Sterile Dosage Forms

Their Preparation and Clinical Application

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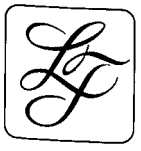

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Chapter 4

Large Scale Preparation

Whether sterile products are prepared on an industrial scale or made extemporaneously by the hospital pharmacist, the raw materials used, the procedures involved, the packaging, and the care taken determine whether the final products will have the required characteristics previously described. Quality must be built into the products from the beginning; it cannot be imparted after the products have been made. Although the extemporaneous preparation of one or two units of sterile products by the hospital pharmacist may appear to be simpler than the preparation of tens of thousands of units by a large group of personnel in an industrial setting, in essence there is a great similarity in factors that must be considered. The main differences are found only in the steps taken, owing to the large quantity of materials used and the number of personnel involved in industrial operations. In the following discussion, the preparation of a large number of units of sterile products is described. In Chapter 5, the conditions necessary in the extemporaneous preparation of a few units are described, and the similarities between the two operations are noted.

Environmental Control

If sterile products are to be free from particulate matter, they must be prepared, sterilized, and packaged in an environment free of particulate matter. In the overall processing, certain steps have more critical requirements than others. In Figure 4–1, note that critical steps include the preparation of the filling area, the procedures of washing and sterilizing the packaging components, and the preparation of the personnel who fill or subdivide the product into its final package.

The filling area, or room in which the solution is subdivided into its final package, is critical, because at this point, the solution is exposed to both the environment and the personnel involved. Thus, this area must be maintained as free as possible from particulate matter, such as dust, lint, and fibers. The air supplying these areas can be passed through high efficiency particulate air (HEPA) filters capable of removing particles of 0.3 μm or greater with an efficiency of 99.97%. Microbial contaminants present in air are usually found on dust and other particulate matter and are also hereby removed. Thus, the filtered air coming into this critical area is free of both particulate and microbial contamination. The air is supplied under positive pressure, i.e., the air in the critical area, having a higher pressure than air in the adjoining areas, flows outward when doors are opened. This prevents particulate contamination from sweeping into the critical filling area.

The critical filling area is constructed from materials that can easily be cleaned and disinfected. The walls can be stainless steel or regular wall material covered with an epoxy resin paint. Likewise, the work surfaces and floor are smooth and free of cracks and crevices. The entire facility may be irradiated with ultraviolet lamps

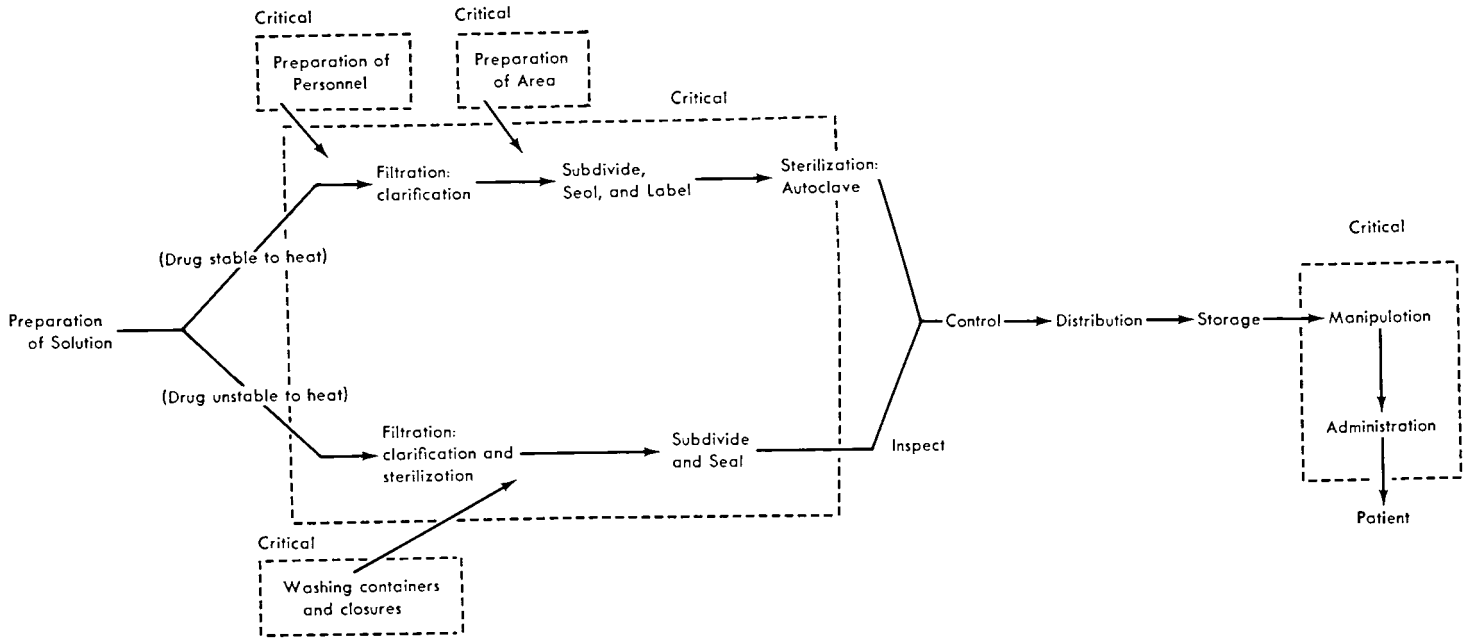

Figure 4–1. Flow sheet for the preparation of sterile products.

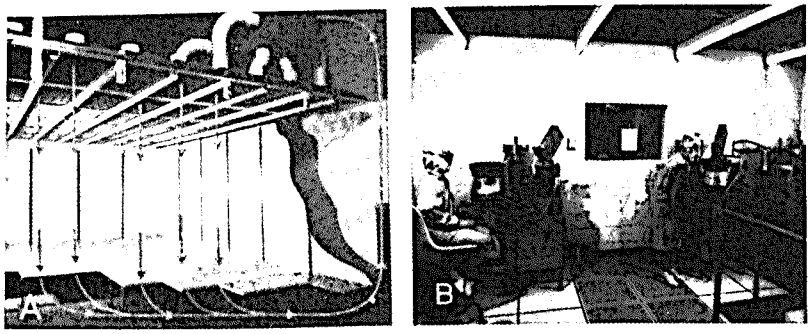

Figure 4–2. *A*, Vertical laminar air flow in production facility. Air turbulence is minimized and environmental control can be achieved. *B*, Prefiltered air is forced through a high efficiency particulate air (HEPA) filter and flows downward over filling equipment, continually bathing the area with clean air. (Courtesy of Wyeth Laboratories, Philadelphia, PA.)

to assure the disinfection of all surfaces exposed to the rays and to maintain sterility once personnel have entered the room. Personnel must be protected from ultraviolet irradiation while they are working in this area.

Laminar Air Control

From his work in the space technology program in the early 1960s, Dr. Willis Whitfield developed the concept of laminar air flow while trying to improve on conventional clean rooms.[1] He noticed that filtered air forced through wall or ceiling ducts creates swirls in the airstream that can trap particles and microorganisms in a room. His concept of laminar air flow is a bank of filtered air that moves through a work area in a parallel configuration and at sufficient speed to sweep contamination with it and create a minimum of turbulence (Fig. 4–2). Laminar flow is defined in federal regulations as "air flow in which the entire body of air within a confined space moves with uniform velocity along parallel lines with a minimum of eddies." The velocity of the air for effective laminar air flow is usually stated as 90 ± 20 feet per minute throughout the undisturbed room area.

The concept of laminar air flow has been applied in the parenteral drug industry in a number of ways. Some companies, when building new facilities, have constructed laminar air flow rooms for their critical operations. In these rooms, an entire wall consists of HEPA filters through which the air is forced. The most critical operations are placed closest to the laminar air flow wall, and the less critical are placed farther away. Laminar air flow units have been placed above filling machines, with the vertical laminar air flow washing all particulate material from the area where the open containers receive the solutions. Constructed in the form of hoods, laminar air flow equipment is used extensively for sterility testing and for aseptic manipulations in hospitals; the latter application is discussed in the next chapter.

By federal standards, clean rooms have been classified into three groups: Class 100, Class 10,000, and Class 100,000.[2] This classification is based on the particle count. The maximum allowance of particles permissible is 0.5 μm and larger or 5.0 μm and larger. The limits are expressed as follows:

Class 100—Particle count not to exceed a total of 100 particles per cubic foot of a size 0.5 μm and larger.

Class 10,000—Particle count not to exceed a total of 10,000 particles per cubic

foot of a size 0.5 μm and larger, or 65 particles per cubic foot of a size 5.0 μm and larger.

Class 100,000—Particle count not to exceed a total of 100,000 particles per cubic foot of a size 05 μm and larger, or 700 particles per cubic foot of a size 5.0 μm and larger.

