DEVELOPMENT OF A PROTOTYPE SPACE FLIGHT INTRAVENOUS INJECTION SYSTEM

FINAL REPORT

BY

GERALD V. COLOMBO

MAY 1985

PREPARED UNDER CONTRACT NO. NAS9 16337

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UMPQUA RESEARCH COMPANY
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LYNDON B. JOHNSON SPACE CENTER
NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

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INTRAVENOUS INJECTION SYSTEM

1.0 INTRODUCTION

Medical emergencies, especially those resulting from accidents, frequently require the administration of intravenous fluids to replace lost body liquid. A system to provide this capability in space is required. Existing systems do not meet space flight requirements.

2.0 BACKGROUND

Storage and weight limitations on space vehicles preclude the inclusion of large quantities and varieties of injectables or infusables. In addition, the handling and transfer of fluids under conditions of micro gravity further impact an intravenous injection system.

The weight and volume of an injection system can be reduced significantly by providing the injectables in a concentrated form. These can then be reconstituted prior to being administered through the addition of water. System weight and volume can be further reduced by utilizing water from the spacecraft potable water system. As long as the water in the potable system meets the potability requirements, it will meet most of the requirements for injection as outlined in the U. S. Pharmacopoeia. However, aseptic transfer from the potable system cannot be guaranteed with present equipment, consequently

provision must be made to prevent the inclusion of microorganisms, (or other contaminants), during attachment of the reconstitution hardware to the water dispenser. In addition, in an emergency situation, the chemical quality of the water may be questionable.

The administration of fluids in the absence of gravity requires a positive feed system which can be controlled and monitored. Due to the anticipated infrequency of need, a system which has no vehicle interfaces such as pneumatic and electical, and has a long unattended shelf life is desireable.

3.0 TECHNICAL APPROACH

The development of a prototype space flight intravenous injection system was accomplished by six tasks: The definition of requirements, injectable concentrates development, water polisher, reconstitution hardware development, administration hardware development, and prototype fabrication and test.

3.1 Definition of Requirements.

The basic requirements for the system were defined at a meeting at JSC in May of 1981. At this time the basic proposed system approach was presented and JSC medical and engineering personnel made appropriate decisions regarding the requirements.

It was agreed that the goal of the program was to provide the capability to provide emergency IV therapy to a Shuttle crew member for a period long enough to permit return to the ground. The assumption was that any injury or illness serious enough to require IV therapy would result in a mission abort within one or two days. Consequently, the administration hardware could be designed for single use.

The initially proposed hardware approach (circa March 1983) is shown in Figure 3-1. Potable water from a dispenser is passed through a purifier and fills a bag containing a glass ampule containing dehydrated solute, which is broken before the filling process is started.

Administration will be accomplished by pressurizing the bag and controlling the flow with adjustable restrictions.

After presentation of the proposed approach and deliberation, the major conclusions of the meeting were:

a. Solutions must meet requirements of the USP Reference 1.

b. Standardize on a 1 liter capacity system.

c. Provide ports on both the bags and IV tubing to permit the addition of medication.

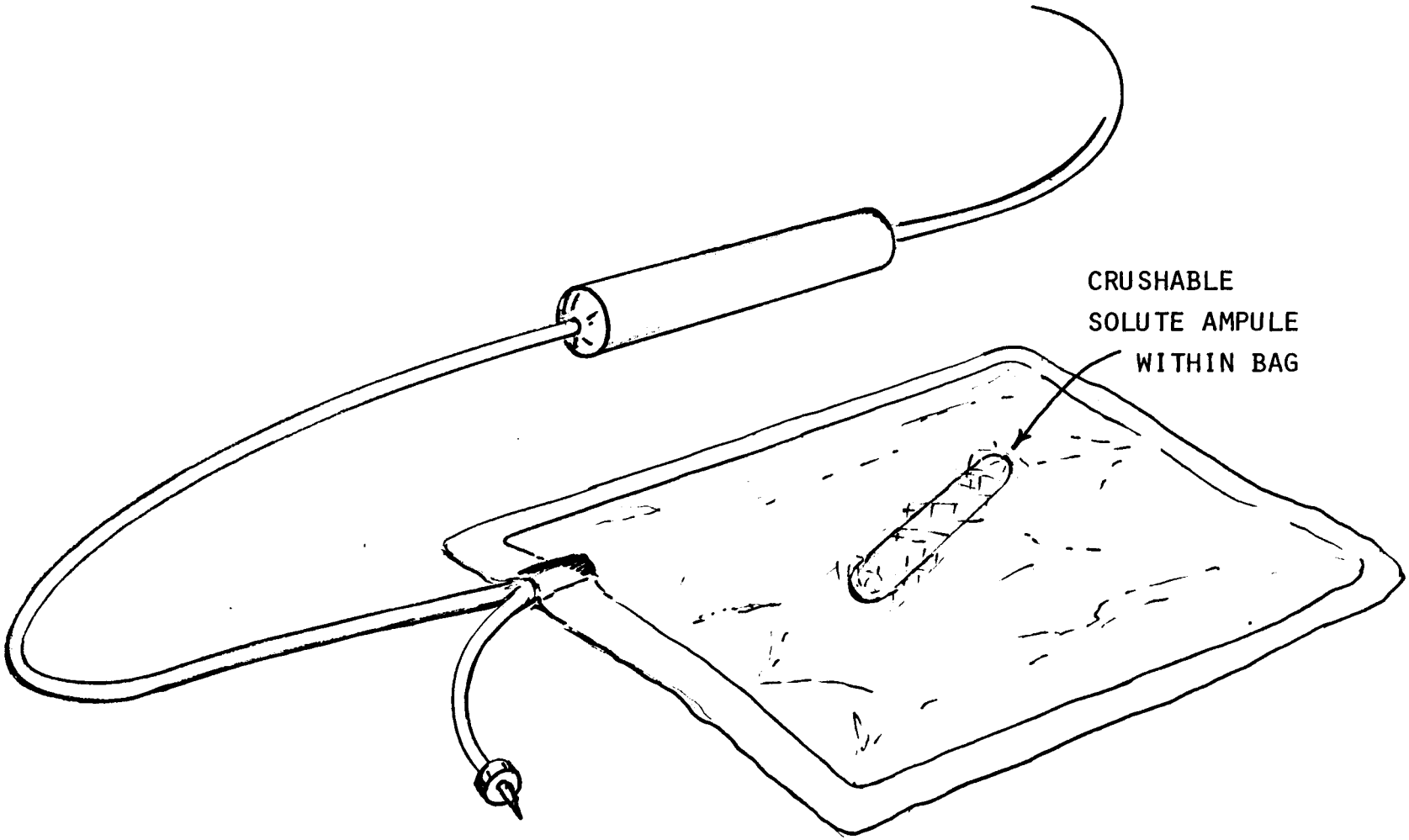


FIGURE 3-1.

ORIGINAL PROPOSED CONCEPT

d. Two solutions will be provided, Normal Saline and Lactated Ringers.

e. A strong objection was made to the breaking of glass ampules inside the system. This presented a design problem with isolating the various zones of the purification system.

f. Flow rate capabilities shall range from the maximum possible to TKO (To Keep Open, 1cc/hr). Normal maintenance flows should be around 100 to 150 cc/hr.

g. Shelf Life 1 year minimum.

Based on the above design requirements, the following development programs were initiated.

4.0 INJECTABLE CONCENTRATES DEVELOPMENT

During the Definition of Requirements, two injectable solutions were specified, Normal Saline and Lactated Ringers. The USP specifications and tolerances for the solutes in these injectables are shown in Table 4-1.

Normal Saline for Injection contains 0.9% Sodium Chloride. Salt is readily soluble at this level and could be used either as the USP powder, or a concentrated solution in the IV bag. One reservation on using the powder is the possible inclusion of insoluble particulates.

Another potential problem with using a dry powder is the absorption of small amounts of moisture through the bag which would result in cakeing of the salt. This makes dissolution more difficult, and complete solubilization and mixing questionable in a reasonable amount of time.

Lactated Ringers is a solution of calcium chloride, potassium chloride, sodium chloride, and sodium lactate. Sodium lactate is a hygroscopic liquid at room temperature, and is purchased as a 60% solution. This solution contains no preservative, but the osmotic pressure is apparently very high, since an aerobic plate count taken on a sample from the reagent bottle showed less than 10 organisms/ml. A readily soluble slurry was prepared from pure sodium lactate and the other salts. Enough slurry to make 1 liter of Lactated Ringers was easily dissolved in 30 ml of water. Thus the concentrate can be introducted into the bag either as the slurry or the 30 ml concentrated solution.

In light of the possible dissolution problems with salt, and the fact that sodium lactate is a liquid, it was decided that both solutes would be best provided in the form of a concentrated liquid. Each can be provided as a stable solution of 30 ml for a one liter final solution.

All solute concentrations are prepared from USP grade reagents. The sodium chloride and potassium chloride are heated at 180 degrees centigrade for 1 hour to destroy any possible pyrogen contamination, (these comprise the bulk of both concentrates),

TABLE 4-1. USP SOLUTE REQUIREMENTS FOR INJECTABLES

	Lactated Ringers for Injection mg/liter
Sodium	2850 - 3150
Potassium	141 - 173
Calcium	49 - 60
Chloride	3680 - 4080
Lactate	2310 - 2610

	Saline for Injection mg/liter
Sodium	3364 - 3719
Chloride	5187 - 5733

the liquid sodium lactate can not be heated since it decomposes at 140 degrees centigrade, and the calcium chloride dehydrates unpredictably, making weighing difficult.

The concentrates are prepared by weighing the solutes in pyrogen free glassware and dissolving in pyrogen free water. After autoclaving, the solutions are analyzed for each constituent as specified in the USP. Adjustments are made as necessary to provide the proper balance in the individual constituents. An aliquot is then diluted to the final concentration and tested for

Samples of both concentrates were innoculated with 100/ml of a mixture of wild bacteria and incubated for 48 hours at 35 degrees centigrade. Aerobic plate counts after incubation showed no growth, indicating that the concentrates are at least bacteriastatic due to their high solute concentrations. However, it is proposed that the concentrates be sterilized insitu to the containers after they are packaged.

5.0 RECONSTITUTION HARDWARE

The original design concept involved storing the solute concentrates in glass ampules inside the IV bags, which would be broken for reconstitution. This concept was abandoned, and the inclusion of the concentrate within the bag with no other container was considered. This approach is not feasable since the bag materials will not withstand autoclaving, and the sterilization of solutions with ethylene oxide (the process used for bags and other dry equipment), is not practical. Gamma irradiation is a possible approach to this problem. In addition, if the concentrate is included in the "bag" a complete IV bag set would be required for each liter of solution.

Another approach that was considered is the storage of the concentrates in syringes, which would be injected into the bags before filling. This approach was rejected due to the difficulty in hermetically sealing the filled syringes, and the possibility of the crewmember forgetting to add concentrate before filling the bag, and infusing the patient with water.

The adopted approach is the flow-thru pouch shown in Figure 5-1. The pouch is fabricated from pharmacutical grade polyvinylchloride tubing. The end fittings are female luer locks with a membrane incorporated below the end of the tapered section. The pouches are sterilized by ethylene oxide and filled using aseptic techniques with a measured volume of concentrate. Pyrogen free water is then added to displace all the air up into the fill tube. A portion of the fill tube is wetted with methylcyclohexanone (the solvent used to assemble all IV and blood collecting equipment), and clamped overnight to make permanently fused joints. The entire filling process is carried out in a laminar flow bench under irradiation by ultra violet lamps. The filled pouches may be pastuerized to destroy any bacteria included during the filling process, or irradiated with gamma rays.

The concentrate pouches are used to connect the IV bags to the water purifier when being filled. The bag fill tubes and the purifier cartridges have 15 gage needles mounted in male luer lock fittings which puncture the pouch membranes when connected for filling. This fitting arrangement insures that each bag is

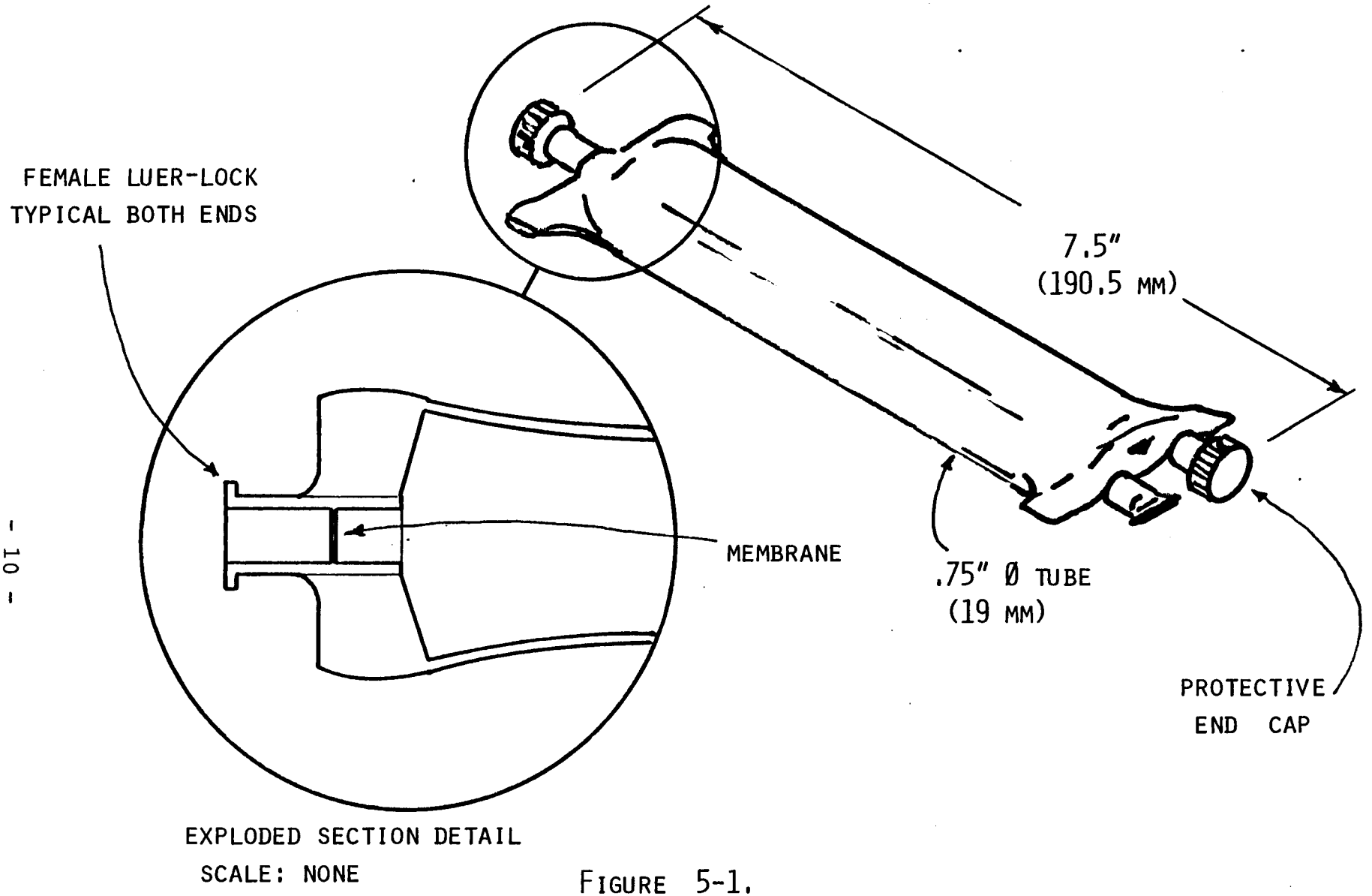


FIGURE 5-1.

