method. After a review of the literature and several personal inquiries, we decided to re-autoclave the ampuls. This did not adversely affect the color of the mannitol solution and, if crystals were present, they would easily redissolve. This method was instituted as a procedure in the Pharmacy and it gave us the assurance that no ampuls containing crystals would be dispensed. Howev this procedure was quite time-consuming. One way us to have circumvented this problem would be to der a large amount of mannitol injection in the ea fall and maintain it under suitable conditions throug out the winter. This procedure would have involv the allotment of large areas of valuable storage spa which was not readily available. Also, there w many times when the demand for the preparati which we placed on the pharmaceutical manufactu was so great that it could not be met.



Pharmacist Everett C. McBride adj temperature of hot plate in preparation of the mannitol filtration pro

ALBANY MEDICAL CENTER HOSPITAL
DEPARTMENT OF PHARMACY
BULK COMPOUNDING RECORD

NO.

Preparation

FORMULA	Gm/ml		√

Checked by

Made by
Time
Date
Filled by
Container
Size
Seal
No. Units
Time
Date
Inspected by
Date
Labeled by
Time
Label No.
Date

LABORATORY DATA

Date

pH Before sterilization
After sterilization

Assay

Sterility

Checked by

Time

STERILIZATION DATA

Date

Method

Temperature oC

Exposure

NOTES

Disposition of Vials

Miscellaneous
Bacteriology
ph
Rejects
Control
To stock

Total

Method of Preparation

Because of the many difficulties we were having this area, we decided to investigate the possibility preparing mannitol injection. The task was assign to the Division of Research, Control and Developme of the Department of Pharmacy. The initial step w to find a procedure. When we were not able to find a references to a specific procedure for compounding, proceeded to develop our own.

Some of the problems incurred in the manufactu of a solution of mannitol 25 percent are described the following paragraphs. Since this preparation is supersaturated solution, it was necessary to heat t water to boiling to effect solution of the crystals. If t solution were allowed to cool in a container which w not tightly sealed, small amounts of water would lost through evaporation. Crystals of mannitol th formed in the beaker. Upon cooling, the solution c not contain the labeled quantity. The supersaturat solution was prepared by adding boiling water to t mannitol in a flask, and then stoppering the fla

After working with this solution for quite sometime, we concluded that there were too many obstacles for us to solve in working with this high concentration. To resolve the problem created by the supersaturation of the mannitol solution, we varied the percent of chemical until we achieved a concentration with which we found that it was easy to work. We consulted with the members of the medical staff concerning a desirable concentration. It was concluded that a 20 percent solution of mannitol was the optimum concentration which presented the least number of problems. The 20 percent solution was of low enough concentration to virtually eliminate the problems of precipitation during manufacturing process. It was still high enough to assume the concentration needed in surgical and medical procedures. Heat is still required to prepare a 20 percent solution of mannitol, but crystallization did not occur during the handling of the solution. The decision to prepare a 20 percent solution also made it relatively easy for the nursing and medical staff to calculate dosage. The solution was to be packaged in 50 ml. vials, thus each vial contained 10 grams of mannitol. The final product maintained an essential element of the preparation—the highest possible concentration in the least amount of fluid volume.

Although Mannitol N.F. was used, there was present a significant amount of insoluble contaminants in the chemical. This created another problem. In the small volume parenteral procedures, we use the Millipore