All clean room facilities must be monitored to assure that they are receiving proper maintenance.[3,4] The rooms are monitored for both viable and other particulates to confirm adherence to established standards. The microbial content of the ambient air can be determined by settle plates (fallout plates) or mechanical air-sampling devices such as the Anderson sampler and the Reynier slit air sampler. Settle plates consist of open Petri dishes containing sterile nutrient agar, which are exposed to the air for a prescribed length of time. After the plates are incubated at a specified temperature and for a specified period of time, a count is made of the number of colonies on each plate. The disadvantages of the technique are that only the larger particles settle rapidly and that the volume of air tested is not known. These drawbacks are avoided when the mechanical air-sampling devices are used. Air is drawn through these instruments at a specified rate over a Petri dish containing sterile nutrient medium. After incubation, the counts can be expressed as the number of colonies per cubic foot of sampled air. Surface swabs subjected to the same procedures are used to determine microbial contamination of floors and flat surfaces.

Nonviable particulates are counted by electronic devices such as the Royco particle counter. Standards are established, and deviation from these standards for both viable particles and other particulates can be readily detected. Cleaning procedures and schedules are of utmost importance in maintaining the low levels of particulate contamination required for the satisfactory manufacture of sterile products.

Likewise, HEPA filters, whether they are located in hoods, walls, or ceiling, must be routinely checked for the presence of cracks and the maintenance of proper velocity (see "Environmental Control" in Chap. 5). Manufacturers of laminar flow equipment, as well as private laboratories, offer maintenance contracts for the continued safe operation of the equipment.

Personnel

The greatest source of particulate matter and possible microbial contamination in the preparation of sterile products, and the most difficult to monitor, is the personnel involved. When working in this critical area, personnel are garbed in jumpsuits, including hood and gloves. Their shoes are covered with disposable boots. The uniforms are most satisfactory when made from monofilament fabrics, such as Dacron or Ty-Vek, which do not shed lint or fibers. By nature, the personnel should be conscientious and reliable. The best standard operating procedures fail when they are not followed. Motivation of personnel is accomplished by giving them a thorough understanding of the importance of their tasks, and such motivation becomes critical to the operation. These personnel include not only the persons involved in the filling operation but also those given responsibility in other areas, such as maintenance. Failure to do their jobs adequately can result in the failure of the production lot, or worse, the passing through control of a lot of material that fails in one or more of the requirements for sterility, freedom from particulate matter, or freedom from pyrogens.

Packaging Components

Materials used for packaging and administering parenterals include components made of glass, rubber, stainless steel, and plastic. Regardless of its composition or form, the packaging material constitutes a likely source for stability problems, particulate matter, and pyrogens.[5] Since the initial use of glass for sterile products early in this century, much progress has been made in glass technology, and many problems rising from its use as a packaging material have been solved.

Glass

The degree of resistance of the product to glass varies with the type of product to be packaged in the container. The chemical attack rate of aqueous solutions on glass is high but varies with the pH and the constituents of the aqueous solution. On the other hand, solutions of a hydrophobic nature, such as oils, organic solvents, or dry sterile solids, show little chemical attack on the glass. Aqueous solutions containing heat-stable drugs frequently are terminally sterilized in the final glass container, and the heat of the sterilization process accelerates the chemical attack on the glass. The chemical attack by parenteral products on glass is due primarily to released alkali, which can cause deleterious effects on the parenteral solution following changes in pH, composition, color, and stability.

Glass is made by fusing amorphous silicon dioxide (sand) with metallic oxides at high temperatures.[6] The characteristics of the resultant glass depend on the nature and quantities of the alkaline earth and metal oxides. Glass prepared from silica, in combination with a relatively high amount of boron oxide and small amount of the alkaline earth oxides, is a borosilicate glass with high chemical stability, low coefficient of thermal expansion, and high resistance to heat shock. Glass containing no boron oxide and high quantities of the alkaline earth oxide is a "soft" glass having poor chemical and heat resistance. The latter glass is more easily worked (i.e., molded), and therefore is lower in cost. Amber glass used for products sensitive to light contains manganese oxide, which gives the glass its color.

For parenteral products, the compendia have classified glass based on its resistance to water attack and its release of alkali. The *U.S.P.* classification is as follows: Type I—highly resistant borosilicate glass; Type II—treated soda-lime glass; and Type III—soda-lime glass. Type II glass is essentially soda-lime glass that after being molded into the desired form is treated with acidic gas under controlled humidity and elevated temperatures to neutralize the alkali present on the surface of the glass; the alkali forms sodium sulfate, which is subsequently removed in washing the containers. The sterilization of glass packaging components is also influenced by the type of glass. Glass components molded from Type I glass may be sterilized before or after filling with solution, whereas Type II glass *should* be sterilized by dry heat prior to filling; Type III glass *must* be sterilized by dry heat before filling.

Initially, glass packaging components for new products are made from Type I glass to eliminate as many container problems as possible. As experience and stability data are collected for a product, the manufacturer may find it possible to use a less expensive glass, such as Type II or Type III. Products having a pH greater than 7.0, or one that may become alkaline before the expiration date, should not be packaged in Type II or Type III glass containers. Type II glass containers may be used for solutions having pH values less than 7.0. Both Types II and III are suitable for oils and sterile powders.

TABLE 4–1. Composition of Rubber Packaging Components

Component	Composition
Rubber	Natural, neoprene, or butyl
Vulcanizing agent	Sulfur
Accelerator	Guanidines, sulfide compounds
Activator	Zinc oxide, stearic acid
Fillers	Carbon black, kaolin, barium sulfate
Plasticizer	Dibutyl phthalate, stearic acid
Antioxidants	Aromatic amines

One source of precipitate observed in solutions packaged in glass results from the reaction of components of the solution with the alkali leached from the glass, or the leaching of metallic ions, which act as catalysts for other reactions. Solutions containing phosphates, citrates, or tartrates are subject to flake formation, owing to reaction with materials from the glass. Precipitates were observed when commercially prepared solutions of dextrose 5% in water are combined with solutions containing 40 mEq potassium chloride.[7] The precipitate was shown by analysis to be silica and alumina. It is highly probable that the silica was material leached from the glass container.

Another example of the leaching of solids from glass is the total solids requirements for Sterile Water for Injection. Whereas Water for Injection has a limit of 10 ppm, Sterile Water for Injection is permitted higher limits depending on container size: 40 ppm for containers up to and including 30-ml size, 30 ppm for containers 30- to 100-ml size, and 20 ppm for larger sizes. A greater limit is permitted for Sterile Water for Injection because of the leaching of material from the glass during sterilization. The requirement decreases as the volume increases, because the ratio of the volume to the wetted inner surfaces decreases.

Rubber

To provide closures for multiple-dose vials, intravenous fluid bottles, plugs for disposable syringes, and bulbs for ophthalmic pipettes, rubber is the material of choice. Its elasticity, ability to reseal after puncture, and adaptability to many shapes tend to make it unique. One must remember, however, that the composition of any single piece of rubber represents the combination of many ingredients to give it the characteristics required. To understand some of the problems arising from the use of rubber for packaging components, it is necessary to understand the variety of materials in the final composition of the package (Table 4–1).

The rubber compound is the basic ingredient, and this polymer is vulcanized in the presence of sulfur with heat. The vulcanization reduces plasticity and improves the resistance of the rubber to changes in temperature. To increase the rate of vulcanization, compounds such as guanidine derivatives are present as accelerators; these in turn are activated with materials such as zinc oxide and stearic acid. The tensile strength, hardness, and permeability are influenced by materials such as carbon black and barium sulfate; these materials are called fillers. Plasticizing agents and antioxidants are added to reduce the effect of oxygen on the rubber compound. The rubber and the additives are mixed, then subjected to heat and pressure during the molding process for the given rubber packaging components. Thus, the rubber piece that serves as a closure for a parenteral vial or a plug in a disposable syringe is a complex material.

Several problems originate from the rubber closure. It the closure is incompatible with the solution, the solution can become discolored, turbid, and degraded. Surface-active agents in the solution can extract chemicals from the closures; the extractives in turn can catalyze or react with ingredients in the solution, causing physical or chemical instability. There may be loss of the preservative or other added materials in the solution, owing to their absorption into the closure. For moisture-sensitive sterile solids, the closure may permit the transfer of moisture, causing the degradation of the drug. For every product, the compatibility of the rubbr closure with the sterile solution, suspension, or powder must be determined and the best closure selected. Once a given rubber closure has been selected for a parenteral product, the rubber manufacturer has the responsibility to maintain consistently all characteristics of the closure. To do this, tests such as ash, specific gravity, ultraviolet, and infrared spectrophotometric analysis of solvent extract are used.[8,9]

One of the most frequently encountered problems associated with rubber closures is that of coring.[10] Coring is the generation of rubber particles cut from the closures when needles or medical devices are inserted; the particles are known as "cores" (see "Techniques of Parenteral Administration" in Chap. 6). Cores are deposited in the solution or remain in the cannula. It is believed that the cores are cut from the lower surface of the closure when the heel of the needle enters the rubber. Although coring is primarily attributed to the design of the needle, the composition of the rubber used for the closure also can influence the degree of coring. The tendency of a rubber closure to core sometimes represents a compromise in composition to obtain a rubber closure with good stability.