CONCENTRATE POUCH

filled through a concentrate pouch, and prevents the accidental filling of a bag with water without concentrate since it is physically impossible to directly connect the polishers to the bag.

A series of tests were conducted to evaluate the reliability of the filling process, and the efficiency of flushing the concentrate from the pouch into the bag. The results of tests on ten pouches are shown in Table 5-1. The first five tests were conducted with the pouches horizontal, the closest simulation of microgravity operation. The last five were conducted with the pouch on a vertical position, some with flow from the top to bottom, and bottom to top which is the worst case in terms of density stratification. In all cases, the resulting solution, after mixing was well within the plus or minus 5% tolerances specified by the USP.

Additional testing showed solutions prepared from pouches to be sterile and pyrogen free.

TABLE 5-1. RECONSTITUTION TEST RESULTS.

TEST	ORIENTATION	FLOW	DEVIATION %
1	horizontal	horizontal	2.1
2	" "	" "	3.7
3	" "	" "	0.4
4	" "	" "	-0.2
5	" "	" "	1.8
6	vertical	up	-1.2
7	"	"	-1.8
8	"	"	-2.8
9	"	"	1.1
10	"	down	-1.5
Limit			±5.0

6.0 Water Polisher Development

The goal of this task was to develop a device that will guarantee that the water used to reconstitute the concentrate results in IV solutions that meet all USP criteria. The potability requirements for Shuttle water are shown in Table 6-1. With the exception of copper and zinc, which are not used or have ever been detected in the Shuttle water system, all parameters meet or exceed those of the USP for injectable water. The three types of possible contaminants that must be addressed to guarantee USP suitability are microbiological, inorganic chemicals (primarily heavy metals), and organic chemicals (most importantly, pyrogens). Microbiological contamination will be prevented by iodination, inorganics removed with ion exchange resins and organics by activated carbon.

The basic configuration of the device to be used as a polisher, or purifier, is shown in Figure 6-1. Potable water is supplied from the drinking water dispenser via a hose fitting with a needle mounted in a locking fitting. The needle punctures the first membrane of a sealed cartridge containing iodinated resin. This resin produces 2 ppm of Iodine and is the active biocide used in the Microbial Check Valve in the Shuttle water system. A summary of the successful challenges of this resin is shown in Table 6-2. This resin is maintained in a sealed cartridge to prevent the migration of elemental iodine from the resin into the remainder of the purifier at the other end during storage. The second membrane is punctured to permit flow by pushing the two sections together.

The water then passes through the anion exchange resin and a cation exchange resin where inorganic chemicals are removed. The activated charcoal removes any organic contaminants which may be in the feed water in addition to materials which may bleed from the ion exchange resins.

6.1 Contaminant Control Beds

The goal of this task was to develop a device to produce water which meets all the requirements of USP for Sodium Chloride for Injection and Lactated Ringers for Injection. The primary requirements listed in the USP citations for each solution

Table 6 - 1 , Space Shuttle Potable Water Requirements

Ref. SD-W-0020

Properties	Limits (Maximum Allowance)
a. pH	5.0-8 at 25 degrees C (77 F)
b. Total Solids	20 ppm
c. Taste and Odor	None at Threshold (Odor No. of 3)
d. Turbidity	11 Units
e. Color, True	35 Units
f. Total Organics	10 ppm

Particulate Size Range	No. of Particles per 500 ml Fluid
a. 0-10 microns	Unlimited
b. 10-25 microns	1000
c. 25-50 microns	200
d. 50-100 microns	100
e. 100-250 microns	10

Ionic Species	Maximum Allowable Concentration
a. Aluminum	For reference only
b. Cadmium	0.01 ppm
c. Chloride	1.0 ppm
d. Chromium (Hexavalent)	0.05 ppm
e. Copper	1.0 ppm
f. Iron	0.3 ppm
g. lead	0.05 ppm
h. Magnesium	For reference only
i. Manganese	0.05 ppm
j. Mercury	0.005 ppm
k. Nickel	0.05 ppm
l. Potassium	For reference only
m. Selenium	0.05 ppm
n. Silica	For reference only
o. Silver	0.05 ppm
p. Ammonia	0.5 ppm
q. Zinc	5.0 ppm

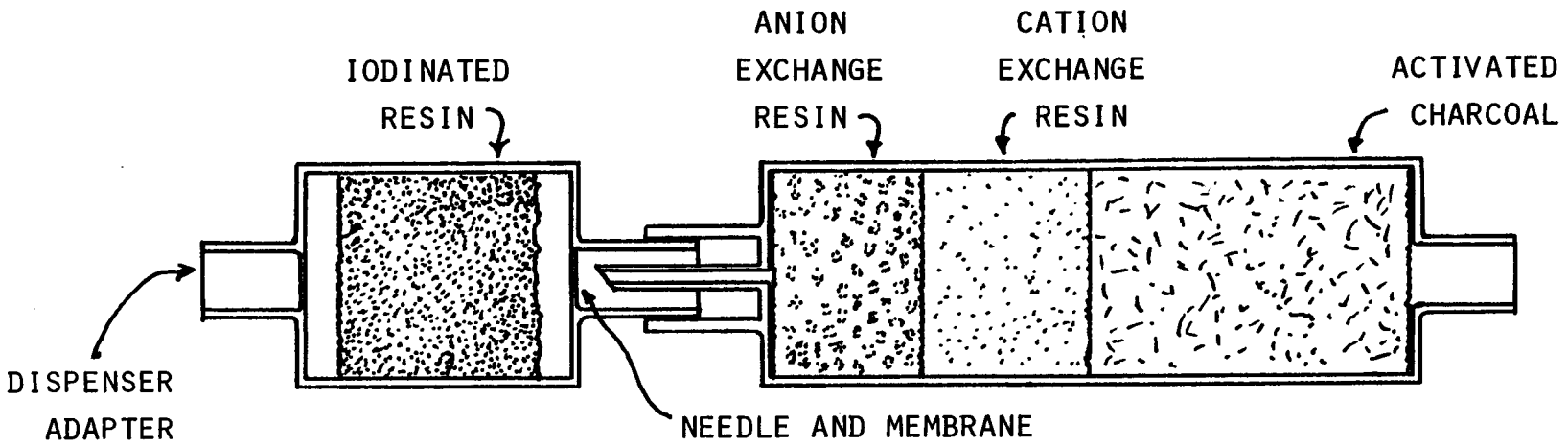


FIGURE 6-1.
WATER POLISHER BASIC CONCEPT

TABLE 6-2. MICROBIAL CHECK VALVE CHALLENGES

SUSPENSIONS	No. of Organisms Per Milliliter
1. Escherichia coli	10^6
2. Streptococcus faecalis	10^6
3. Staphylococcus aureus	10^6
4. Bacillus subtilis	10^6
5. Pseudomonas aeruginosa	10^6
6. Clostridium perfringens	10^6
7. Aspergillus niger	10^6
8. Mixture of all the above organisms	10^4
Complete deactivation of all organisms in effluent.	
9. Reovirus	Instantaneous deactivation of $TCD_{50}>10^4$
10. Adenovirus	
11. Type 1 Polio	Complete deactivation after 15 min of $TCD_{50}>10^4$

involve the concentration limits for the various solutes. In addition each references the requirements for Sterile Water for Injection which has a few specific requirements, and it in turn references the requirements for Purified Water. This sequential referencing, in some cases, results in requirements which are of questionable importance, as will be discussed later. The various requirements are presented in Table 6-3, as well as the results of test results from challenges to verify the ability of system components to remove potential contaminants. One liter of water containing approximately ten times the USP limit or ten times the drinking water limit was passed through a 4 cubic centimeter bed of cation and anion exchange resin, previously sieved to 30 to 40 mesh. (Preliminary tests with resin in the form supplied by the manufacturer, 16 to 50 mesh showed unreliable results.) The resulting effluent was then tested for removal efficiency. A discussion of the individual test results follows:

Water Parameters and Test Results

pH - The water produced by the ion exchasnge columns will have essentially no ions, consequently the purity of the salts used to produce the solutions will have the major effect on the resulting pH.

Cl - The tolerances of both solutions are in the neighborhood of 4 grams/liter. It is inconceivable that water containing enough chloride to produce a solution that would not meet the specification would ever be encountered.

SO4 - The Purified Water test is sensitive at a level of approximately 5 mg/liter. The anion bed reduced an 11 mg/liter solution to 3 mg/liter.

NH3 - The cation bed reduced a 2.4 ppm solution to less than 0.01 ppm.

Ca - The Purified Water test is sensitive to approximately 5 ppm Ca. The cation bed reduced a 49 ppm solution to less than 4 ppm.

CO2 - The Purified Water test is sensitive to

Table 6-3, USP REQUIREMENTS AND CHALLENGE DATA -

(1 Liter thru 4cc Bed)

	Challenge Concentration(ppm)	Effluent Concentration(ppm)	USP XX MAC (ppm)
Sulfate	11	3	5.0
Ammonia	2.4	<0.01	0.3
Calcium	49	3.7	5.0
Carbon Dioxide	36	4	60.0
Heavy Metals			
Copper	10	0.5	
Selenium	1.5	0.13	
Cadmium	0.26	0.03	
Lead	0.15	0.008	
Silver	0.57	0.15	
Nickel	0.6	0.02	Total
Manganese	0.12	0.028	<0.3
Chromium			
Cr^{++}	1.08	0.06	
CrO_4^{++}	0.07	<0.01	
$Cr_2O_7^{++}$	0.07	<0.01	
Arsenic	0.81	0.07	0.08
Iron	23	1.9	2.0
Ferricyanide	0.08	0.009	0.01
Particulates			<50/ml >10 <5/ml >25
Pyrogens	10ng/ml	<0.25ng/ml	Rabbit Test
Sterility			Sterile
Oxidizable Substances			NDwKMnO_4
Total Solids			10
Infusion Fluid Components			
Potassium	156	7.7	157±16
Sodium	196	22	3000±150
Chloride	197	114	3880±200

approximately 60 mg/liter. This is approximately equivalent to the theoretical capacity of a 4 cc bed. It does not appear to be realistic to use a bed large enough to handle ten times this limit. Medical advice indicates that the effect of high CO2 or carbonate levels is of little concern, and a failure mode of the potable water system that would produce high CO2 levels in the water is not immediately obvious. There is no known source of CO2 in this water system.

As - The limit for arsenic is 0.08 ppm. A mixed bed reduced 0.8 ppm to 0.07 ppm.

Fe - The total iron limit is 2 ppm. The cation bed reduced a 23 ppm mixture of ferrous and ferric iron to a total of 1.9 ppm.

Heavy Metals - The detection level for total heavy metals is 0.3 ppm. The data for the individual metals are self-explanatory.

Particulates - The limits for injectables are less than 50/ml for particles larger than 10 u and less than 5/ml for particles larger than 25 u. A 0.2 u final filter will easily meet this requirement.

Pyrogens - The Limulus Amebocyte Lysate Test is sensitive to 0.25 ug/ml, which the test manufacturer claims is "several fold more sensitive than the rabbit test". The anion bed in OH form reduced a 10 ug/ml solution of E. coli 0111 endotoxin to less than the detectable level of the LAL test kit obtained from M.A. Bioproducts, Inc.

Bacteria - Sterility - The USP Purified Water specifications require less than 2.2 Total Coliform/100 ml. The Sterile Water for Injection specification requires sterility when added to nutrient broth. The iodinated resin bed has shown the capability to meet these requirements.

Oxidizable Substances - This test is an attempt at a simple test for organic materials, however it will respond to a wide variety of materials from ferrous iron to glucose. No direct attempt was made to challenge this requirement.

Total Solids - This limit is irrelevant due to the levels of dissolved solids in the IV solution.

Potassium - Sodium - Lactate - These are the tolerances for the final IV solutions. The cation bed was challenged with Na and K just to demonstrate the ion exchange capability. There is no conceivable way lactate ion could be in the raw water.

6.2 Cartridge Design and Manufacture.

The basic cartridge concept as shown in Figure 6-1 consists of an iodination section, interface section, and sorbent bed section. The contaminant challenge tests previously described, showed that a 4 cc bed of each type of sorbent would adequately protect one liter of water. Although it is not likely that any purifier would be exposed to the levels as high as the challenges, a margin of safety was desired in addition to the capability of use for more than one liter. These factors as well as the pressure drop exhibited by the small mesh size resins led to the adoption of larger beds. Experiments with various prototype configurations led to the adoption of a bed diameter of approximately 2 cm providing 6 cc of each resin.

One of the primary criteria for the selection of a material for the cartridge was compatibility with the iodinated resin. Experience showed that polypropylene is the mose desireable material, other than fluorocarbons, from a standpoint of stability, easy machinability, and cost. Polypropylene cannot be glued, however heat bonding techniques have been developed to provide strong and reliable joints. The ready availability of a disposable polypropylene syringes has proven to be a convenient source of materials for cartridge construction. The materials are known to be FDA approved, and the availability of syringes with luer lock fittings make them ideal housing materials.

A schematic of the iodinated resin cartridge is shown in Figure 6-2. This cartridge is sealed by membranes at each end to prevent the loss of iodine during storage, and more importantly when the entire purifier assembly is autoclaved. An iodine cartridge is assembled by cutting a 20 cc syringe to the appropriate length, and forming a membrane at the end by placing a drop of molten polypropylene over the hole and forming with an

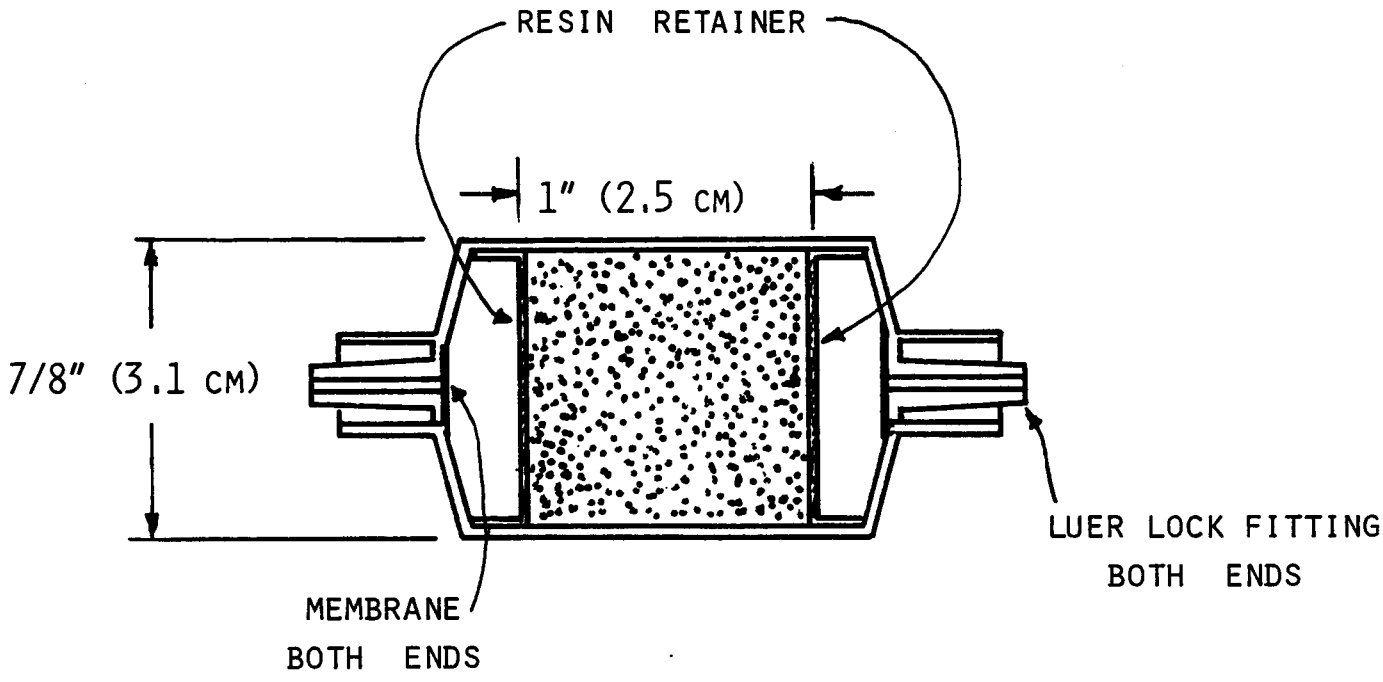


FIGURE 6-2.