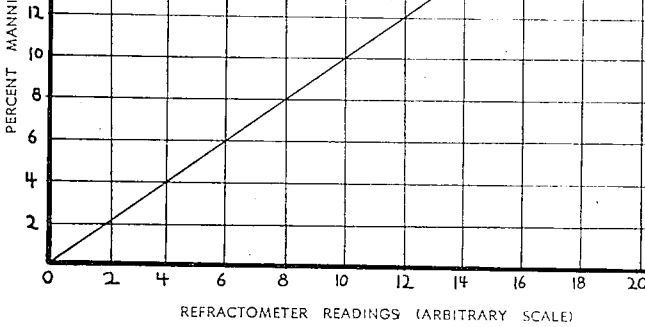
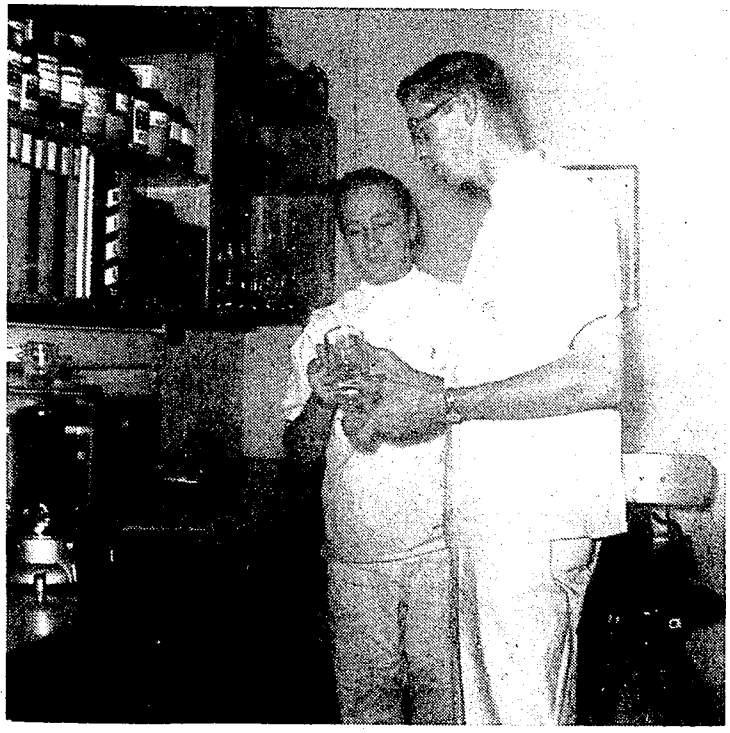


Figure 1. Refractometer Readings versus Percentage of Mannitol in Aqueous Solution at 25°C.

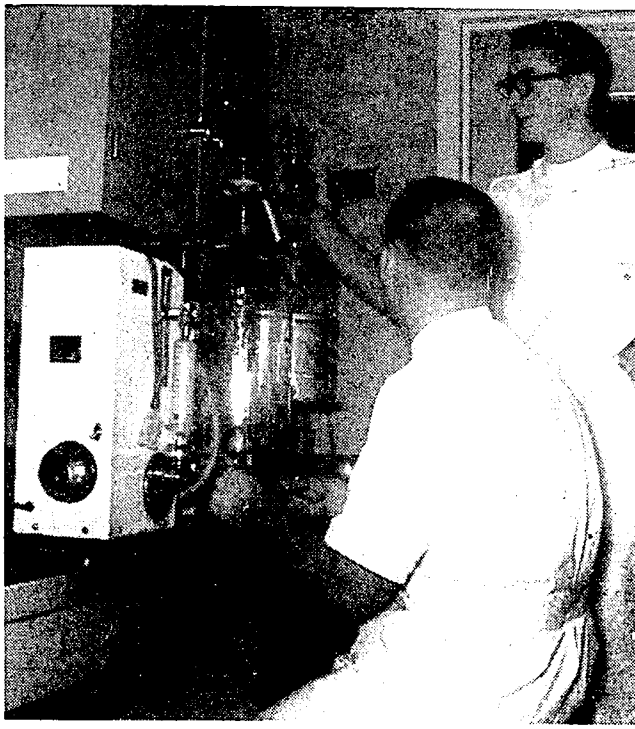
filter.[5] The porosity in the filter disc is 0.45 m This is small enough to remove from the solutio tically any insoluble material. This was the cas the mannitol solution, which contained enou soluble particles to cause the filter to become c after only a few hundred milliliters had passed t it.

This problem of impurity was discussed by pondence with the chemical manufacturer and quest was made for a more highly purified gr chemical. We were informed that the only av grade was the one which we had purchased, an this grade meets the *N.F.* requirements. Since a refined powder was not available, we attemp solve the problem through technicological m The solution proved to be relatively simple. Af mannitol solution was made, it was filtered thr

Pharmacists Fay Peck, Jr. (left) and Kenneth Fish, Jr. discuss problems involving filtration of the mannitol solution



Equipment used in preparing the solution is checked by Pha Everett C. McBride and Kenneth H. F



Procedure

The last of the problems concerned the procedure in filling the mannitol solution into vials. It was noted that a cool solution would at times "throw out" crystals when it was filled into a cool vial. To circumvent this, the solution was filled, while warm, into vials that had been recently autoclaved. No precipitation took place using this procedure.