Coring is observed at time of use of the product. Unduly large gauge needles increase the chance of coring. Some precautions may be taken to minimize it. A minimum gauge needle should be inserted with the bevel side up at an angle less than 45 degrees. After penetration of the closure, but before entrance into the container, the needle should be in the vertical position. Rubber closures on products that require refrigeration or freezing become more prone to coring. Delaying the reconstitution of the product until after the closure has warmed to room temperature alleviates the coring tendency. Similar care must be exercised when inserting plastic spikes into large volume intravenous fluids. The prepared or reconstituted product should be examined for cores. The presence of cores indicates that the product should be discarded, or in some instances, it may be necessary to remove the cores by filtration to salvage the product.

Plastic

The plastic used in preparing packaging material is also complex.[10] The primary constituent is the plastic polymer, usually polyethylene or polypropylene. The polymers differ in their characteristics. Polyethylene exhibits low water absorption, high resistance to most solvents, and low resistance to heat. For this reason, polyethylene items cannot be sterilized by autoclaving. On the other hand, polypropylene shows high resistance to most solvents and can be autoclaved. In addition to the plastic polymer, other chemicals are added to modify the physical characteristics of the material, e.g., plasticizers to improve flexibility; stabilizers to protect the plastic from light and discoloration; accelerators to increase the rate of polymerization of the resin; antioxidants to retard oxidation; fillers to modify physical properties such as strength; colorants; and lubricants in the case of molded pieces. The composition of the plastic and of the solution determines the degree of reactivity between the additives of the

plastic and the components of the solution. Substances can be leached from the plastic into the solution, and ingredients from the solution can be absorbed by the plastic. The plastic may be permeable to moisture, permitting loss of volume and modification of concentration of the solution. The degree to which these problems occur depends on whether the plastic device or container, such as a disposable plastic syringe, is for short-term, one-time use, or whether the device is to be used as a package in which a solution is to be stored over a long period of time.

Preparation of Packaging Components

Before being used to package sterile products, glass and rubber components are washed and sterilized. Improper handling of packaging materials in the preparation stage is one of the greatest sources of contamination by particulate matter. Glass containers received in cardboard and chipboard boxes contain dust generated by these packaging materials. This dust and other particulates are difficult to eliminate, and frequently, the empty glass containers are vacuumed prior to washing. Another approach to reducing troublesome particulates has been the use of "shrink wrapping." Groups of empty glass containers are wrapped tightly together with plastic film before shipment, thus eliminating the contact of the glass with the cardboard cartons. The glass containers are passed through a number of cycles in automatic washing equipment. The cycles vary depending on the type of equipment, but usually consist of rinsing the container alternately with cold water and then with steam. The expansion and contraction of the glass break down films and allow steam to penetrate and clean the surface. This "shock treatment" promotes the removal of all particulate material. The washing consists of the following steps: (1) outside, rinse with filtered water; (2) inside, rinse with steam; (3) outside, rinse with filtered water; (4) inside, rinse with steam; (5) outside, rinse with filtered water; (6) inside, rinse with steam; (7) inside, rinse with steam. Rough treatment of glassware in the washing equipment or during handling can generate glass particulate matter, which subsequently contaminates the filled containers. After washing, the glass containers are placed in stainless steel boxes and are rendered pyrogen-free and sterile by means of dry heat. The handling area for the wet containers is maintained under vertical laminar air flow to prevent the particulates in the environment from contaminating the clean wet containers (Fig. 4–3). After heating, the containers are moved to a sterile area and allowed to cool.

Washing procedures for glass containers have been made more effective for removing particulate matter by including a fluoride treatment in the wash cycle. The containers are washed with either dilute hydrofluoric acid or ammonium bifluoride solutions. The glasses are allowed to remain in contact with the fluoride solution for approximately 30 seconds before the solution is rinsed away. This treatment removes a thin surface layer of the glass with its adherent particulate matter. When this procedure is used, the safety of personnel must be a consideration.

As a method of sterilization, dry heat is not as efficient as moist heat, and therefore higher temperatures and longer exposure times are required. Dry heat sterilization is effective for oxidizing, or "burning up," and sterilizing chemicals and oils, provided temperatures below their decomposition temperatures are used. Many variables must be considered in using dry heat sterilization, including size of the oven, size of the load, arrangement of the load, and nature of the material being sterilized. Ovens usually have circulating forced-air heat. Glass containers are usually heated at 180°

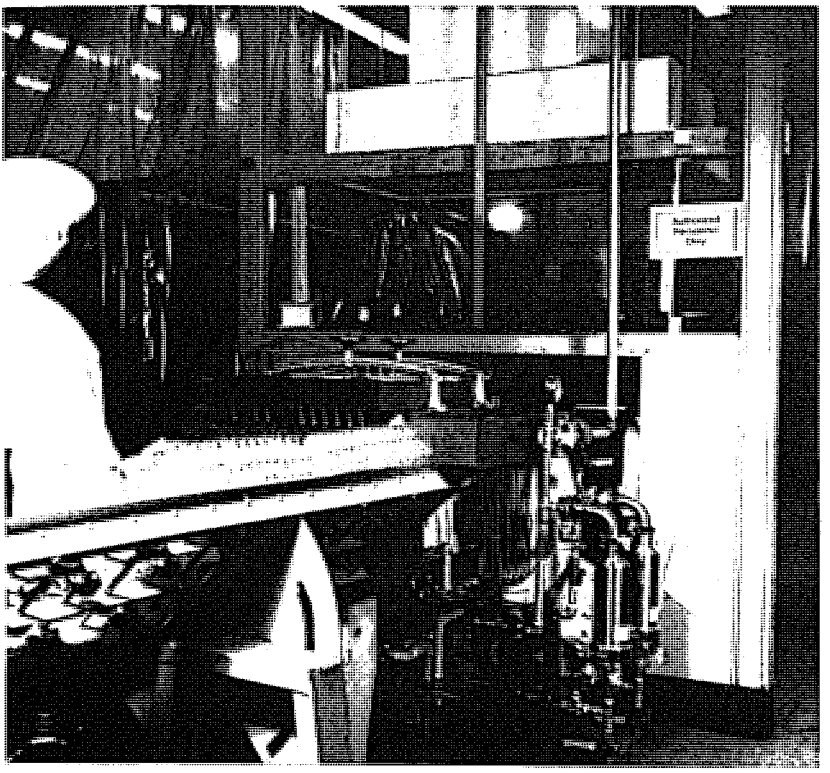

Figure 4–3. Cozzoli vial washer equipped with filters (arrow) for the water used for the two final rinses. The washed vials pass from the machine into a laminar air flow area. (Courtesy of Pall Trinity Micro Corporation, Cortland, NY.)

C or higher for 4 hours. This period would be in addition to the time necessary for the contents to reach 180° C and would vary considerably with the factors mentioned previously.

In preparing rubber components such as closures and plugs, the objective is to eliminate surface dirt, rubber particles, and water-soluble extractives, and to render the closures sterile. The danger is that, if they are handled roughly, particles will be generated by the rubbing surfaces of the rubber pieces; this can be a source of particulate matter found later in the filled container. Methods of preparation vary in the industry, but usually they consist of gently agitating the closures in a mild detergent, thoroughly rinsing the detergent away, autoclaving the closures immersed in Water for Injection several times, autoclaving the wet closures in a suitable sealed package, and drying at low heat. Autoclaving involves the use of moist heat under pressure. Autoclaving the closures in Water for Injection allows for the extraction of the water-soluble constituents before the closure is placed on a filled container and autoclaved. If this step were not performed, any water-soluble extractives present would pass into the parenteral solution.

Plastic containers are usually washed with filtered air to remove particulate material, then are suitably wrapped and sterilized with ethylene oxide. One of the great advantages of ethylene oxide sterilization of plastics is that the gas, owing to its ability to diffuse and penetrate, sterilizes the plastic materials after they have been assem-

bled and placed in their final packaged form. Chemically, ethylene oxide is a cyclic ether, a liquid to 10° C; above this temperature, it is a gas. It is miscible with water and common organic solvents. On the skin, it acts as a vesicant, and on inhalation, it has the toxicity of ammonia gas. It forms an explosive mixture with air and therefore is usually used in combination with carbon dioxide (10% ethylene oxide and 90% carbon dioxide) or fluorinated hydrocarbons (12% ethylene oxide and 88% fluorinated hydrocarbons). For some industrial applications, 100% ethylene oxide is used.