IODINATED RESIN CARTRIDGE

aluminum mandrel. A resin retainer, made by machining rod stock and heat fusing 100 mesh polypropylene screen, is inserted to provide space for the membrane penetrating needle above the membrane. The iodinated resin, prepared and certified per References 2 and 3, is then added, and another retainer pressed in place to compact the resin bed. The end of the cartridge, made from another 20 cc syringe with a membrane added, is then heat sealed to the body. This results with a hermetically sealed resin cartridge with luer lock fittings on each end.

The interface section contains the needle used to penetrate the membrane of the iodine cartridge and provide a secure flow path. Some of the approaches that were considered are shown in Figure 6-3.

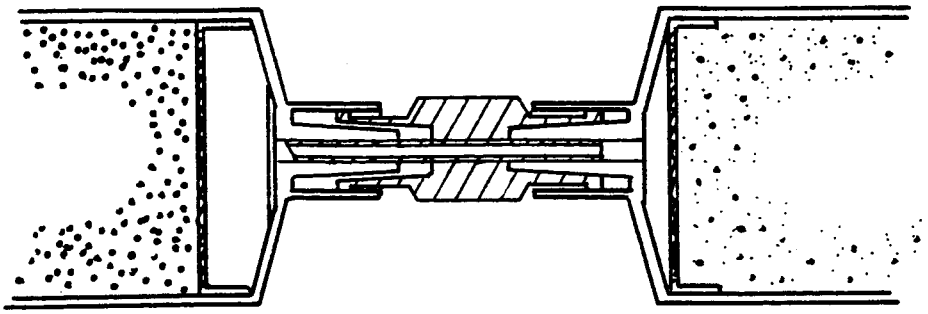
The first approach used a male luer lock attached to the needle. After the needle penetrated the membrane, the fitting was seated and twisted locking the fitting. It was found that a positive lock was difficult to achieve without being able to observe the relative positions of the fittings, and the seal between the cartridges could leak if twisted during handling.

The second approach used a bellows to provide a perfect seal no matter how the cartridge was handled after the membrane was punctured. The disadvantage of the bellows was a large dead volume which could introduce air bubbles during use.

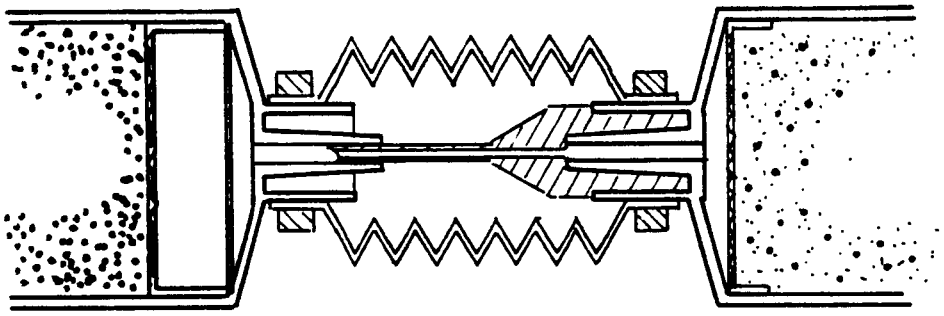
A third approach used a double ended needle mounted in a double ended luerlock fitting. Two membrances are punctured when the two sections are connected and twisted. This approach has the same disadvantages as the first.

The adopted approach, shown in Figure 6-4, is similar to the bellows but uses surgical grade Silicone rubber tubing to connect the two cartridges. It is flexible enough to allow the membrane to be punctured, but there is essentially no dead volume surrounding the needle. This system has been tested up to 60 psi without failure, however it's tensile strength is limited and a nylon cord is used to prevent the two cartridges from being pulled apart due to mishandling.

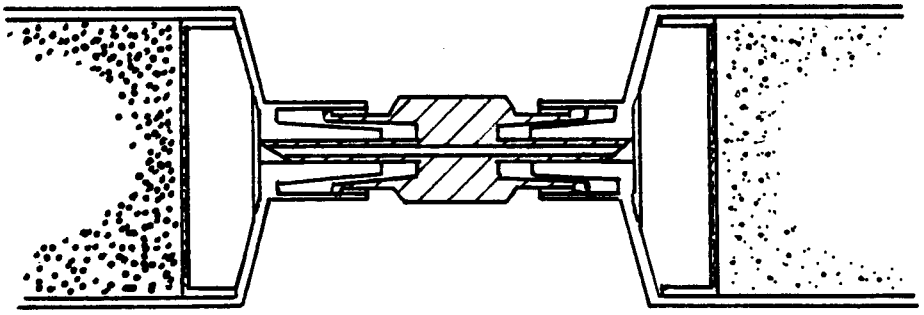
A schematic of the sorbent bed section is shown in Figure 6-5.



DOUBLE ENDED LUER-LOCK



FUSED NEEDLE WITH BELLOWS



DOUBLE ENDED LUER-LOCK WITH DOUBLE NEEDLE

FIGURE 6-3.
INTERFACE SECTION CONCEPTS

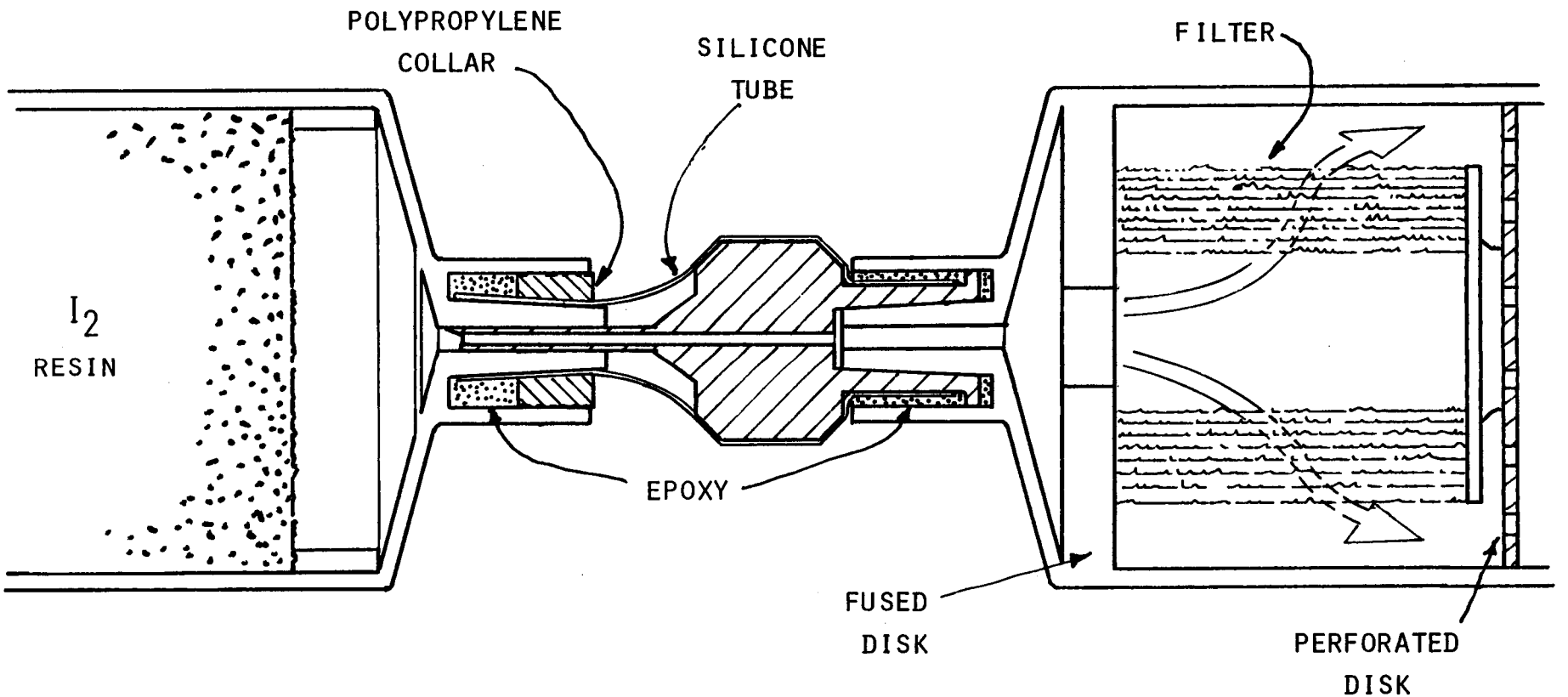


FIGURE 6-4.

PRESENT INTERFACE SECTION

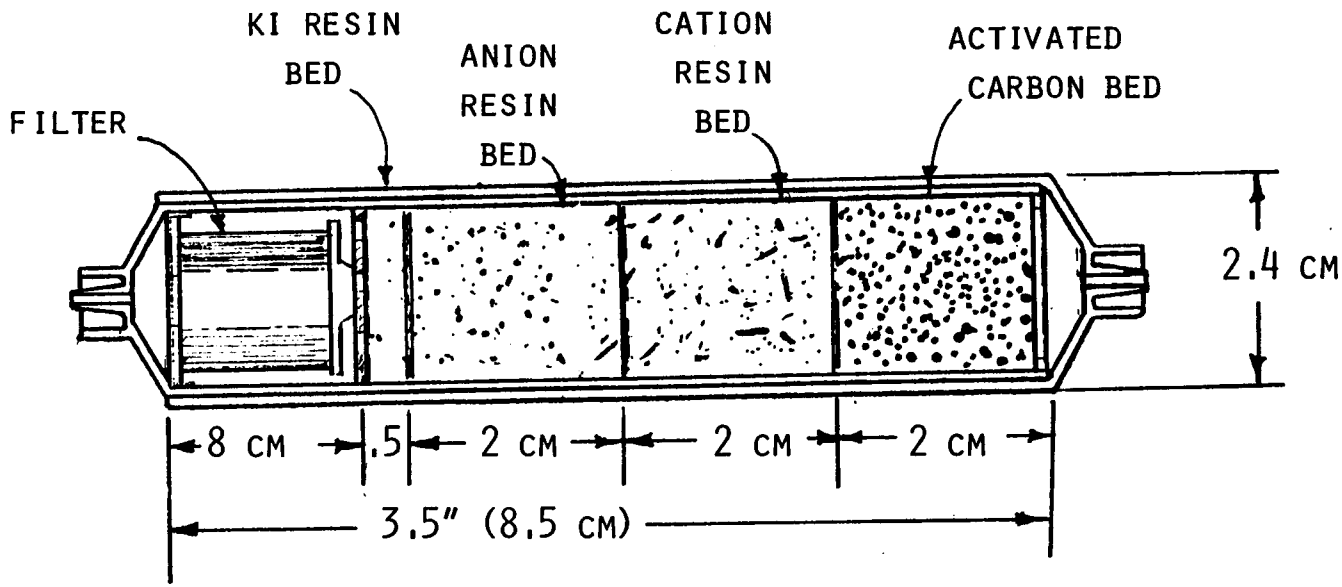


FIGURE 6-5.

SORBENT BED SECTION

This is the final configuration and is somewhat different from that shown in Figure 6-1. During testing with units in the Figure 6-1 configuration, traces of iodine were detected in the bed effluent. A small bed of anion resin in the iodide form was added to remove all traces of iodine. In a test with a bacterial challenge using a mixed population of wild organisms in excess of 10,000/ml, the effluent was not completely disinfected, approximately 10 colonies per ml were observed when plated on agar. The most logical explanation of this phenomenon is that the immediate removal of iodine from the stream did not allow sufficient contact time to deactivate any spores. The solution to this problem was the addition of a filter between the iodinated resin and the iodine removing resin. The filter selected was a depth type filter which is rated at a nominal 0.3 microns. Although it is not an absolute filter like a membrane, challenges with bacteria containing water showed that the filter completely retains any viable organisms and spores. An absolute membrane filter was not selected because a membrane filter with an acceptable pressure drop would make the device unacceptably large. The filter retains all organisms larger than 0.3 microns, and is continuously exposed, after activation by puncturing the membrane, to iodine. Thus any spores that are trapped will be deactivated.

The raw anion exchange resin is Dowex-1 purchased in the chloride form. The as received resin was found to contain a high level of viable bacteria and pyrogens. The resins were cleaned by boiling in pyrogen free water, and rinsing with ethyl alcohol. The resin was then cycled by converting it to the hydroxide form, rinsing, converting back to the chloride form, rinsing, and finally converting to the hydroxide form. This process yielded a resin that was pyrogen free. The washing and cycling process was all accomplished in a single day, and the final product autoclaved. A portion of this resin was converted to the iodide form for use as the iodine removal bed.

The cation exchange resin is Dowex-50W purchased in the hydrogen form. The as received resin was found to contain very few bacteria and was pyrogen free. This resin was also cleaned by boiling and an alcohol wash, followed by converting to the sodium form and back to the hydrogen form before autoclaving. This process also resulted in pyrogen free resin. Both resins were

purchased as 50-100 mesh.

The activated charcoal was Sigma No 6-3014, 14-60 mesh. The as received charcoal was dry, and when rinsed showed a high specific conductance, indicating leachable inorganic salts, and contained pyrogens. An analysis of the water showed the salts to primarily be calcium and a trace of magnesium. The charcoal was washed with hydrochloric acid and rinsed until the specific conductance showed the acid was removed. The charcoal was then heated to 180 degrees Centigrade in a nitrogen atmosphere to insure the destruction of pyrogens. Activated charcoal treated in this manner and stored dry remains pyrogen free.