The following is the formula for mannitol injection 20%.

Mannitol Powder N.F. (98%)	204 Gm.
Water for Injection, to make	1000 ml.

The mannitol is accurately weighed and dissolved in water for injection, which has been previously heated to 80°C. The solution is allowed to cool to approximately 50°C. and the volume is adjusted if necessary. The solution is then filtered through a medium porosity, fritted disc funnel. The vacuum bottle into which the mannitol solution is filtered rests on a hot-plate which has the temperature adjustment set at 60°C. This keeps the solution warm so that crystals are not likely to form. This step is repeated, exactly, during the second filtration process using the Millipore filter. The filtered solution is kept warm. The vacuum bottle is attached to the automatic pipetting machine[7] and the solution recirculated through the filter. This step assures that no dust particles or other impurities remain in the solution. After the solution has been recirculated several times, it is ready to be filled into vials. The 50 ml. vials, which have been properly washed and treated, should be autoclaved and allowed to cool slightly. Fifty-five (55) ml. of the warm solution is pipetted into each vial. The vials are capped with a one piece tear-away aluminum seal, crimped and autoclaved at 121°C. for 15 minutes.

Procedure for Control

After the vials are autoclaved they are packed into a case and sent to a quarantine area. One vial is sent to the Bacteriology Laboratory for a sterility test. Two vials are sent to the Pharmacy Control Laboratory where the preparation is checked on these points.

1. *p*H—6.5 to 7.3 (N.F. XI 1960)
2. Quality—qualitative tests for mannitol (N.F. XI 1960)
3. Refractive Index[8]—19 to 21
4. Assay—the refractive index reading provides a reliable assay.[8] The readings on the arbitrary scale have a direct relationship to the percent of mannitol in solution. (See Figure 1)
5. Stability—One sample is held as a control. It is observed for several weeks to check stability.
6. Sterility—The Bacteriology Laboratory sends to the Department of Pharmacy a report on the sterility

vials are now visually inspected and those contain any macroscopic contamination are discarded. The maining vials are labeled and delivered to the st room. All compounding and control statistics are tered on the Bulk Compounding Record and card is filed for future reference.

Summary and Conclusion

If mannitol solution 20 percent is to be prepar certain steps must be followed to develop and prep an acceptable product. The mannitol is dissolved in water and kept warm. It is filtered through a medi porosity fritted disc funnel and then through a Mi pore filter. The solution is filled while warm into p heated vials. This procedure is easy and effective. T possibility of crystallization occurring is practica eliminated.

The medical and surgical staff at this hospital ha found mannitol injection 20 percent to be suitable all cases in which mannitol is indicated. We now ha control over the supply of mannitol injection, and hospital is never without an adequate supply in sto The reserve which we have is stable and there is problem with storage. The manufacture of this pr aration is also economical.

Perhaps the most gratifying and satisfying conc sion to this work was the fact that the Department Pharmacy has rendered a valuable service to the tients, physicians, and nurses at the Albany Medi Center Hospital. With the addition of this valuable junct to their armamentarium, we have assisted medical staff in their effort to control acute re failure.

Notes and References

1. *Albany Medical Center Hospital, Annual Report,* 19
2. Merck Sharp and Dohme, Division of Merck and Co pany, Inc., West Point, Pa.
3. *Remington's Practice of Pharmacy,* Martin and Co 11th Edition 1956, Mack Publishing Company, pp. 636-6
4. *Ibid.*: p. 143.
5. Millipore Filter, "Pyrex Filter Holder," Catalogue N XX10 047 00, Millipore Filter Corporation, Bedford, Ma
6. Buchner-type funnel, with fritted disc. "Pyrex" bra glass (Corning No. 36060), Will Corporation, Box 10 Rochester 3, N. Y.
7. Brewer Automatic Pipetting Machine, Baltimore B logical Laboratory, Inc., 1640 Gorsuch Avenue, Baltim 18, Md.
8. American Optical Company, Buffalo, New York, Ha Refractometer, Series 25-A.
9. *U.S.P.* XVI, page 856.