As in dry heat sterilization, many variables have to be considered when using ethylene oxide as a sterilant. The material to be sterilized is wrapped and placed in a chamber, which is subsequently heated to 130° F to increase the effectiveness of the ethylene oxide. The relative humidity of the chamber and the moisture content of the material are important factors in determining the efficacy of the method. Under ideal conditions, a relative humidity of 30 to 50% is desirable. Sufficient ethylene oxide is introduced into the evacuated chamber to reach a concentration of 450 mg per liter. An exposure time of 4 hours or longer is used, depending on the material, type of packaging, and size of the chamber. After the sterilization cycle is completed, the material is placed in quarantine for five days to two weeks to allow the residual ethylene oxide to vaporize. The time required for the residual amount of ethylene oxide to dissipate depends on the nature of the material, the method of packaging, and the conditions under which the material was sterilized.[11]

Another concern in the use of ethylene oxide is the presence of reaction products; ethylene oxide can react with water to form ethylene glycol, with chloride ion to form 2-chloroethanol, and with sulfhydryl groups to form 2-mercaptoethanol. When present in sufficient concentration on the sterilized item, these reaction products can cause untoward and toxic reactions. As a sterilization process, ethylene oxide must be adapted to the material and conditions involved. Recommendations can be considered only in general terms.

Preparation of Product

Equipment used for the preparation of sterile products should be clean, sterile, and free of pyrogens. If the size of the mixing containers precludes the elimination of pyrogens with dry heat, they should be thoroughly rinsed with Water for Injection prior to use. The purest chemical grades of the added substances should be selected. Following its formulation in a clean but not necessarily sterile area, the solution is ready to be taken into the sterile filling areas. In some manufacturing facilities, the mixing tanks are taken into the filling areas; in other facilities, the solution is pumped through the lines installed through the walls. Since the solution is not sterile at this point, it should be packaged and sterilized within 24 hours. If this is not possible, the bulk solution must be sterilized and stored as a sterile solution.

Clarification and Sterilization

Subsequent handling depends on whether the drug in solution is heat stable or heat labile. Heat-stable solutions are clarified (passed through a suitable filtration medium to remove particulate matter), subdivided into the final containers, sealed, and subjected to terminal sterilization by autoclaving (Figs. 4–4 and 4–5). Heat-labile solutions are passed through a suitable filtration medium for both clarification and sterilization, and then subdivided into the final sterile containers and sealed (see Fig. 4–1).

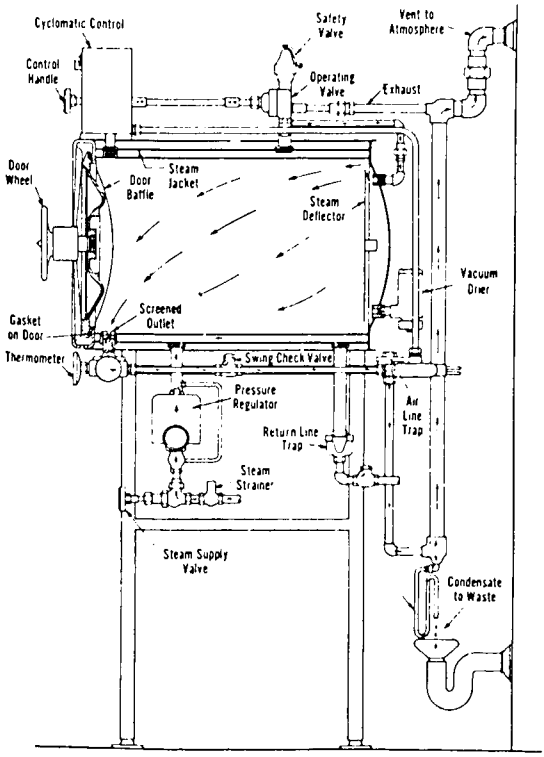

Figure 4–4. Schematic drawing of parts of an autoclave. (Courtesy of American Sterilizer Company, Erie, PA.)

In general, filtration media can be divided into two broad groups, depth filters and screen filters. Depth filters have been made from asbestos, fritted glass, and unglazed porcelain. They trap particles in tortuous channels, thereby clarifying the solution. All the media are available in a large number of pore sizes, the finest being suitable for removing microorganisms with subsequent sterilization of the solution. These media represent an older group of filters. As a group, they have a number of disadvantages and have been replaced by the screen-type filters for clarification and sterilization of parenteral solutions.

Screen or membrane filters are made from cellulose esters, microfilaments, polycarbonate, synthetic polymers, silver, or stainless steel in the form of films 1 to 200 μm thick. The films have a meshwork of millions of microcapillary pores of uniform size. Membrane filters are available in a number of pore sizes, ranging from 8 to 0.22 μm. Membranes having pore sizes 0.45 μm and smaller are considered to be sterilizing filters, i.e., capable of removing microorganisms as well as other particulate material. Since the pore volume of a membrane filter represents approximately 70 to 85% of the total filter volume, relatively high flow rates are obtained compared to those obtained with the depth filters. Membranes are used either as single sheets of varying diameters supported within stainless steel holders or as fluted columns packaged within plastic cartridges.

In addition to the main clarifying and/or sterilizing filtration steps, filters may be placed at other sites in the filling line. The sterile, clarified solution may be filtered

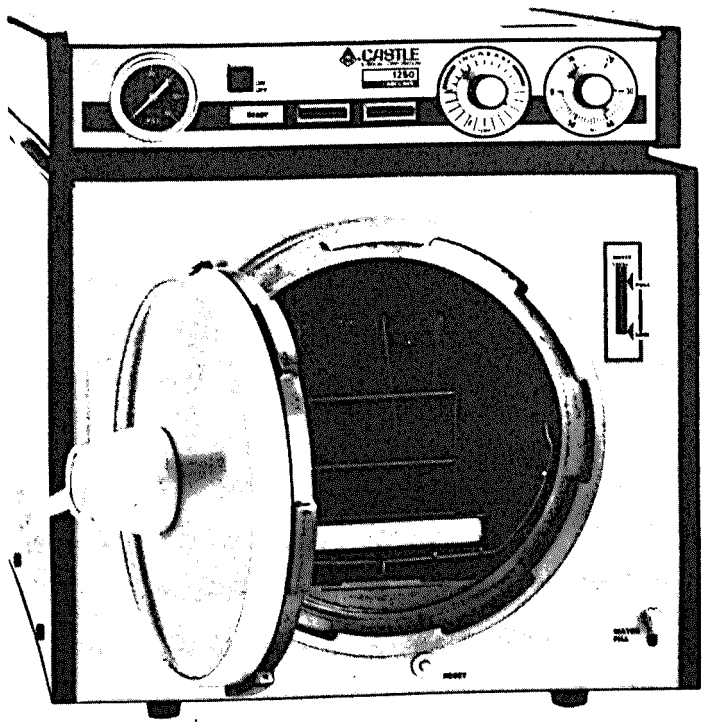

Figure 4–5. Tabletop autoclave designed to sterilize heat and moisture-stable materials. (Courtesy of Castle Company, Rochester, NY.)

again as it leaves the bulk tank or immediately before it passes through the filling needle into the final container. Clarifying filters are placed on line after the main clarifying and/or sterilizing filtration to remove particulate matter generated by the filling lines and the equipment regulating the filling volume.

Vertical laminar air flow units are frequently placed directly above the filling machine to prevent particulate matter in the environment from falling into the open container while it is being filled. An excess volume of solution is placed in all parenteral containers so that the labeled volume of solution can be withdrawn from the container; a 10% excess is used for a 1 ml container and 2% for a 100-ml container. The *U.S.P.* provides a guide listing the recommended excess volume for a container of a given size. Slightly larger allowances are made for viscous solutions. Checking for proper volume fill is an in-process control as well as a control for the finished package.

When the solution is subdivided into glass vials or bottles the containers are sealed with rubber closures and aluminum caps. The aluminum caps crimped onto the containers over the rubber closures hold the closures securely and protect the surface of the closure prior to use. The center tab or perforated center can be removed and the exposed area of the closure disinfected prior to injecting the needle to withdraw the solution. To close ampules, the stems are sealed by fusion of the glass, either by tip-sealing or by pull-sealing. In tip-sealing, the ampule is rotated while the tip of its stem is held in a hot flame, usually obtained by burning a mixture of natural gas and oxygen. The tip closes by fusion of the glass, forming a "bead." In pull-

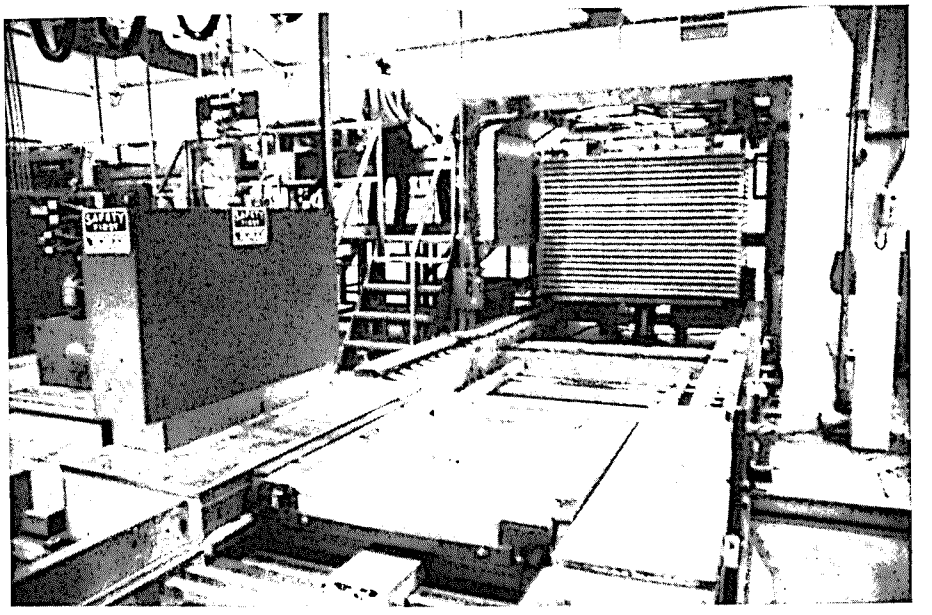

Figure 4–6. Sterilization of LVP bag equipment. (Courtesy of Abbott Laboratories, North Chicago, IL.)

sealing, the ampule is rotated in a hot flame directed at a point midway down its stem. When the glass softens, the top is pulled off and the glass fuses at the breaking point. The pull-sealing method results in fewer leaking ampules and is preferred in large scale operations where it is an automatic process.