A cartridge was assembled by inserting a retaining screen which included a 3 micron fiberglass filter into the bottom of a 20cc syringe body. The filter retains charcoal dust which invariably forms due to handling. The activated charcoal was then added followed by the cation exchange resin, anion exchange resin, iodide form anion resin and a final resin retainer. The depth filter is a cylinder which provides for radial flow. One end of the cylinder is closed with a polypropylene disk by fusing the end with molten polypropylene. The other end is fused to a perforated disk which is fused to the body of the syringe, providing an absolute seal and requiring all water to flow from the inside radially through the filter. An end from a 20 ml syringe is then fused to the perforated disk, completing the assembly. A 15 gage needle is fitted to the filter end of the assembly which has a piece of silicone tubing stretched over its entire length. A polypropylene collar is then forced over the tubing at the base of the needle after a small amount of epoxy is applied. Although the epoxy does not bond to the polypropylene, it forms itself to all the irregularities in the joint and provides a positive seal. The other end of the silicone tube is installed in the end of the iodine cartridge in the same manner and the nylon cord attached to holes in the luer lock collars.

The entire filling and assembly described above is accomplished in a single day, and the completed cartridge autoclaved.

The assembled beds are then inserted in sleeves made from 30 ml syringe barrels and fused at the ends. The retaining ring, a section of syringe barrel is then inserted and tacked in several

places. This ring prevents the inadvertent puncturing of the inner membrane. As long as this ring is tacked in place, it is impossible to activate the bed and the internal integrity is assured. The final configuration is shown in Figure 6-6.

6.3 Purifier Challenges

The three types of contaminants which could conceivably be present in the potable water as it is supplied to the purifier are corrosion products from the water system, bacteria which may be present on the surface of the water dispenser port, and pyrogens on the surface of the dispenser port if bacteria are present. The purifier was tested with these contaminants in the feed water individually and in combinations.

6.3.1 Metals Challenge

Table 6-4 summarizes the results of challenges to a complete unit with the three metals representing the major constituents of stainless steel; iron, nickel, and chromium. The first set of data represent the third and seventh liters of an eight liter challenge. The first liter contained pyrogens, the second bacteria, the third the metals as listed, the fourth and fifth bacteria, and the sixth bacteria but on the following day. The seventh, tested two days later, contained metals. The levels of metals in the feeds were intended to be approximately ten times the USP limits. The USP limit for iron is 2 ppm, while nickel and chromium fall under the general requirement for heavy metals which is 0.3 ppm (total heavy metals). The data indicates that the bed adequately removes all three metals however the chromium limit was reached after the second liter. A sample of the first 100 mls of the eighth liter showed no trace of any of the metals, demonstrating that the metals are irreversibly trapped, and metals removed from a short exposure to contaminated water will not be eluted in a later use.

The data from 12-18 were only taken on the last 100 ml of a metals challenge, to obtain a worst case data point. It is evident that some breakthrough is occuring at the end of the first liter with these feed concentrations.

The composition of 300 series stainless steels is essentially 71%

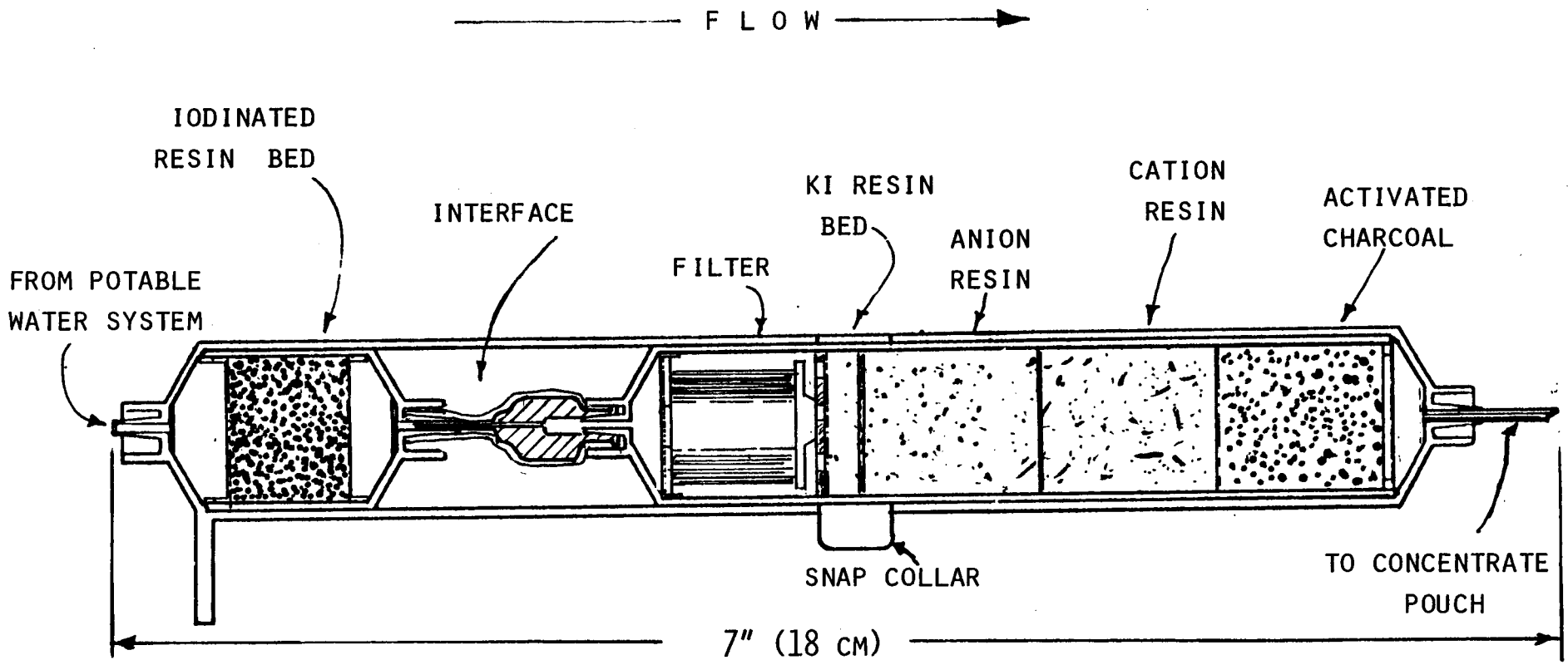


FIGURE 6-6.

PROTOTYPE WATER POLISHER

TABLE 6-4. CORROSION METALS DATA

Test Day		Liter No.	Feed Concentration, ppm Fe	Ni	Cr	Effluent Concentration ppm Fe	Ni	Cr
12-4	[Bed	1	0	0	0	-	-	-
12-4		2	0	0	0	-	-	-
12-4		3	15.3	3.3	1.8	<0.01	<0.05	0.08
12-4		4	0	0	0	-	-	-
12-4		5	0	0	0	-	-	-
12-5		6	0	0	0	-	-	-
12-7		7	16.8	3.2	1.2	0.8	<0.05	0.29
12-7	Same	8*	0	0	0	<0.01	<0.05	<0.05
12-18		1	0	0	0	-	-	-
		2	0	0	0	-	-	-
		3**	16.8	3.2	1.2	<0.01	0.2	0.11
2-5	[Fresh Bed	1	5.7	2.9	2.1	0.1	0.17	<0.05
		2	5.7	2.9	2.1	0.14	0.09	0.07
		3	5.7	2.9	2.1	0.3	<0.05	0.29
		4***	5.7	2.9	2.1	0.35	0.13	0.4
USP limits						2.0	0.3	0.3
Skylab Corrosion Data			0.08	<0.05	0.002			

* Data from first 100 ml

** Data from last 100 ml

*** Data from first 500 ml

iron, 11% nickel, and 18% chromium. The feed concentrations were adjusted to this ratio, maintaining the 10 times USP limit for nickel and chromium. Three successive liters were fed to a fresh polisher assembly on 2-5. This bed contains the iodine removing section, which reduced the size of the otherbeds slightly, however it demonstrates that the unit is effective for 3 liters of water with metals at these levels.

During the preparation of this report, some long sought after data from the Skylab program was located. The Skylab was the first known system in which iodinated water was to be stored in stainless steel tanks for an extended period of time. The highest iron level encountered after 1 month in 304 SS was 0.08 ppm, less than 0.05 ppm nickel in 321 SS after 4 months, and 0.002 ppm chromium in 321 SS after 4 months. The data show the metal challenge protocol to be many orders of magnitude more severe than is expected to be encountered.

6.3.2 Microbial Challenges

Table 6-5 summarizes the microbial challenges of assembled units. In all cases the source of bacteria was the natural population which exists in URC's deionized water system. Although the identity of organisms has not been established, it is known that the predominant species are pseudonomads. These organisms are conditioned to live in very low nutrient environment, and should be quite representative of those encountered as contaminants in a space craft's water system. Challenges were performed either as pure deionized water, or in conjunction with metals or in some cases pyrogen challenges. Challenges with enteroviruses were performed when convenient during a parallel program, NAS9-15854, in which the Microbial Check Valve resin was being challenged with enteroviruses.

The first two liters fed to the unit tested on 12-4 were pyrogen challenges in sterile water, the third liter was a metals challenge made from deionized water. Liters four and five, and liter six which was fed the next day were all deionized water containing large numbers of organisms. The aerobic plate counts of the effluents show that a few viable organisms were getting through. The values shown are from duplicate plates. As previously discussed it is assumed that these are spores which

TABLE 6-5. MICROBIAL CHALLENGE DATA

Test Day	Liter No.	APC*Feed	APC*Out	Remarks
12-4	1	0		
	2	0		
	3	6×10^5	2/2	Contained metals
	4	6×10^5	13/17	
	5	6×10^5	10/14	
12-5	6	6×10^5	8/11	
1-7	1	4×10^4	0/0	
2-5	1	3×10^3	1	Contained metals
	2	3×10^3	9	" " "
	3	3×10^3	5	" " "
	4**	3×10^3	2	" " "
2-21	1	3.1×10^5	0/0	Incorporates Filter
	2	3.1×10^5	44/0	" " "
	3	3.1×10^5	0/0	" " "
	4	3.1×10^5	0/0	" " "
	5	3.1×10^5	0/0	" " "
	6	3.1×10^5	0/0	" " "

* Aerobic Plate Count

** Data from first 500 ml

are not deactivated due to the short contact time with the iodine. The outlet plate counts from the test on 12-5 with the same bed shows that even if the spores do get past the iodine, they do not germinate overnight in the lower portions of the unit, and that a bed may be reused without contamination. The test on a new unit on 1-7 showed complete deactivation. The tests run on 2-5 was an extended metals challenge with a 4 liter batch of challenge solution. The plate counts including the feed showed some viable organisms getting through. The lower feed concentration of bacteria is probably due to the presence of the heavy metals during the time required to conduct the entire test. The unit tested on 2-21 contained the 0.3 micron filter. As previously mentioned, this filter was challenged alone with bacteria containing deionized water and proved to remove them all. This exhaustive test shows the ability of the filter containing purifier to completely remove bacteria from a large amount of contaminated water. The one positive plate from liter two is most likely a sampling error.

The unit used for the 1-7 bacteria challenge was challenged three days later with Reovirus. A liter containing a TCD50 (50 percent Tissue culture Infectious Dose) of 19,000 Reovirus/ml was passed through the cartridge. The effluent contained a TCD50 of less than 0.1, indicating instantaneous complete inactivation of this virus. A plate count also showed no bacteria in the effluent. A fresh cartridge was challenged with one liter of Type 1 Polio virus. The feed contained a TCD50 of 17,800. The effluent contained a TCD50 of 100. Disinfection was not complete. Polio virus is one of the most resistant viruses to chemical disinfection. Results with the microbial check valve show complete deactivation within 15 minutes after iodine contact. Other published data, Reference 7, show Polio to be very resistant to chlorine as well.

6.3.3 Pyrogens (See Appendix 1 for a short description of Pyrogens and their source)

At the beginning of this development program, the current edition of the USP was the 20th. This edition required that all injectables meet the Pyrogen Test <151> which involves injecting rabbits with the solutions in question and observing their temperatures. The 20th edition also included the Endotoxin Test

<85> which uses Limulus Amebocyte Lysate (LAL) to detect endotoxins (pyrogens). At that time it was recognized that the LAL test was more sensitive than the rabbit test, and it was used to evaluate the ability of the water purifier to remove pyrogens from the water stream. One Reference, (4), indicated that the LAL test was from 3 to 300 times more sensitive than the rabbit test, and the manufacturer of a LAL test kit claimed, "several times more sensitive than the average rabbit pyrogen test". It's guaranteed sensitivity was 0.25 ng/ml. Based on this information, the ion exchange resins were challenged with 1 liter of water containing 10 ng/ml of pure endotoxin, and when tested with the LAL kit showed negative response. Thus it was assumed that the water polisher could easily purify pyrogen contaminated water to a level that would pass the rabbit test. The USP is continuously revised, and supplement 4a to the 20th edition replaced the Pyrogen Test <151> with the Endotoxin Test <85> as the pyrogen requirement for Water for Injection. It is also included in the 21st edition. In addition, it specified a limit for endotoxins of 0.25 EU/ml. The endotoxin unit, EU, is defined as an endotoxin which has the same response as an FDA standard endotoxin. Another requirement that was established was that an acceptable endotoxin standard must have a minimum activity of 5 EU/ng.

If we assume that the endotoxin used in the previously described purifier challenge had an activity of 5 EU/ng, and the detection limit was 0.25 ng/ml, then the detection level was 0.25 ng/ml x 5 EU/ng = 1.25 EU/ml. This is five times the new level of 0.25 EU/ml.

An alternative source of LAL was found together with a source of Endotoxin standards with a certified EU activity. This LAL was found to give a reliable positive test of an endotoxin level of 0.125 EU/ml.

Challenges of the water purified were made with water containing 2.5 EU/ml (10 times USP requirement). Four purifiers were challenged, and none was able to produce an effluent with less than 0.25 EU/ml.

The conclusion is that the purifier is capable of producing water which will meet the requirements of USP 20, as was the original intent of the program, but the new limits are not obtainable with the original technology.

A different approach must be used to meet the new endotoxin limit. Hyperfiltration, References 5,6 has been used to physically remove pyrogens from water. The removal is based on physical filtration by a matrix with pores smaller than the endotoxin molecule. The above listed references both report complete removal of endotoxins with membranes with a molecular weight cutoff of 10,000. The small pore size of the membranes produce a very large pressure drop, requiring high surface areas for reasonable flow rates. The solution to this is the hollow fiber membrane module as shown in Figure 6-7. A large number of tubes made from the membrane material are mounted in a housing. Water containing endotoxins is forced through the inside of the tubes and passes through the membrane wall leaving the endotoxin molecules inside the tube.

A hollow fiber membrane module was purchased from Amicon (Model H1P10-20). The module was shipped containing a preservative of 0.2% sodium azide and glycerin. It was found to contain pyrogens as well. The manufacturer recommends that the unit not be repeatedly autoclaved since the pore size of the membrane increases each time it is autoclaved.

