

► 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.<sup>1</sup>

### Background

At the time this procedure was being instituted the Department of Pharmacy was carrying in stock mannitol injection,<sup>2</sup> 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.<sup>3</sup>

### Physical Characteristics

Mannitol, official in *N.F. XI*, is a hexahydric alcohol which is rather widely distributed in the tissue fluids of

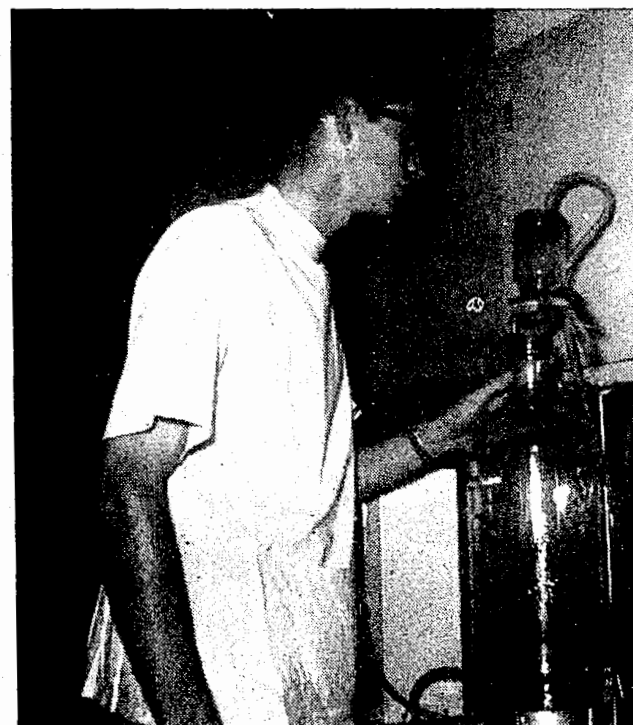
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various plants. It is obtained from manna and natural sources by means of hot alcohol extract. In purified form, it is a white, crystalline powder, odorless and having a sweetish taste. It melts between 160° and 167°C. One gram dissolves in about 5.5 ml. of water (18 percent solubility). It is obvious that a 25 percent solution is a supersaturated one.

Under certain conditions it is possible to produce a solution containing a larger amount of solute than is necessary to form a saturated solution. This may be done when a solution is saturated at one temperature and the excess solid solute removed, and the solution cooled. The solute present in solution, even though it is less soluble at the lower temperature, does not separate from the solution and there is produced a supersaturated solution. Such solutions may be caused to deposit their excess of solute in one of the following ways: by vigorous shaking; by scratching the bottom of the vessel in contact with the solution; by introducing into the solution a small crystal of the solute; or by reducing the temperature of the solution to a lower extent.

This information gives us some idea of the physical characteristics of mannitol injection 25 percent. Under normal conditions, it is a stable solution. But during shipping, handling, and storage of the injection at extreme temperatures and conditions may prevent

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



each case and each box to which 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 am-



Pharmacist Everett C. McBride adjusting temperature of hot plate in preparation of the mannitol filtration products.

puls containing crystals would be dispensed. However, this procedure was quite time-consuming. One way for us to have circumvented this problem would be to order a large amount of mannitol injection in the early fall and maintain it under suitable conditions throughout the winter. This procedure would have involved the allotment of large areas of valuable storage space which was not readily available. Also, there were many times when the demand for the preparation, which we placed on the pharmaceutical manufacturer, was so great that it could not be met.

### Method of Preparation

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

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

ALBANY MEDICAL CENTER HOSPITAL DEPARTMENT OF PHARMACY BULK COMPOUNDING RECORD				NO.
Preparation				
FORMULA	Gm/ml	✓	Made by	Time
			Date	
			Filled by	Time
			Container	
			Size	Time
			Seal	
			No. Units	Time
			Date	
			Inspected by	Time
			Date	
			Labeled by	Time
			Date	
Checked by				Label No.

LABORATORY DATA	STERILIZATION DATA
Date	Date
pH Before sterilization	Method
After sterilization	Temperature °C
Assay	Exposure
Sterility	NOTES Disposition of Vials _____ Miscellaneous _____ Bacteriology _____ pH _____ Rejects _____ Control _____ To stock _____ Total _____
Checked by	
Time	

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

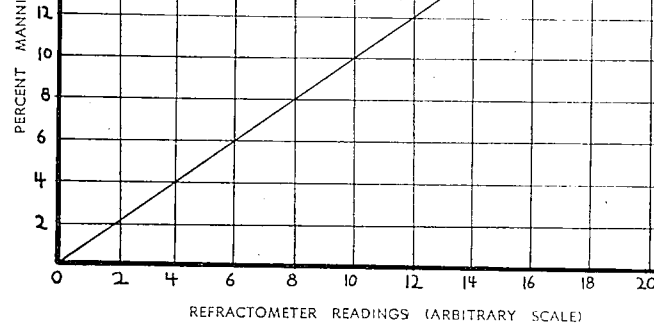


Figure 1. Refractometer Readings versus Percentage of Mannitol in Aqueous Solution at 25°C.