When the aqueous parenteral product is heat stable, the sealed final container can be sterilized by autoclaving. This type of processing is known as terminal sterilization, sterilization of the aqueous solution after it has been packaged. The sterilization of LVP bag equipment by autoclaving is shown in Figure 4–6.

Autoclaving is the most widely used and most reliable sterilization method available. Steam normally has a temperature of 100° C, but its heat content can be increased by placing the steam under pressure. At sea level and under 15 pounds of pressure, the temperature of steam rises to 121° C. Pressure plays no role in the sterilization process other than to increase the temperature of steam. When the steam contacts a cooler object, it imparts its heat to the object until the latter reaches 121° C. The mechanism of action of steam is the coagulation of protein, which thus disrupts the vital processes of the organism. Once the entire object or the total contents of a container reach 121° C, sterilization requires only 10 minutes. The time required for the autoclave and the contents to reach the sterilization temperature is referred to as the "lag time." The lag time is subject to a number of variables, and these variables in turn determine the length of the sterilization cycle.

Variables that must be considered in determining the lag time include the size of the autoclave, the nature of the material in the load, and the manner in which the material is arranged in the autoclave. The larger the autoclave, the longer the time required to heat it to 121° C. The nature of the material, e.g., whether cloth or metal, influences the rate at which heat penetrates the load. Consider two ampules, one 5 ml and the other 50 ml, both containing Water for Injection. The time required

for the contents of the 50-ml ampule to reach 121° C will be longer than that for the 5-ml ampule. Once the contents of the two ampules reach 121° C, the sterilization time will be the same. Loading the autoclave chamber is important, inasmuch as it determines how easily steam will have access to the load. For example, tightly packed bed linen requires a long sterilization cycle in an autoclave because of the time required for the steam to penetrate to the center of the material.

Because of the importance of knowing when conditions of sterilization have been achieved, it is common practice to include sterilization indicators in the load. A number of types of sterilization indicators are available. They may indicate by either physical or chemical changes the temperatures attained, or they may be biological indicators based on the ability of the available heat to destroy heat-resistant bacterial spores. Regardless of type, it is important that indicators be distributed throughout the load to demonstrate that proper heating conditions have been reached.

The simplest sterilization indicators consist of chemicals that undergo change in color when subjected to temperatures of 121° C. These chemicals may be present on tape used to wrap packages for the autoclave, or they may be impregnated on cardboard and placed strategically throughout the load. Chemicals melting at 121° C and contained in glass capsules can be used. The change of the material from a crystalline form to a melted form indicates that the sterilization temperature has been reached.

The most reliable and precise sterilization indicators are thermocouples (electrical thermometers) inserted in various parts of the autoclave load. The temperature at each site is recorded continuously on a time chart located outside the autoclave. The time chart provides a permanent record of the conditions under which the autoclave load was sterilized.

Currently, the use of biological indicators is being recommended. Biological indicators are spores of heat-resistant organisms, such as *Bacillus stearothermophilus*, held in suspension in ampules or impregnated on paper. The ampules or spore strips are placed strategically throughout the load, and following sterilization, the indicators are placed in a sterile nutrient medium and incubated. If conditions of sterilization have been reached, the spores will not grow. When growth occurs, it is an indication that conditions of sterilization were not attained. Sterilization indicators are an important aspect of control. Their proper use and interpretation help to prevent the release of nonsterile products. Biological indicators are available not only for steam sterilization, but also for dry heat and ethylene oxide sterilization procedures.

Control

When tens of thousands of units are prepared on an industrial scale, control measures appear to be more complex and greater in scope than those exercised by the hospital pharmacist who prepares one or two units extemporaneously. In both instances, however, control measures are taken to assure that each unit will provide at time of use a sterile preparation of the labeled drug in the potency stated that is free of particulate matter and pyrogens and that is safe to use if the directions for administration are followed. Controls used by the industry to assure that the product meets their claim include chemical assays for the drug substance and antimicrobial preservative, when one is present; pH specification; freezing point depression value; sterility test; pyrogen test; clarity test; and, in some instances, safety testing (Table 4–2).

TABLE 4–2. *U.S.P.* XXI Official Tests for Parenteral Products*

Title	Page in USP XXI
Injections	1137
Clarity test	1137
Definition	1137
Vehicles	1137
Added substances	1137
Containers	1138
Volume in containers (overfill)	1138
Labeling	1138
Packaging and storage	1139
Particulate matter	1257
Sterilization	1347
Methods	1348
Biological indicators	1284
Sterility testing	1156
Antimicrobial Agents—Effectiveness	1151
Bacterial Endotoxins Test	1165
Pyrogen Test	1181
Container Specifications	1233
Light transmission	1233
Chemical resistance (glass)	1233
Biological test (plastic)	1235
Physicochemical test (plastic)	1237
Permeation	1240

*Individual monographs specify assay, pH, identification test, and other requirements.

Sealed ampules are routinely tested for proper sealing through the leaker test. In this test, the ampules are immersed in a dye solution (methylene blue), and a vacuum is applied. When cracks or other openings due to an incomplete seal are present in any of the ampules, a vacuum forms within the leaking ampule. Then when the outside vacuum is released, the vacuum within the leaking ampule draws the dye solution into the ampule. The ampules with the colored contents can then be easily identified as "leakers" and removed. It has also been suggested that vial closure systems be subjected to integrity testing to demonstrate that sterility will be maintained during the lifetime of the product. Both physical and microbiologic methods have been proposed for determining vial-closure integrity.[12]

Chemical assay of the preparation assures that the product initially contains the labeled amount of drug substance and serves as the basis for future stability testing. The presence of the antimicrobial preservative in the proper concentration is also determined initially and can be rechecked at later dates for its stability with time in the formulation. Agreement of the solution's pH and freezing point depression values serves as a qualitative indication that the quantities of additives stated in the formula have been used.

Each batch of a parenteral product is subjected to a sterility test to meet the requirements of the compendium. In terminal sterilization, each autoclave load is considered to be a batch. In a cold sterilization process, the units filled during a normal 8-hour working day are considered to be a batch. The number of samples removed for sterility testing depends not only on the sterilization method, but also on the procedure to be used for sterility testing.

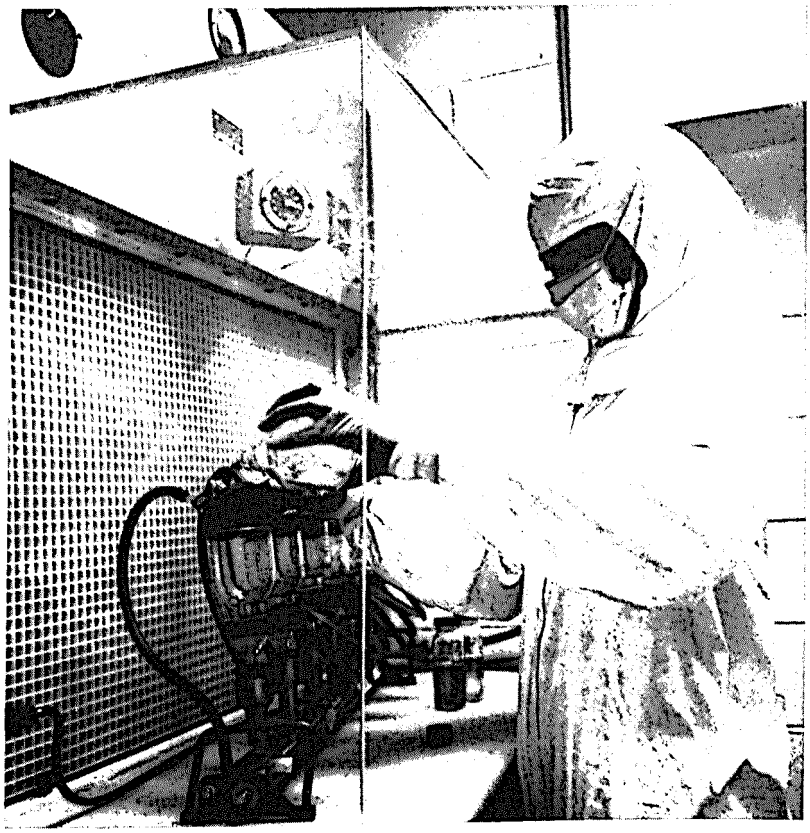

Figure 4–7. Sterility test using the membrane filtration method. (Courtesy of Elkins-Sinn, Inc., Cherry Hill, NJ.)