Three liters of water were passed through the module to remove the glycerin/azide. The specific conductance of the first water was 140 umho/cm, but was less than 5 after the 3 liters. A liter of pyrogen free water was then fed through the module followed by a liter containing 25 EU/ml of endotoxins (100 times the USP limit). The effluent from the 25 EU/ml water showed less than 0.1 EU/ml. In an effort to evaluate the effect of autoclaving, the module was autoclaved for 15 minutes and challenged with a liter containing 25 EU/ml. No pyrogens were detected in the effluent. The module was autoclaved two more times and challenged with 25 EU/ml water. No pyrogens were detected in either effluent. After the fourth autoclaving, the effluent showed an inconclusive positive test, estimated at 0.08 EU/ml. After the fifth autoclaving, the effluent showed a positive test, greater than 0.125 EU/ml. The above series of tests shows that the unit may be safely autoclaved at least once, and is a viable solution to the pyrogen removal problem. The module also provides another positive barrier to microbial contamination. It is also sold as a device which can be used to concentrate virus,

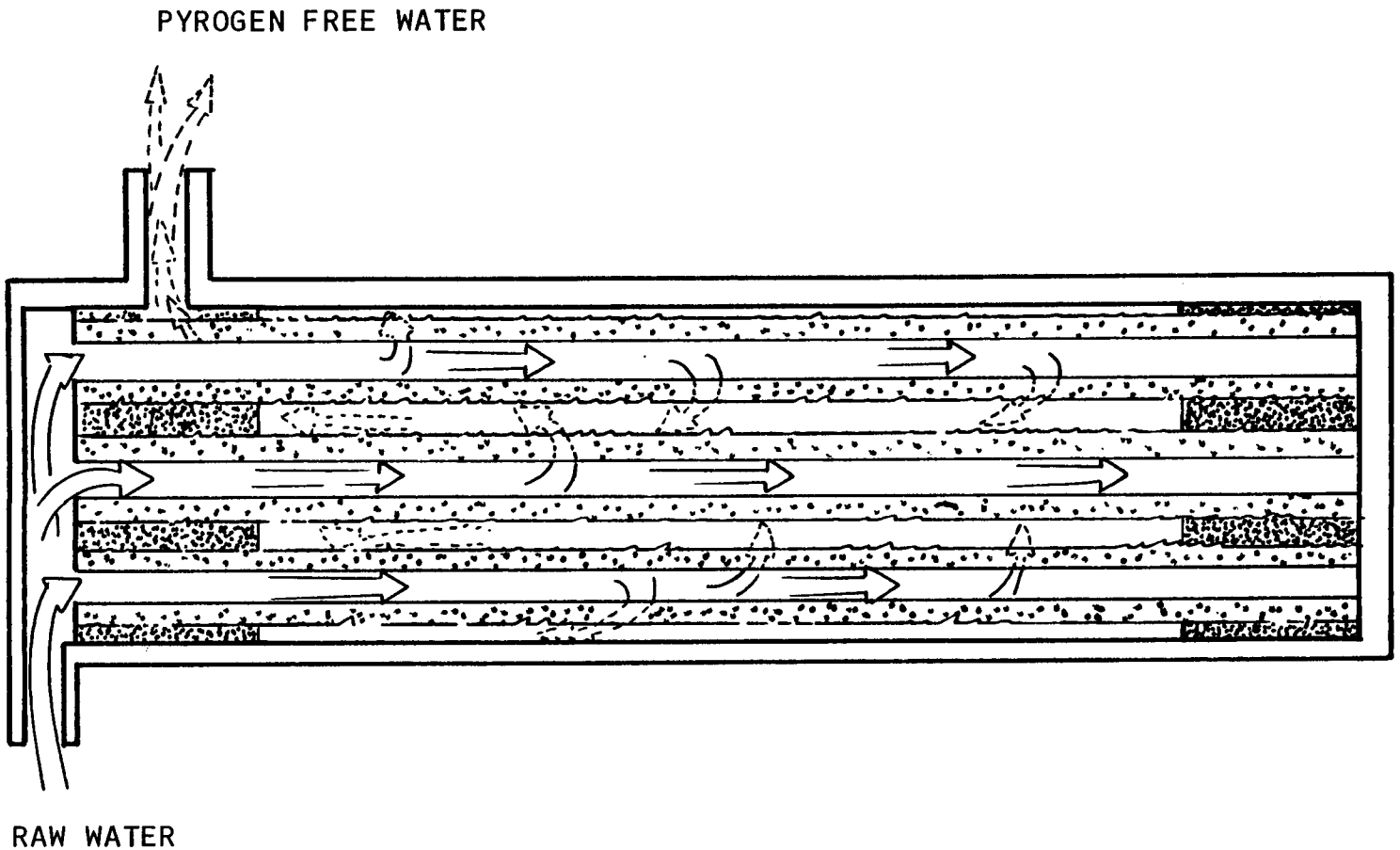


FIGURE 6-7.

HOLLOW FIBER MEMBRANE MODULE

although this has not been investigated.

A schematic of a water purifier which will meet all the requirements of USP 21 is shown in Figure 6-8. A hollow fiber module is attached to the original purifier such that the effluent from the cartridge is fed to the inner tubes of the hollow fiber module. The effluent from the module is then available for reconstituting concentrates as before. The entire assembly can be autoclaved as a unit after manufacture, thus guaranteeing sterility before use.

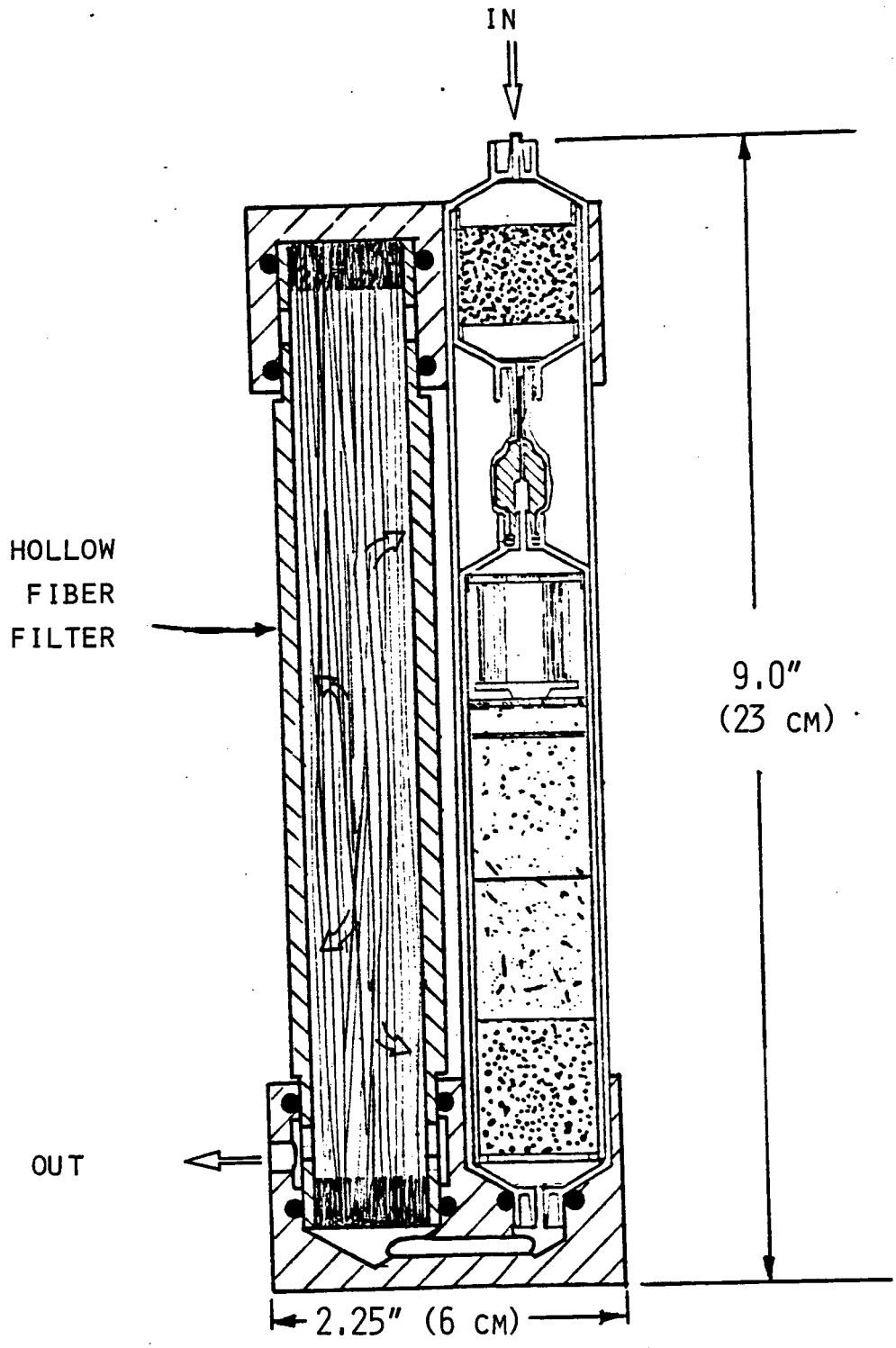


FIGURE 6-8.
ADVANCED WATER POLISHER

7.0 ADMINISTRATION DEVICES

The major challenge in the administration device is the development of a system that is capable of producing a steady, verifiable and controllable flow under conditions of micro quality. Two methods of expulson of the fluids were considered, mechanical and pneumatic.

The most obvious form of mechanical expulsion is a pump. A wide variety of variable speed positive displacement pumps are readily available. These devices are widely used in hospitals to ensure stable infusion especially in long term applications. This approach was not selected due to its high stored weight and volume, and more importantly its requirement for either a vehicle interface for power or battery charger, or the necessity of providing a supply of fresh batteries for each mission.

Another form of mechanical expulsion is a spring loaded bag squeezing device. An ideal device is one that uses a spring that has a constant force over a long distance of travel. This provides a constant delivery pressure and allows the use of very simple flow controllers. The IV-Stat, shown in Figure 7-1 is ideally suited for this application. It is designed to provide continuous and steady pressure throughout the expulsion of a one liter IV bag. The device is quite heavy, however, and very difficult to operate. The locking and release mechanism is unpredictable (and relies on gravity), and could be dangerous to the operator if accidentally released.

The ideal pneumatic system would provide a constant gas pressure. One approach would be to use vehicle nitrogen through a regulator, but it is not desireable to have any vehicle interfaces. Another approach would be an independent compressed source of gas and regulator, but that approach would be heavy, and reqùire extensive ground support before launch and extensive testing before flight certification. Chemical generation of CO2 through the reaction of sodium carbonate and acetic or citric acid could provide an easily stored and instantly activated pressure source, however flight certification would be expensive, and would not provide a constant pressure supply. Other chemical propellants such as flurocarbons and hydrocarbon mixtures which can be selected to provide a constant pressure would be useful,

Figure 7-1

I.V. STAT

without adjustment, until it is completely empty. It provides the same constant pressure whether it is full or partially infused. The spring produces a pressure of 100 mm Hg.

QUICK AND CONVENIENT APPLICATION

The I.V. STAT can easily be put in service within 10 seconds. Constant pressure operation eliminates need for extra staff to hold or hang bag overhead. The lightweight unit can be placed next to patient on stretcher or bed. Reduces monitoring work. Also handy for use by ambulatory patients.

I.V. STAT SPECIAL FEATURES

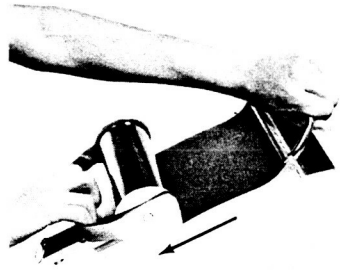
- Supplies a constant, safe pressure for blood, plasma or I.V. solutions.
- Maintains uniform flow rate, as originally set, throughout infusion.
- Eliminates monitoring during infusion since removing fluid from the container does not alter the output pressure.
- Operates without necessity of being elevated above the patient.
- Provides complete portability and eliminates need for I.V. stand, but may be hung from one when convenient. May be placed on any convenient surface near patient.
- Works with any standard I.V. tube set.
- Activates rapidly — in operation within 10 seconds.
- Sterilizes by steam autoclaving, gas or dry heat and is washable in hot water detergent.
- Simple to operate — instructions on unit.
- Non-breakable metal components for maintenance free, long life.
- Thoroughly engineered and attractively designed.
- Does not require electrical wiring or batteries.
- No "wind-up" or "pump up." No "plug-in."

SPECIFICATIONS

	MODEL 250	MODEL 250-X
Output Pressure	100 mm Hg.	100 mm Hg.
Capacity	600 cc	1,000 cc
Overall Dimensions:		
Height	9 cm (3.5")	9 cm (3.5")
Width	15 cm (6")	15 cm (6")
Length	39 cm (15.5")	46 cm (18")
Weight	1 Kg (2.2 lbs)	1.05 Kg (2.3 lbs)
Activating Force and Stroke:	9 Kg x 22 cm (20 lbs x 8.7")	9 Kg x 28 cm (20 lbs x 11.2")

Construction:
All metal, satin anodized aluminum and stainless steel with silicone rubber pad.

HERE'S HOW IT WORKS



1. **ACTIVATE** — Retract handle to activate and lock open.

2. **LOAD** — Drop I.V. bag on pad to load.

3. **RELEASE** — Retract handle to unlock and release to pressurize bag.

I.V. STAT CORPORATION
Box 961, La Jolla, California 92038
(714) 459-4577

Clinical reference:
BIOMATERIALS, MEDICAL DEVICES, AND ARTIFICIAL ORGANS
2(1), 41/46 (1974)

5-76

but would not be allowed in the spacecraft.

A hand pump is the lightest, most flexible, most reliable solution to the problem. A commercially available device was found that is designed to pressurize blood bags. The Fenwal Number 4R 4403 Pressure Infusor is ideally suited to the needs at hand. It consists of a cuff which will hold a 1 liter bag connected to a bladder. The bladder is inflated with a bulb, and the pressure indicated on a gage, see Figure 7-2. This system does not provide constant pressure, but will satisfactorily function with the flow system described below.

A flow regulator suitable for use with a constant pressure system is shown in Figure 7-3. A tapered flow path is formed between the flattened walls of a piece of plastic tubing. This can be used to form a variable size precalibrated orifice. By placing a clamp at calibrated positions along the tubing, it is compressed to the flats, but the orifice remains open. The tube is open above and below the clamp, thus producing a variable and predictable orifice. A similar device is shown in Figure 7-4. This device uses a tapering spiral groove, the orifice point of which can be adjusted by moving a rubber retainer to a precalibrated point. This device was shown to function reliably with the IV Stat pressurization device.

A flow controller that is relatively insensitive to pressure is shown in Figure 7-5. This device operates on a pressure feedback principle, and has been found to maintain a constant flow rate through a relatively wide range of upstream pressures. When combined with the Fenwall Pressure Infuser, the resulting system is a simple, reliable, and light infusion system which has no expendables and requires no interface with the vehicle. The Umpqua Research modified pressure gage on the infuser is marked with a red zone which defines the pressure range over which the regulator maintains constant flow. Flow characteristics are given in Table 7-1.