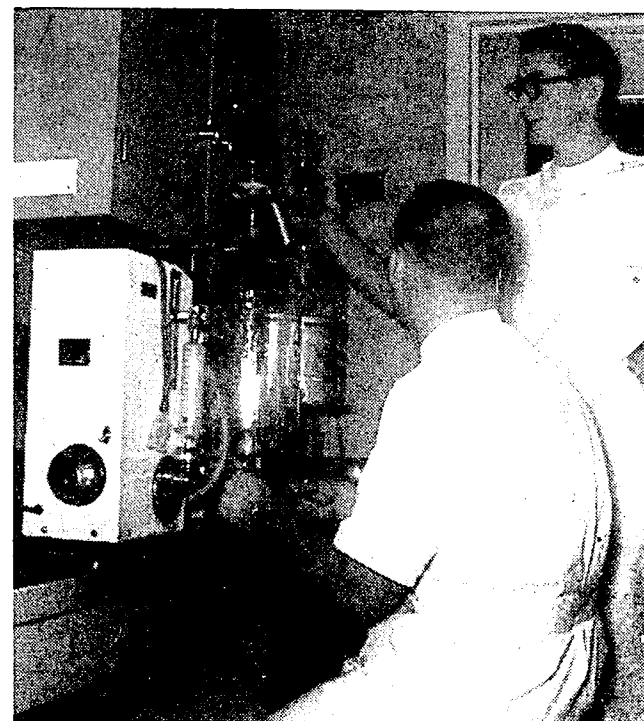
filter.<sup>5</sup> The porosity in the filter disc is 0.45  $\mu$ . This is small enough to remove from the solution virtually any insoluble material. This was the case with the mannitol solution, which contained enough insoluble particles to cause the filter to become clogged after only a few hundred milliliters had passed through it.

This problem of impurity was discussed by correspondence with the chemical manufacturer and a request was made for a more highly purified grade of chemical. We were informed that the only available grade was the one which we had purchased, and that this grade meets the N.F. requirements. Since a more refined powder was not available, we attempted to solve the problem through technological means. The solution proved to be relatively simple. After the mannitol solution was made, it was filtered through

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



Equipment used in preparing the mannitol solution is checked by Pharmacist Everett C. McBride and Kenneth H. Fish



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<sup>7</sup> 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. pH—6.5 to 7.3 (N.F. XI 1960)
2. Quality—qualitative tests for mannitol (N.F. XI 1960)
3. Refractive Index<sup>8</sup>—19 to 21
4. Assay—the refractive index reading provides a reliable assay.<sup>8</sup> 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 as now visually inspected and those containing any macroscopic contamination are discarded. The remaining vials are labeled and delivered to the storeroom. All compounding and control statistics are entered on the Bulk Compounding Record and a card is filed for future reference.

### Summary and Conclusion

If mannitol solution 20 percent is to be prepared certain steps must be followed to develop and prepare an acceptable product. The mannitol is dissolved in water and kept warm. It is filtered through a medium porosity fritted disc funnel and then through a Millipore filter. The solution is filled while warm into preheated vials. This procedure is easy and effective. The possibility of crystallization occurring is practically eliminated.

The medical and surgical staff at this hospital have found mannitol injection 20 percent to be suitable in all cases in which mannitol is indicated. We now have control over the supply of mannitol injection, and the hospital is never without an adequate supply in stock. The reserve which we have is stable and there is no problem with storage. The manufacture of this preparation is also economical.

Perhaps the most gratifying and satisfying conclusion to this work was the fact that the Department of Pharmacy has rendered a valuable service to the patients, physicians, and nurses at the Albany Medical Center Hospital. With the addition of this valuable adjunct to their armamentarium, we have assisted the medical staff in their effort to control acute renal failure.

### Notes and References

1. *Albany Medical Center Hospital, Annual Report*, 1960.
2. Merck Sharp and Dohme, Division of Merck and Company, Inc., West Point, Pa.
3. *Remington's Practice of Pharmacy*, Martin and Co., 11th Edition 1956, Mack Publishing Company, pp. 636-637.
4. *Ibid.*: p. 143.
5. Millipore Filter, "Pyrex Filter Holder," Catalogue No. XX10 047 00, Millipore Filter Corporation, Bedford, Mass.
6. Buchner-type funnel, with fritted disc. "Pyrex" brand glass (Corning No. 36060), Will Corporation, Box 100, Rochester 3, N. Y.
7. Brewer Automatic Pipetting Machine, Baltimore Biological Laboratory, Inc., 1640 Gorsuch Avenue, Baltimore 18, Md.
8. American Optical Company, Buffalo, New York, Hand Refractometer, Series 25-A.
9. *U.S.P.* XVI, page 856.