There are two official methods of sterility testing—the direct transfer of the samples to sterile culture media and the membrane filtration procedure. In the first method, aliquots of the samples are transferred aseptically into each of two sterile culture media, fluid thioglycollate medium and soybean casein digest. The inoculated fluid thioglycollate medium samples are incubated at 32° C, and the soybean casein digest samples at 22° C for 14 days. Negative and positive controls are prepared, along with the samples. For the product to pass the sterility test, none of the tubes with either medium can show turbidity or signs of growth (except the positive control) at the end of the incubation period.

In cases where the parenteral product contains a bacteriostatic agent or the drug substance present in the product possesses inherent bacteriostatic activity, the membrane filtration procedure is followed (Fig. 4–7). In this method, the entire contents of the samples are filtered through a sterile membrane filter having a porosity of 0.45 μm, thereby isolating any microbial contaminants present on the membrane. The membrane is washed with a sterile diluting fluid to remove all traces of the bacteriostatic agent. The membrane is then aseptically removed and divided into two segments. One part is placed into 100 ml of sterile fluid thioglycollate medium, and the other is placed into 100 ml sterile soybean casein digest. The former is incubated with a positive and negative control at 32° C for 7 days, and the latter

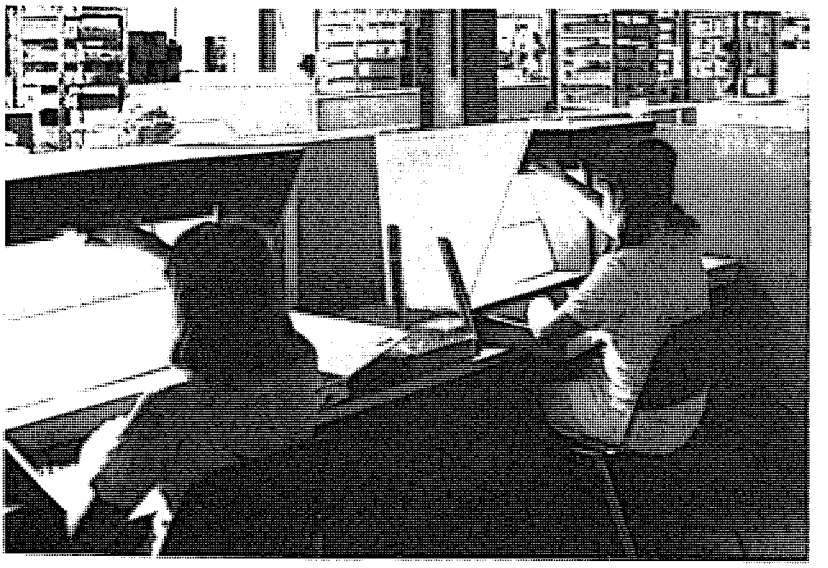

Figure 4–8. Visual inspection of parenteral containers for clarity or absence of particulate matter. (Courtesy of Elkins-Sinn, Inc., Cherry Hill, NJ.)

with controls at 22° C for 7 days. The product passes the sterility test if no turbidity or signs of growth appear at the end of the incubation period. The exact procedures for sterility testing are found in *U.S.P. XXI.*[13]

Samples of the production batch are tested in rabbits for the presence of pyrogens (see "Pyrogen Test" in Chap. 3). Certain drug substances, owing to their physiologic activity, make pyrogen testing in rabbits difficult; administration of a normal human dose to rabbits can be toxic and can result in death of the rabbits. In some cases, the limulus lysate test is applicable.

All units in a production batch are checked individually for clarity, i.e., for the absence of particulate matter. The contents of the container are swirled before a well-lighted white and black background, and those containers with particulate matter are rejected (Figs. 4–8 and 4–9).

With many products, an acute LD_{50} toxicity test (safety test) in the mouse is performed to assure that the total packaged product has no greater inherent toxicity than did previous batches. Changes in the toxicity of preparations can come from many sources, including the raw materials used, the packaging components, and errors made during the compounding of the solution.

Labeling

After satisfactory completion of the control tests, the material is labeled. By law, the labels of parenteral products must indicate the vehicle used, if other than Water for Injection; the drug; and all additives, with the percentage of each present. If the product is for veterinary use, it must be so stated; if it is intended for irrigation, the label must indicate that is not intended for injection. Expiration dating is required for all products.

Figure 4–9. Inspection of label and bailing of intravenous fluid bottles.

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Sterile Dosage Forms

Their Preparation and Clinical Application

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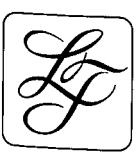

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Chapter 8

Large-Volume Sterile Solutions

Large-volume intravenous solutions refer to injections intended for intravenous use, and they are packaged in containers holding 100 ml or more. Other sterile large-volume solutions include those used for irrigation or for dialysis. These may be packaged in containers designed to empty rapidly and contain a volume of more than 1000 ml. They are packaged in single-dose units in suitable glass or plastic containers and, in addition to being sterile, are pyrogen-free and free of particulate matter. Because of the large volumes administered, bacteriostatic agents are never included, since toxicity may result from administering large quantities of bacteriostatic agent.

Large-Volume Solutions for Intravenous Use

Large-volume parenterals intended to be administered intravenously are frequently called "intravenous" (I.V.) fluids or "infusion" fluids (Fig. 8–1). The most common uses of intravenous fluids include the correction of serious disturbances in electrolyte and fluid balances in the body and a means of providing basic nutrition. In recent years, they have been used as vehicles for other drugs and as a method of providing parenteral hyperalimentation. Infusion or intravenous fluids are packaged in containers having a capacity of 150 to 1000 ml. Mini-type infusion containers of 250-ml capacity are available with 50- and 100-ml fills for the dilution of drugs when used in the the "piggyback" technique (Fig. 8–2). This technique refers to the administration of a second solution through a Y-tube or gum rubber connection with the administration set of the first intravenous fluid, avoiding the need for another injection site. Special automatic piggyback sets are now available and are described later in this chapter.

Solutions to be administered intravenously or by infusion (venoclysis) must be clear and contain substances that can be assimilated and utilized by the circulatory system, such as ethyl alcohol, amino acids, dextrose, electrolytes, and vitamins. Manufacturers have made available many different kinds and combinations of intravenous solutions. The most commonly used are listed in Table 8–1.

Although it is desirable that intravenous fluids be isotonic to minimize trauma to the blood vessels, hypertonic or hypotonic solutions can be administered successfully. Highly concentrated hypertonic nutrient solutions are being used in parenteral hyperalimentation. To minimize vessel irritation, these solutions are administered slowly with a catheter in a large vein such as the subclavian.

On rare occasions, intravenous fluids are administered into the subcutaneous tissues. This type of administration is called "hypodermoclysis" and is used in infants or obese patients, in whom veins are inaccessible (Fig. 8–3), and it has been used in the past to reduce speed shock. The potential for speed shock has been reduced with the advent of new types of intravenous administration devices. Administration

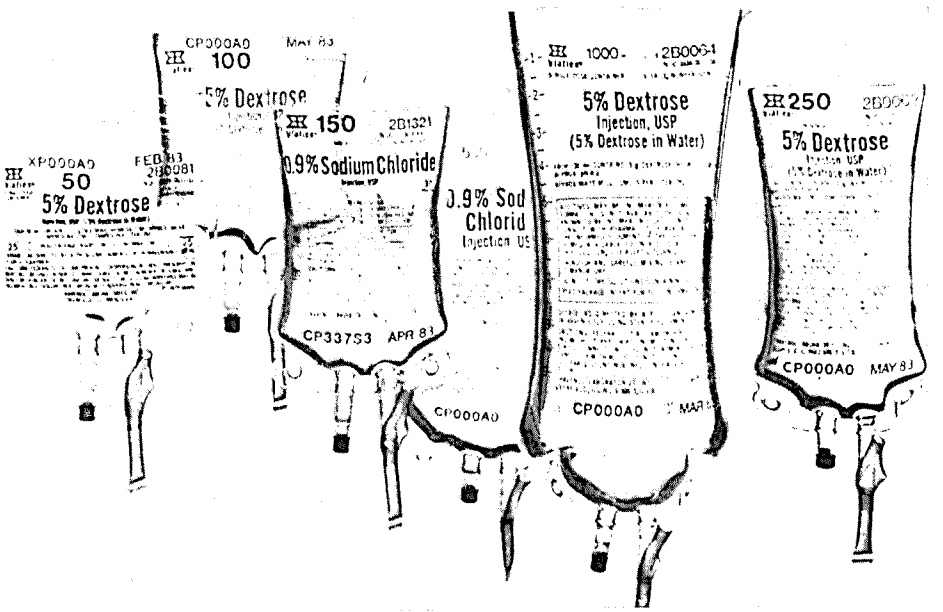


Figure 8–1. Large-volume intravenous solutions. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

of solutions by this route requires that they be isotonic and of low molecular weight. Hypertonic solutions cause body fluids and electrolytes to be drawn into the interstitial areas, resulting in edema. Suitable solutions for hypodermoclysis include Sodium Chloride Injection, Dextrose (2.5%) and Sodium Chloride (0.45%) Injection, and Ringer's Injection. Although Dextrose Injection, 5%, is isotonic, it has been shown to cause plasma volume loss. In a volume-depleted patient, this may result in vascular collapse. Solutions to be administered are infused slowly through a Y-type administration set employing two needles to facilitate absorption. A needle is usually inserted subcutaneously into each thigh. The rate of administration depends on many factors, including the individual's ability to absorb the fluid. Most large volume parenteral solutions are given by the intravenous route, but a few are administered by hypodermoclysis. Intraosseous fluid administration in emergency situations was reported to have been successful, with no serious complications.[1]