Conventional infusion systems use a drip chamber to verify flow and give some indication of flow rate. A gravity independent drip chamber was developed which will give the same information, see Figure 7-6. As liquid is fed to the tube contained in the Transparent chamber, a drop forms on the end. It continues to

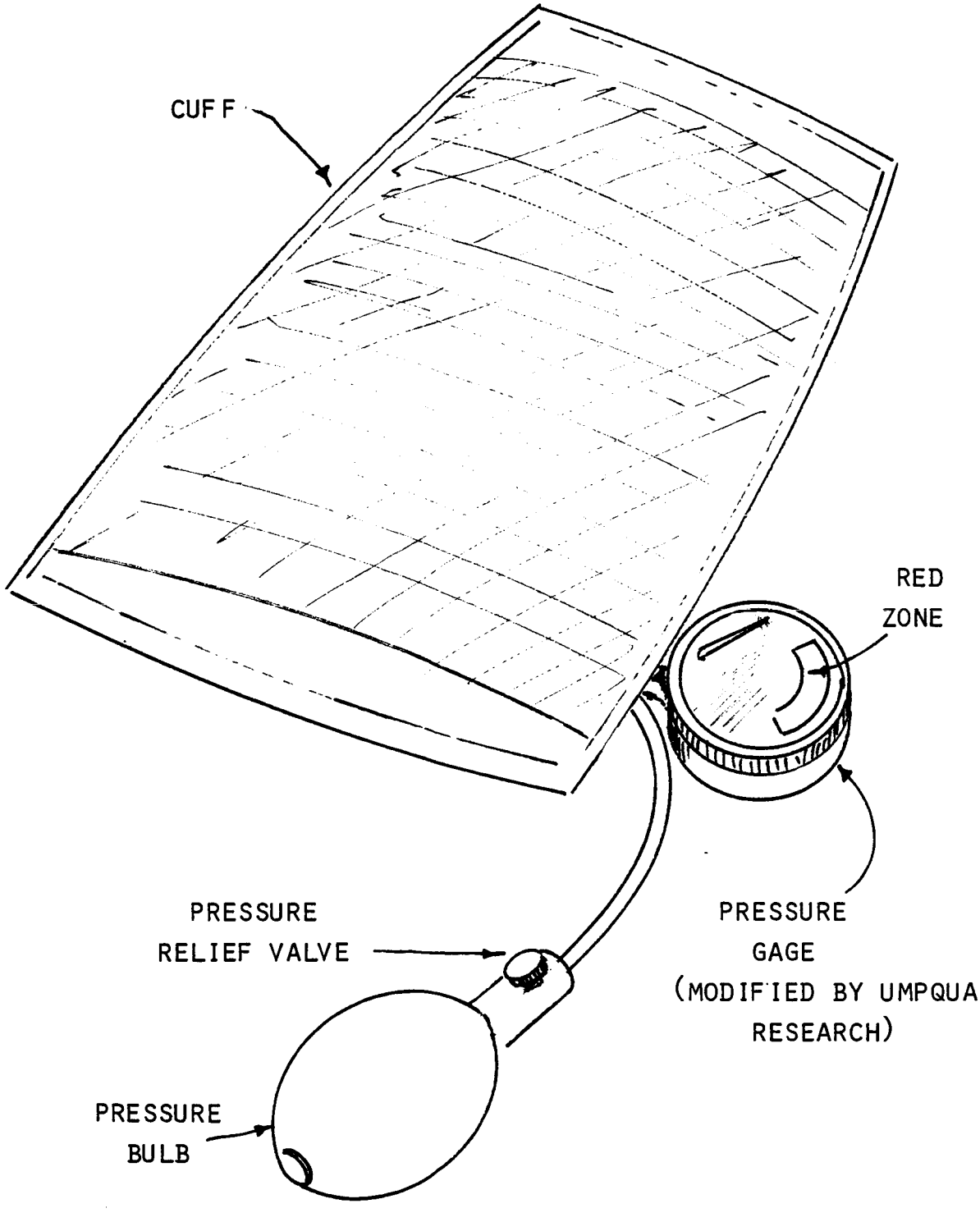


FIGURE 7-2.

FENWALL PRESSURE INFUSER

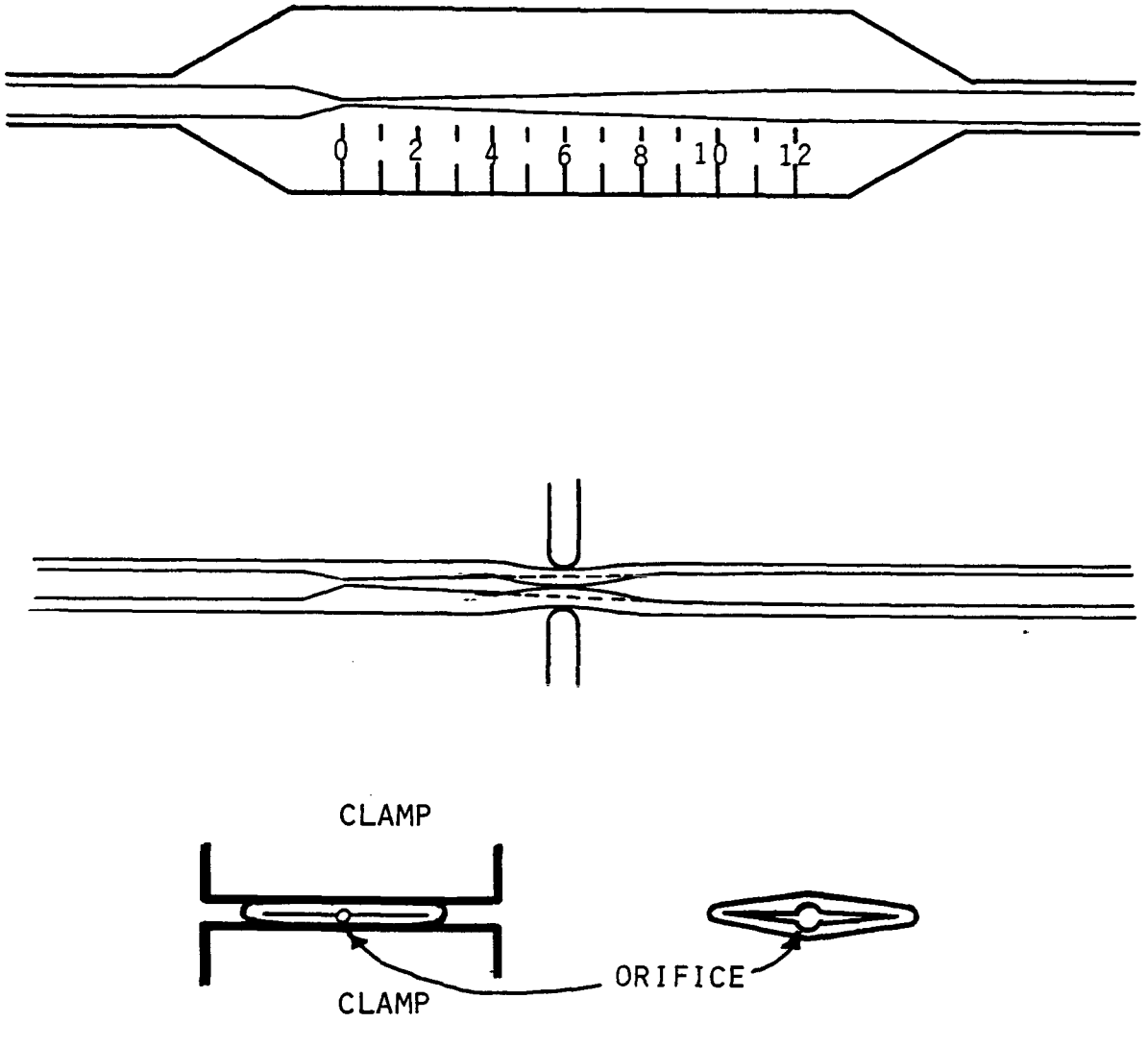


FIGURE 7-3.

VARIABLE ORIFICE DEVICE

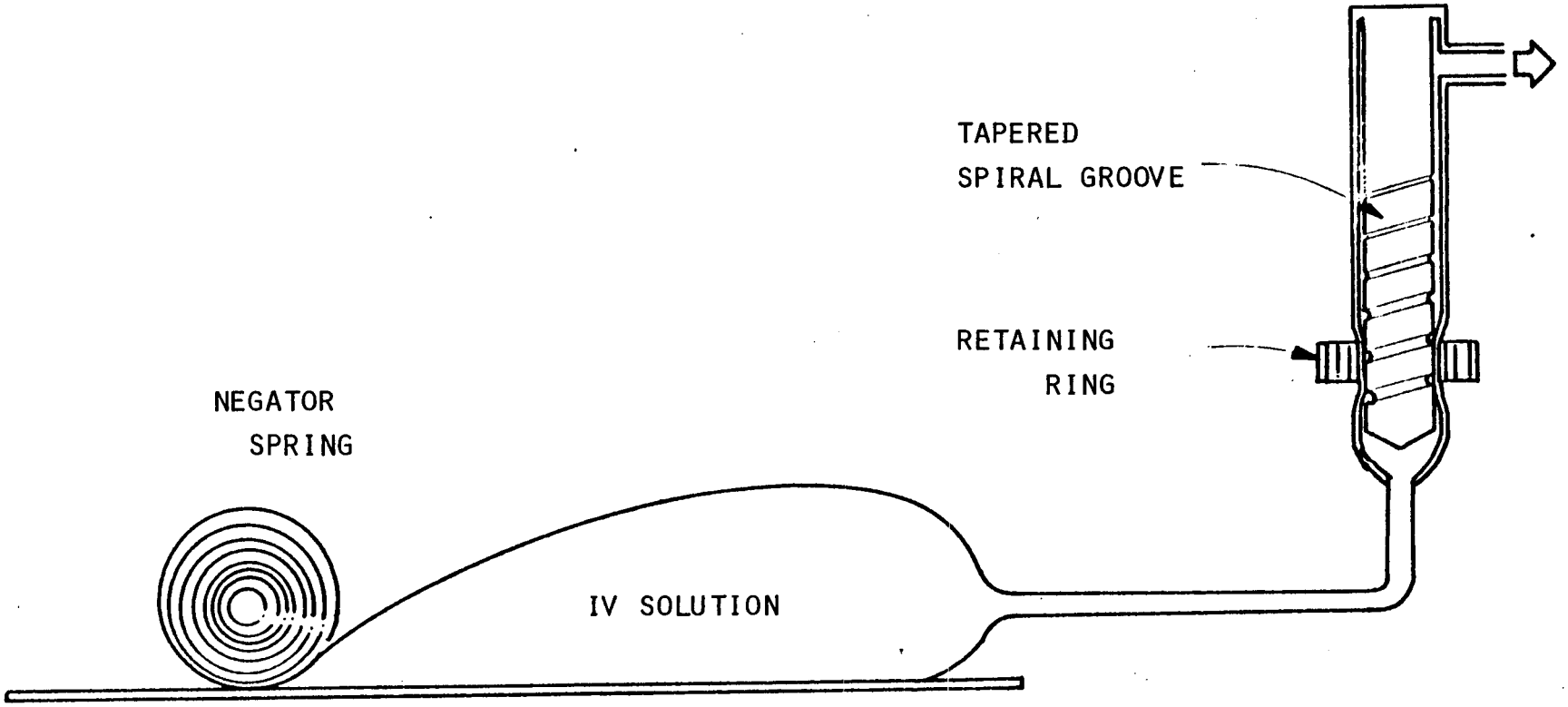


FIGURE 7-4.

SPIRAL GROOVE FLOW CONTROL

Figure 7-5

ENCES

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experiments and clinical experiences with JX administration sets for Parenteral Nutrition.

2)
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R. KAPADIA, J. E. J. BIGLIN, P. HALL, L. P. FIELDING. roved flow control in parenteral nutrition. British rnal of Intravenous Therapy, volume 2, March 1981.

IUM:
eer Medical, de Smet de Naeyerlaan 454, bus 2,
0 Brussels
2-4799964

NCE:
eer Medical, 135, Route Neuve, 69540 Irigny
78-511445

MANY:
eer Medical, Postfach 1261, 7840 Müllheim/Baden
7631-7803

AND:
eer Medical, P.O. Box 25, 1180 AA Amstelveen
20-5402911

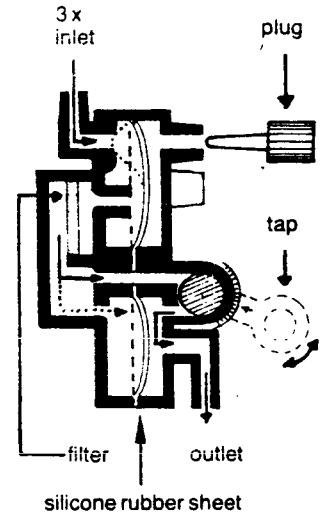
ED KINGDOM:
eer Medical, Cyclops Works, Victoria Crescent,
n-on-Trent, Staffordshire DE14 2QE
283-61313

ISOFLUX

The unique, constant-flow regulator in an i.v. set for single use

schematic diagram:

A Silicone rubber sheet separates the two halves of a thin, plastic sandwich. Internal, two circular membranes are formed which are completely tight.
A tap for the drip rate is located at the front of the regulator.
A filter (15 micron) is incorporated in the back of the regulator.



dimensions: 28 x 48 x 6 mm

note: membranes are completely tight

Flow-rate and stabilisation: The tap is a variable resistance. It serves for selecting the drip rate.
The resistance in the groove of the tap causes a difference in pressure, depending on the flow rate.
This is the 'signal' in a feed back system. It causes a displacement of the lower membrane, which is opposite the outlet orifice.
The displacement of the lower membrane causes a steeply increasing resistance at the outlet orifice.
This reduces the flow, the signal, and finally the displacement of the lower membrane. **The circle is closed.**

During the normal operation, the membrane is trapped in a position which is very close to the orifice. Any initial variation of the drip rate is followed by an immediate change in resistance, which counteracts the initial variation of the flow.

The infusion via **one or more inlets** can be selected. Normally, they are interconnected.
If a red indicator plug is inserted, the tip of the plug acts on the **dry side** of the upper membrane.
The membrane is pushed inwards and it obstructs the corresponding inlet.

When the liquid level drops below the container, the pressure behind the **upper membrane** decreases rapidly. The membrane returns to its natural position, thereby closing the filter inlet, and the infusion stops.

TABLE 7-1.

FLOW CHARACTERISTICS

DELIVERY NEEDLE GAGE	MAXIMUM FLOW, cc/min
25	10
21	40
20	42
16	67
14	67

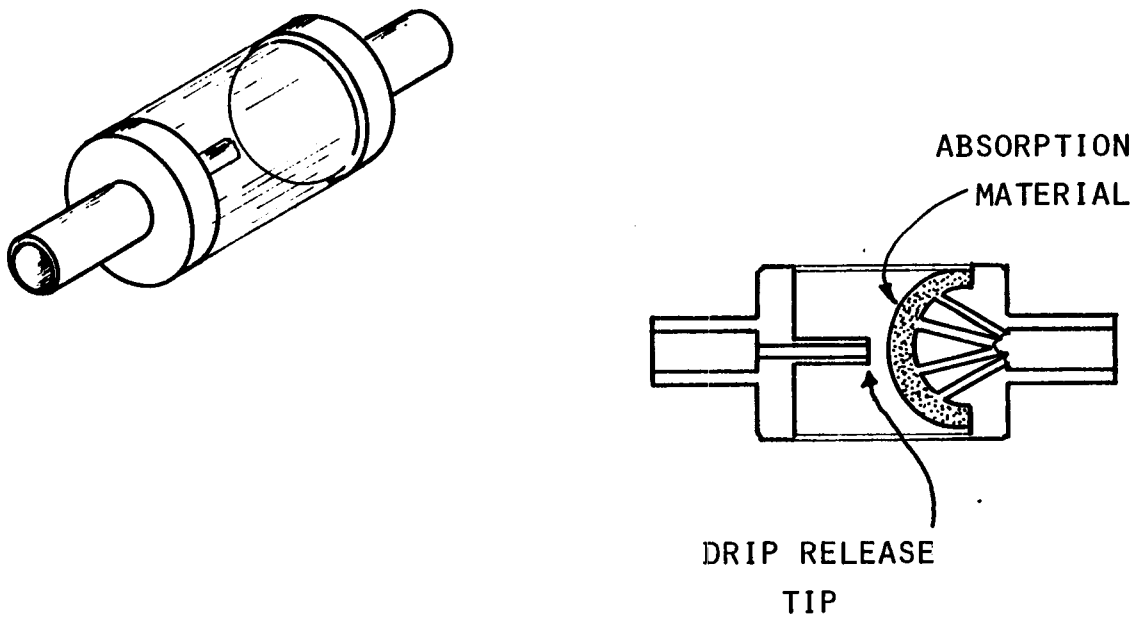


FIGURE 7-6.

GRAVITY INDEPENDENT DRIP CHAMBER

grow until it is large enough to touch the hydrophilic material, which wicks the liquid by capillary action into itself and conducts it to the exit tube. In micro gravity the drop could be quite large if left undisturbed, but the actual device was designed to operate in any orientation under normal gravity, and the spacing between the end of the tube and wick, and consequently the drop size, is limited. This gives a device which will operate in any orientation and is insensitive to being bumped or moved when operating.

The system used to quantitatively measure the flow rate is shown in Figure 7-7. A small bubble of air is introduced in to the flow path. This is accomplished with a syringe through a hydrophobic membrane filter which prevents the liquid from flowing out, eliminating the need for a check valve, and preventing bacteria from entering the system (maximum pore size 0.2 microns). The bubble is swept along the tube and as it passes through the calibrated section, an observation is made of the distance it travels in 30 seconds. The calibrations on the tube indicate the flow rate in cc per hour. Before the bubble reaches the patient it is removed in the gas separator. This separator consists of a 0.2 micron hydrophilic membrane which will not allow air (or bacteria) to pass through it once it is completely wet. The tapered upstream section contains a hydrophobic membrane vented to the outside. The shape of this chamber insures that any air is swept along the hydrophilic membrane until it reaches the hydrophobic, where it readily passes through. This separator has been tested in all orientations and flow rates and has performed flawlessly.

A schematic of the administration system is shown in Figure 7-8. The fill tube ending in a needle to penetrate a concentrate pouch is connected to an upper corner of the bag. The outlet from the bag, also at the top is directly connected to the flow regulator. The outlet from the regulator has a tee which contains the hydrophobic air injection filter. The other leg of the tee connects to the calibrated tube which terminates at the drip chamber. The outlet from the drip chamber goes to the air separator. The outlet at the separator goes to a medication port tee which is terminated with a short tube and a male luer lock. A small purge bag is installed at the end with a female luer lock. Another medication port is provided at an upper corner of the bag.

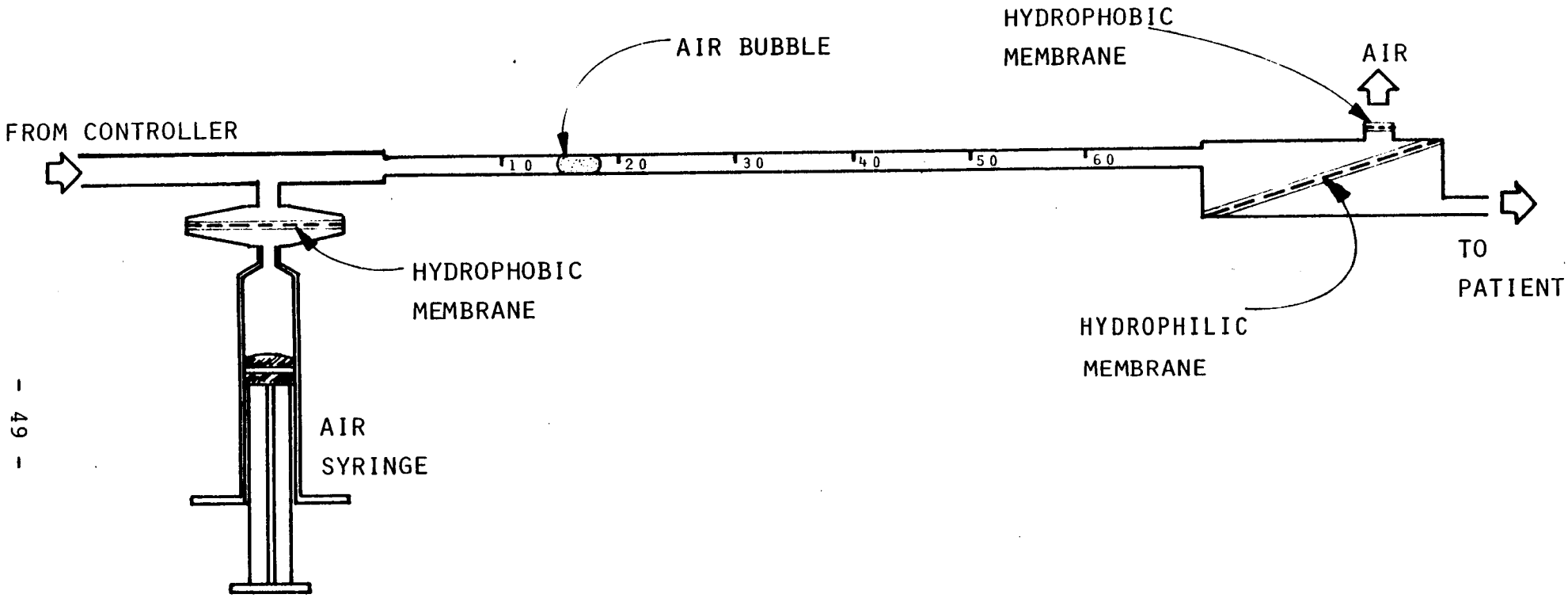


FIGURE 7-7.

FLOW MEASUREMENT SYSTEM

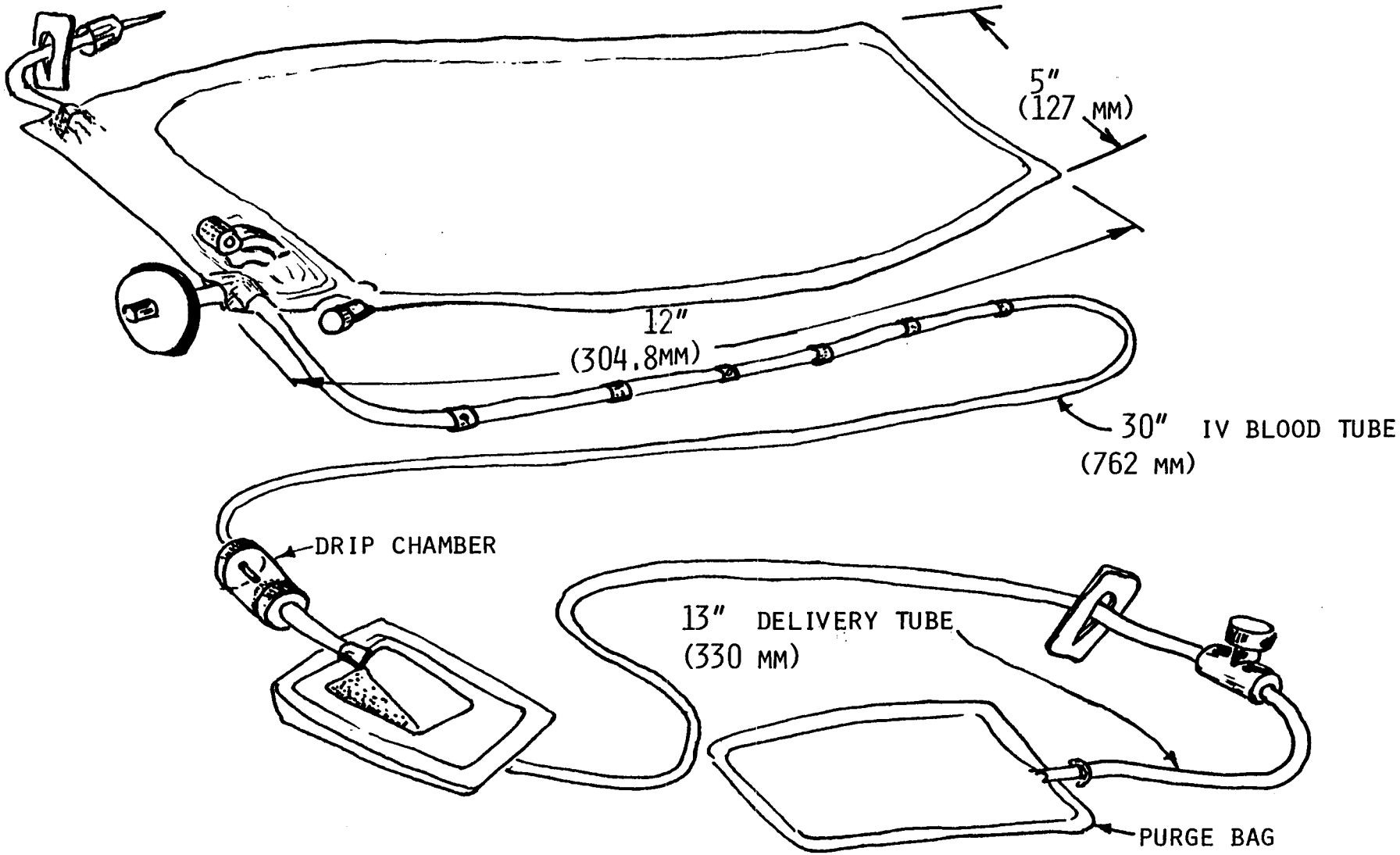


FIGURE 7-8.

ADMINISTRATIVE SYSTEM

8.0 SYSTEM DESCRIPTION AND OPERATION.

8.1 System Description

The system is composed of a fill hose, purification cartridge, concentrate pouch, and administration set. These items are shown in Figure 8-1. The only item that has not been described in detail is the fill hose. This hose is a length of tygon tubing with a female luer lock fitting in which an 18 gage needle is mounted. This needle is used to penetrate the membrane on the fill end of the purifier. The other end of the fill hose is to be fitted with an adapter compatible with the shuttle potable water dispenser. The fill hose is packaged separately in a non-sterile envelope. The water polishers and concentrate pouchs are indivdually packaged in foil envelopes. The administration sets are packaged in sterile transparent envelopes which contain purge bags for the water polisher, and the administration set. It also contains an illustrated instruction sheet, Figure 8-2. This envelope is also wrapped in a foil package. The pressure infuser is packaged in a separate foil envelope.

8.2 Operation

The first step in the use of the system is to remove the pressure infuser and an administration set from the foil envelopes. The administration set is then removed from the plastic envelope and the large purge bag set aside for later use. The IV bag is slipped under the mesh covering of the pressure cuff, and the flow regulator turned off by moving the handle to the bag surface and the clamp on the fill line opened. The pressure cuff is then inflated by closing the knurled knob on the squeeze bulb and pumping until positive pressure appears on the gage. This procedure removes all the air from the bag through the fill line. When positive pressure is observed, the clamp on the fill line is closed, and the pressure released in the cuff by unscrewing the knurled knob on the bulb.

Note: All fittings have been selected so that there is only one way to connect the components.

The water polisher is removed from it's foil envelope and activated by removing the snap ring from the center of its body.

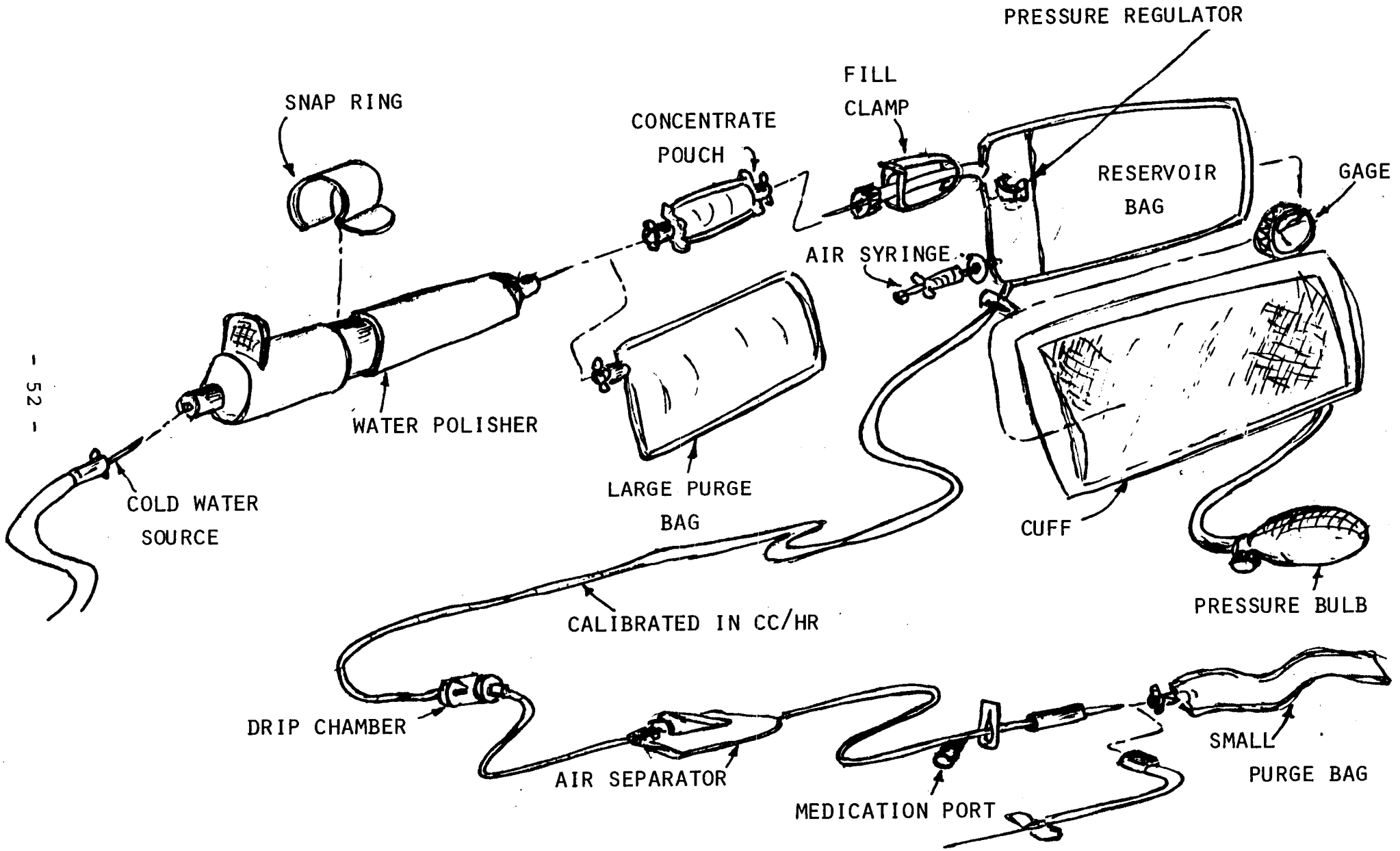
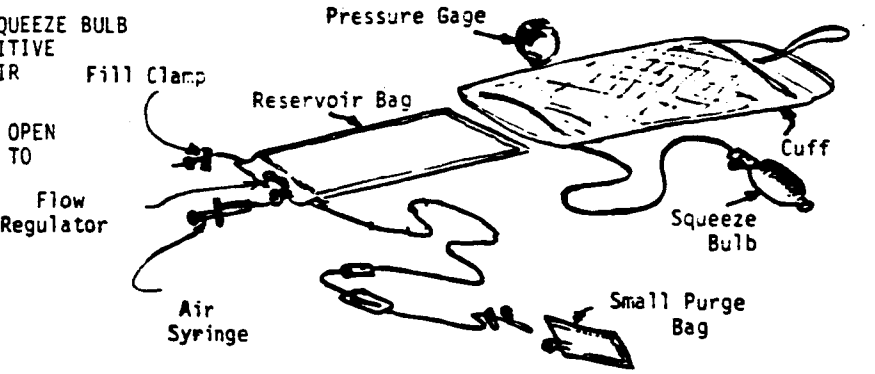
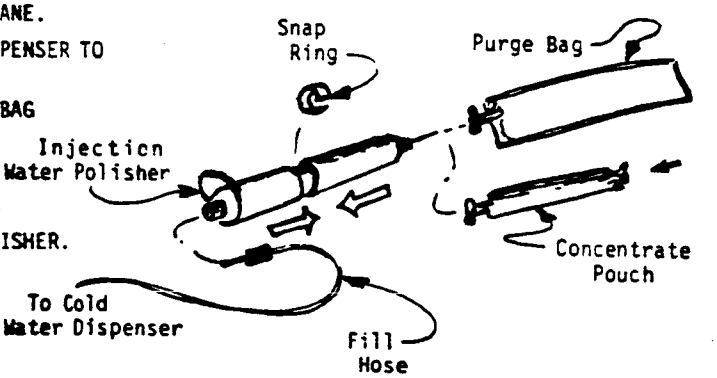