Basic Nutrition

In addition to the need to maintain normal body functions, hospitalized patients require adequate caloric intake to survive the insults of illness or operation. Adequate caloric intake is a requirement for wound healing. For those patients who are not able to satisfy their food requirement orally, nutrition must be supplied by the intravenous route. Administration of proteins, carbohydrates, and vitamins can be accomplished in this way. Various protein solutions containing amino acids are available commercially. These solutions are used to supply the body's nitrogen requirements. Recommended daily allowances of protein are approximately 0.9 g/kg of body weight for a healthy adult and 1.4 to 2.2 g/kg for healthy growing children and infants. Protein requirements may be higher for traumatized or malnourished patients. To

Figure 8–2. Intravenous administration using the automatic piggyback technique. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

supply adequate protein parenterally, various kinds of solutions and combinations of amino acids are available as enzymatic digest of casein or as the new synthetic amino acids. Proteins are used when oral feeding is not possible or when gastrointestinal absorption is impaired. Protein is available as 5% or 10% solutions.

Since 1 g of dextrose provides 3.4 cal, 1000 ml Dextrose Injection, 5%, containing 50 g dextrose, supplies 170 cal, or approximately 200 cal. Traditionally, 1 g of dextrose has been calculated to provide 3.75 cal. Commercial dextrose is in the monohydrate form, however, and a 0.91 correction factor is indicated: 3.75 cal $\times$ 0.91 = 3.4 cal. The body utilizes dextrose at a rate of 0.5 g/kg of body weight/hour. Therefore, 1000 ml of Dextrose Injection, 5%, requires 1½ hours for assimilation. The *U.S.P.* pH range for Dextrose Injection, 5%, is 3.5 to 6.5. The low pH is due to the sugar acids present. Some practitioners believe that the acidity of dextrose solutions and other acid intravenous solutions may cause vein irritation and phlebitis. A few investigators have advocated the addition of sodium bicarbonate to neutralize the acid pH of intravenous solutions. One per cent sodium bicarbonate solution packaged in 20-ml containers is available for this purpose (Neut, Abbott; Buff, Travenol). An acid pH is essential to ensure stability of the dextrose solution during sterilization and storage. As the pH increases, caramelization occurs, and the dextrose solutions darken in appearance.

TABLE 8–1. Large Volume Solutions for Intravenous Use

Injection	Common Name	Concentration (%)	pH	Therapeutic Use
Dextrose	Glucose	2.5	3.5–6.5	Hydration, calories
	5 D/W	5		Hydration, calories
		10		Insulin shock, calories
		20		Insulin shock, calories
		50		Insulin shock, calories
Sodium Chloride	Normal Saline N.S.S.	0.9	4.5–7.0	Extracellular fluid replacement
	½ Normal Saline	0.45		Dehydration
		3		Hyponatremia
		5		Hyponatremia
Ringer's	Ringer's			
NaCl		0.86	5.0–7.5	Fluid and electrolyte replacement
KCl		0.03		
$CaCl_2$		0.033		
Lactated Ringer's	Hartmann's			
NaCl		0.6	6.0–7.5	Fluid and electrolyte replacement
KCl		0.03		
$CaCl_2$		0.02		
No lactate		0.3		
Sodium Bicarbonate		1.4	8	Metabolic acidosis
		5		Metabolic acidosis
Ammonium Chloride		2.14	4.5–6.0	Metabolic alkalosis, hypochloremia
Sodium Lactate	M/6 Sodium Lactate	⅙ molar	6.0–7.3	Metabolic acidosis
Fructose	Levulose	10	3.0–6.0	Calories, fluid replacement
Fructose w/Electrolytes		10		
Invert Sugar		5	4	Calories, fluid replacement
		10		
Mannitol		5	5.0–7.0	Osmotic diuresis
also in combination with		10		
dextrose or sodium		15		
chloride		20		
Alcohol				
with 5% D/W		5	4.5	Sedative, analgesic, calories
with 5% D/W in N.S.S.		5		Sedative, analgesic, calories
Dextran 40				Priming fluid for extracorporeal circulation
in N.S.S.		10	5	
in 5% D/W		10	4	Priming fluid for extracorporeal circulation
Dextran 70				
in N.S.S.		6	5	Plasma volume expander
in 5% D/W		6	4	Plasma volume expander
Multiple electrolyte solutions				
varying combinations of electrolytes, dextrose, fructose, invert sugar			5.5	Fluid and electrolyte replacement

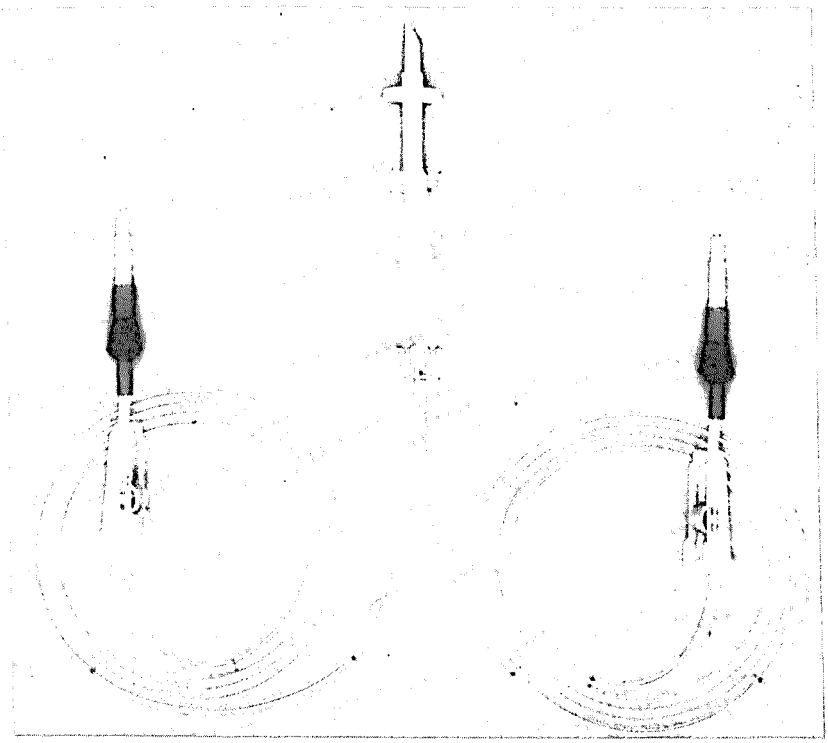


Figure 8–3. Hypodermoclysis set. (Courtesy of Travenol Laboratories, Deerfield, IL.)

Other sources of calories include ethanol solutions supplying about 7 cal per g of ethyl alcohol. When administered too rapidly, ethanol solutions elicit depressant effects on the central nervous system. Fructose is available, and in combination as invert sugar (fructose and dextrose), it has the claimed advantage of more rapid utilization by the body. The dangers of administering fructose have been described. During the infusion of fructose solution, the rate of formation of lactate has been noted to exceed the rate of disposal of lactate, resulting in high levels of lactic acid in the blood.

Currently, a suitable form of fat is available for intravenous feeding. To be administered intravenously, the fats or oils must be emulsified. In the past, difficulty with fat emulsions was related to untoward reactions believed to have been caused by the emulsifier used. Fat emulsions for intravenous administration are being used both in Europe and in the United States (Fig. 8–4). A sterile fat emulsion used in Sweden (Intralipid, Vitrum) contains 10 to 20% of fractionated soybean oil, 1.2% of fractionated lecithin from egg yolk, 2.5% of glycerin, and Water for Injection. Intralipid is supplied in the United States by KabiVitrum.