FIGURE 8-1.
PROTOTYPE SYSTEM

1. PLACE RESERVOIR BAG IN CUFF AND OPEN FILL CLAMP.
2. INFLATE CUFF USING SQUEEZE BULB UNTIL GAGE SHOWS POSITIVE PRESSURE (REMOVING AIR FROM RESERVOIR BAG).
3. CLOSE FILL CLAMP AND OPEN VENT ON SQUEEZE BULB TO DEFLATE CUFF.



4. REMOVE INJECTION WATER POLISHER FROM FOIL PACKET.
5. REMOVE SNAP RING FROM WATER POLISHER AND PUSH TOGETHER TO PUNCTURE INNER MEMBRANE.
6. CONNECT HOSE FROM COLD WATER DISPENSER TO INJECTION WATER POLISHER.
7. CONNECT WATER POLISHER TO PURGE BAG AND FLUSH POLISHER WITH APPROX. 6 OUNCES OF WATER. (TURN OFF DISPENSER WATER.)
8. DISCONNECT PURGE BAG AND CONNECT DESIRED CONCENTRATE POUCH TO POLISHER.
9. CONNECT RESERVOIR BAG TO CONCENTRATE POUCH, OPEN FILL CLAMP AND TURN ON DISPENSER WATER.



10. FILL RESERVOIR BAG THROUGH POLISHER AND CONCENTRATE POUCH WITH 32 OUNCES OF WATER. (TURN OFF DISPENSER WATER AND REMOVE POLISHER.)
11. KNEAD RESERVOIR BAG TO MIX INGREDIENTS AND REPLACE IN CUFF IF BAG WAS REMOVED.
12. INFLATE CUFF TO TOP OF RED ZONE ON GAGE.
13. OPEN FLOW REGULATOR ABOUT HALFWAY AND PURGE AIR IN LINES INTO SMALL PURGE BAG.
14. CLOSE FLOW REGULATOR AND REMOVE SMALL PURGE BAG.
15. CONNECT END OF TUBE TO NEEDLE AND INSERT IN PATIENT.
16. OPEN FLOW REGULATOR ABOUT ONE THIRD, AND MONITOR FLOW BY OBSERVING DISTANCE BUBBLE PRODUCED BY AIR SYRINGE MOVES IN 30 SECONDS. (CC PER HOUR)
17. ADJUST FLOW AS DESIRED. (OBSERVE IN-LINE DRIP CHAMBER TO VERIFY FLOW)
18. MAINTAIN PRESSURE CUFF WITHIN RED ZONE ON GAGE TO ENSURE CONSISTENT FLOW.
19. REFILL AIR SYRINGE BY REMOVING FROM FILTER.

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FIGURE 8-2.

OPERATING INSTRUCTIONS

If this snap ring is not securely tacked to both sections of the unit it should be discarded and another unit selected. When the snap ring is removed, the two ends are pushed together to puncture the inner membrane and activate the unit. The relative position of the two sections after activation is not siginificant.

The Fill Hose is removed from its packet and connected to the potable water dispenser. The needle end is inserted into the fill end of the polisher to puncture the membrane and then locked by turning clockwise. The large purge bag obtained from the administration set package is installed at the outlet end after removing the protection cap, inserting the needle in the bag fitting and locking by turning clockwise. This end of the purifier must remain sterile and all connections from this point on must be made using aseptic technique. Air is purged from the polisher by flowing approximately six ounces of water into the purge bag. The bag is then removed prior to reconstituting a solution.

A concentrate pouch is selected and removed from its foil envelope. One end is connected to the purifier by using the needle to puncture the membrane and locking by twisting clockwise. The IV bag in the Pressurization cuff is then connected to the other end of the concentrate pouch in the same manner. The fittings are arranged such that an IV bag cannot be filled without going through a concentrate pouch. The solution is then prepared by delivering 32 ounces of water from the potable water dispenser. After filling, the clamp is closed on the bag and it is disconnected from the concentrate pouch. The pouch is discarded and the cap replaced on the needle end of the polisher. It may be reused if care was taken not to touch the needle. The fill end of the polisher should be disconnected and capped, however this end need not be maintained sterile.

The IV solution is now ready for use. The pressure cuff is equipped with a simple harness which may be placed over the patients head and a strap which goes around the waist to maintain it in a convenient position on the chest. The bulb is then pumped until the pressure gage is reading at the top of the red zone. As long as the pressure is kept in the red zone, the flow regulator will maintain a constant preset flow rate. Once pressurized the flow regulator is opened until flow commences and

reaches the small purge bag at the end of the hose. The bag is then removed, a needle attached and installed in the patient. The regulator is then opened and flow observed in the drip chamber. Quantitative flow measurements are made by installing the small syringe in the filter on the top of the IV bag and injecting a small air bubble into the line. By observing the distance the bubble travels through the calibrated tube over 30 seconds, the numbers on the tube indicate the flow rate in cc/ hour.

Periodic observations of the drip chamber will verify that the system is operating correctly. The pressure gage should always read in the red zone to guarantee consistent flow rates. Medication may be injected directly into the IV bag for long term administration, or directly into the patient by closing the clamp immediately above the lower port and injecting.

If a second liter of solution is required, a fresh administration set must be prepared from a concentrate pouch, and connected to the installed needle.

LIST OF REFERENCES

1. The United States Pharmacopoeia, United States Pharmacopoeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852.
2. Standard Procedure for Idoinated Resin Preparation, SP102, Umpqua Research Company, Myrtle Creek, OR,11-28-78.
3. Standard Procedure for Iodinated Resin Certification, SP109, Umpqua Research Company, Myrtle Creek, OR, 11-2-78.
4. Wachtel, Ruth E. and Tsuji. Comparison of Limulus Amebocyte Lysates and Correlation with the United States Pharmacopoeial Pyrogen Test., Applied and Environmental Microbiology, June 1977, Vol. 33, No. 6, p. 1265-1269.
5. Sweander, K.J., Forte, and Nelson., Filtration Removal of Endotoxin (Pyrogens) in Solution in Different States of Aggregation., Applied and Environmental Microbiology, October 1977, Vol. 34, No. 4, P. 382-385.
6. Amicon Products for Separations Technology, Amicon Corporation, 182 Conant Street, Danvers, Mass 01923. Catalog 553.
7. Weber, Walter J., Physiochemical Processes for Water Quality Control, Wiley Interscience, New York, 1972.

APPENDIX I

U.S. Government

MEMORANDUM

Lyndon B. Johnson Space Center NASA

REFER TO: SD4/85-34	DATE FEB 14 1985	INITIATOR SD4/DLPierson:sj:2-12-85:4086	ENCL 3
TO: SD2/Chief, Medical Operations Branch		CC SB/Mike Reynolds	
FROM: SD4/Duane L. Pierson, Ph.D.		SIGNATURE Duane L. Pierson, Ph.D.	

SUBJ: Pyrogen (Endotoxin) Free Water For Injection - Space Station

A pyrogen is any substance that produces a febrile response when injected in man or other mammals. Endotoxins are high-molecular-weight complexes associated with the outer membrane of gram-negative bacteria (GNB), and are the most significant pyrogen for the pharmaceutical industry (Attachment 1). Although intimately associated with the bacterial cell membrane, these toxins are constantly shed into the environment of the bacterium, much like the daily shedding of superficial layers of human skin. When the bacterium undergoes autolysis, all endotoxin is released from the cell. Unpurified endotoxins contain lipid, carbohydrate, and protein, but highly purified endotoxins do not contain protein and, therefore, are referred to as lipopolysaccharides (LPS) to emphasize their chemical nature. Endotoxins are heat-stable compounds that can survive ordinary steam sterilization cycles; however, they are inactivated by extended dry heat cycles, alkaline conditions, acidic conditions, and polymyxin B, under certain conditions. Although it was first recognized that endotoxin causes fever, in more recent years endotoxin has been shown to have profound effects on a broad spectrum of biological activities.

Recent investigations have demonstrated that virtually all biological activity of endotoxin resides in the lipid portion of the molecule. Where as one portion of endotoxin is responsible in large part for the antigenic individuality of gram-negative bacteria and is thus responsible for thousands of serotypes, another portion, the core portion, is remarkably uniform in many rather diverse groups of gram-negative bacteria (GNB). Thus, endotoxin contributes to the antigenic homogenity and heterogenity of GNB.

Endotoxins are ubiquitous and like bacteria are found in air, water, and food. Due to their ubiquity, relative heat stability, and ability to cause profound physiological changes when administered parenterally, their detection and elimination is of paramount concern to the manufacturer of parenteral products.

The problems associated with utilizing Space Station condensate for rehydratable injectables are numerous and in some instances quite formidable. That is, if NASA intends to meet FDA regulations, a thorough study of the applicable requirements is essential. The FDA uses the standards for "Water for Injection" as outlined in "The

United States Pharmacopeia (Attachment 2). Water for injection is water purified by distillation or by reverse osmosis. Among other requirements the water must pass the Bacterial Endotoxin Test (Attachment 3); the water contains not more than 0.25 USP Endotoxin Unit per milliliter. The Limulus Amebocyte Lysate (LAL) is the official test for pyrogens (endotoxins) according to Dr. Terry Munson, FDA, FTS 87 443-7291. The "rabbit test" is no longer required but is acceptable. One may petition the FDA to use the rabbit test in lieu of the LAL.

I would recommend the use of the LAL test for our purposes. It is not feasible to conduct the "rabbit test" at JSC; it would require a contract with an outside laboratory. Finally, I am not particularly optimistic about meeting FDA standards for injectable water by following the current plan. This very important issue needs an immediate and comprehensive review while we are in the early planning phase.

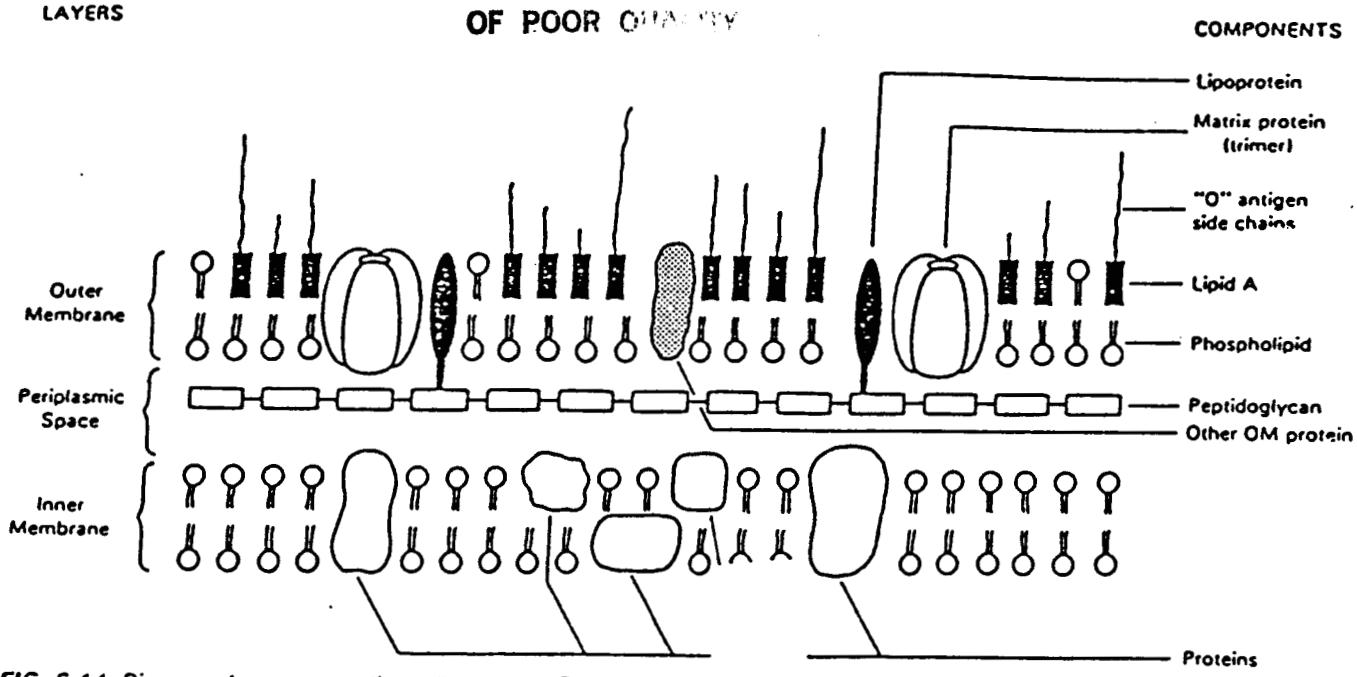

FIG. 6-14. Diagram of a gram-negative cell envelope. Components are listed on the right. The trimers of matrix protein of the Om are associated with lipoprotein and with LPS (of variable polysaccharide length), and lipoprotein is covalently bound to peptidoglycan. Diagram also illustrates some general properties of membranes (see Cytoplasmic Membrane). Phospholipid molecules are illustrated with a circle for the polar groups, and a line for each fatty acid acyl moiety.

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