The Food and Drug Administration released Intralipid (10% solution only) for use in the United States early in 1976. Intralipid contains 10% wt/vol of purified soybean oil, 1.2% egg yolk phospholipid, the emulsifier, and 2.25% glycerin, making the emulsion isotonic. Sodium hydroxide is added to adjust the pH between 5.5 and 9.0; the suspending water is pyrogen-free. Soybean oil comprises a number of neutral triglycerides, most of which are largely unsaturated fatty acids—linoleic (54%), oleic

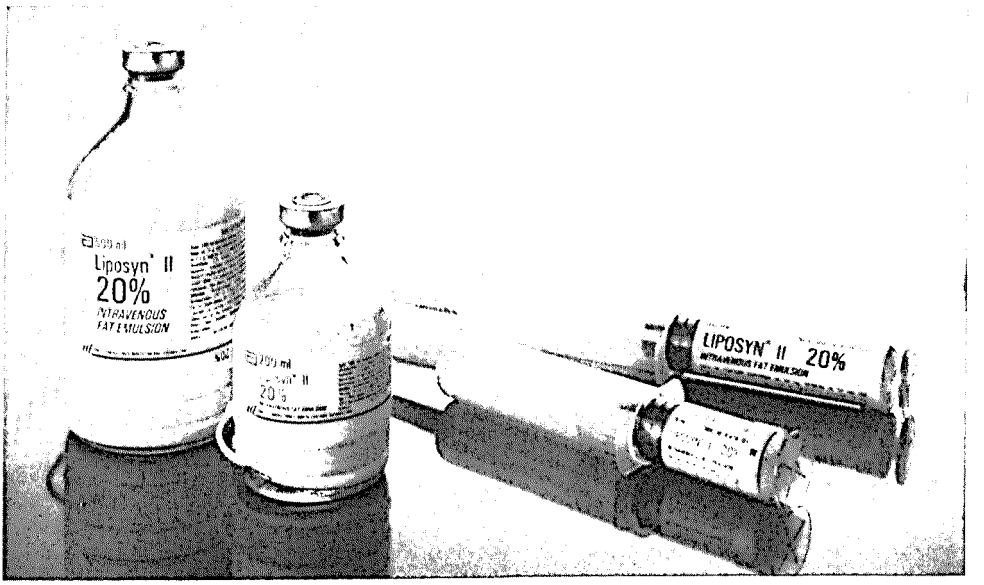


Figure 8–4. Liposyn II (20% intravenous fat emulsion). (Courtesy of Abbott Laboratories, North Chicago, IL.)

(26%), palmitic (9%), and linolenic (8%). These, together with the glycerin and egg lecithin, provide 1.1 kcal per ml emulsion.

The osmolality of Intralipid 10% is 280 milliosmols, comparable to that of blood. The diameter of its lipid particles ranges from 0.1 to 0.5 μm, which is comparable to the size of physiologic blood chylomicrons. Intralipid 10% is bottled under nitrogen and stored under refrigeration; so protected, the milky emulsion can be considered stable for 1 year following its manufacture.

Given intravenously, artificial fat droplets are distributed in the blood and metabolized in essentially the same pathways as are chylomicrons. Most of this lipid or lipoprotein is hydrolyzed by lipoprotein lipase, and the hydrolytic products—free fatty acids and monoglycerides—are taken up by cells and metabolized. The metabolism of 1 g of fat provides 9.1 kcal of energy, compared to 3.4 kcal provided by the metabolism of 1 g of glucose.

In addition to its value as a partial source of calories in a balanced program of total parenteral nutrition (TPN), including amino acids, dextrose, minerals, vitamins, and electrolytes, a lipid emulsion is useful in treating or preventing essential fatty acid deficiency (EFAD).

Frank studied the microscopic and macroscopic effects of 25 parenteral drugs combined with Intralipid.[2] Four of these combinations resulted in unacceptable admixtures. Calcium gluconate and tetracycline hydrochloride produced a cracked emulsion. Hyprotigen produced creaming in an unrefrigerated sample of Intralipid. Phenytoin precipitated as crystals. Although many drugs retain their stability in Intralipid, their bioavailability may be altered in such mixtures. Lynn reported that carbenicillin and cloxacillin provoked aggregation of the emulsion.[3] After 24 hours in Intralipid, methicillin crystallized. Ampicillin did *not* alter the character of the emulsion and was *not* altered itself by the chemical association.

Low toxicity and high stability depend, in large part, on the presence and pres-

ervation of small particles (<1 μm) in a fat emulsion. The brownian movement of small particles protects the emulsion. A change in pH, hydrolysis of the emulsifier, or the presence of a dissociated electrolyte (e.g., NaCl) or of any of a number of macromolecules tend to increase particle size and thus lead to creaming or breaking of the emulsion, or to complete separation of the oil. Aggregation of globules into particles over 6 μm in diameter greatly increases the risk of such serious side effects as emboli.

Restoration of Electrolyte Balance

Electrolyte disturbances can be caused by a variety of clinical conditions: trauma, injury, burns, shock, diarrhea, vomiting, and electrolytic shifts in body compartments. When they occur and the oral route cannot be used to correct the difficulty, electrolytes are administered intravenously. The condition of the kidneys must be considered before electrolyte replacement is initiated. Urinary depression may be the result of decreased fluid volume or renal impairment. A hydrating solution such as 5% D/W in 0.2% sodium chloride is administered. Urinary flow is restricted if the retention is functional. The most frequently used solution is Sodium Chloride Injection, an isotonic solution containing 154 mEq each of sodium and chloride ions. Ringer's Injection and Lactated Ringer's Injection contain small quantities of calcium and potassium ions. Deficits of these ions require additional supplementations. Lactated Ringer's Injection contains sodium lactate, which is metabolized to sodium bicarbonate and is useful for correcting metabolic acidosis. Solutions with multiple electrolytes are available commercially to simplify therapy (Isolyte, McGaw; Normosol, Abbott). These solutions closely resemble the composition of plasma electrolytes.

Fluid Replacement

Dehydration requires fluid replacement. As basic solutions, sodium chloride and dextrose injections can be used for fluid replacement when needed. Excessive use of large volume solutions can cause edema and water intoxication.

Blood and Blood Products

Blood and blood products can only be administered intravenously. In cases of shock, hemorrhage, blood protein loss, these products are used. No drug should be mixed with blood prior to administration (see Chapter 9, Blood Components and Plasma Expanders).

Drug Carriers

Because of convenience, the irritation potential of the drug, and the desire for continuous drug therapy, intravenous fluids are frequently used as vehicles for the intravenous administration of drugs. In some instances, the combination of one or more drugs in an intravenous fluid results in conditions not favorable for drug stability and may promote parenteral incompatibilities.

Parenteral Hyperalimentation

One of the most exciting developments in parenteral nutrition has been the concept of parenteral hyperalimentation. Hyperalimentation is the long-term intravenous feeding of protein solutions containing high concentrations of dextrose (approximately 20%), electrolytes, vitamins, and in some instance insulin. The need to maintain

adequate caloric intake while keeping the volume of solution required to a minimum necessitates the use of this hypertonic solution. The basic solution can be prepared by the combination of commercially available dextrose and protein solutions (Amigen, 5% and 10%, Baxter; Aminosol, Abbott; Hyprotigen, 5%, McGaw). These solutions are usually combinations of 50% dextrose and 5% protein solution. At present, synthetic amino acids are more commonly used. They are supplied as FreAmine III, McGaw; Aminosyn, 3.5%, 7%, Abbott; Travasol 5.5% and 8.5%, Travenol. After mixing, they supply approximately 1 cal per ml of solution. Required supplements such as electrolytes and vitamins are frequently added to the basic solution. Many manufacturers provide the solutions in ready-to-mix kits. The solutions are administered via a large vein, such as the subclavian, over 8 to 24 hours. The purpose of using this vein and slow administration is to minimize adverse effects that may occur with such a hypertonic solution. The subclavian vein is large and close to the heart; therefore, the solution is diluted rapidly by the large volume of blood in the heart. Numerous references in the literature fully describe the methods of preparation and parenteral implications.

Specialized TPN solutions are illustrated in Figure 8–5.

Special Uses

A number of large volume solutions are recognized more readily as drugs and are used for specific clinical conditions.

l-Arginine Hydrochloride Injection (R-Gene). This amino acid is effective in stimulating the utilization of ammonia by the body. Elevated levels of ammonia correlate with cerebral dysfunction and occur in liver damage, high protein feedings, excessive intake of ammonium chloride, and intestinal tract bleeding in liver disease. It is believed that l-Arginine enhances the formation of urea and thus reduces the ammonia level; however, clinical results are poor. R-Gene was removed from the market, but was subsequently reintroduced as R-Gene 10 (KabiVitrum). The official indications for this product are as an I.V. stimulant to the pituitary and as a diagnostic test for human growth hormone (HGH).

Urea—Lyophilized Form (Urevert, Travenol). Solutions of urea are administered intravenously to reduce edema associated with operation, trauma, burns, and especially in the reduction of intracranial and intraocular pressure. Urea is not metabolized by the body. The administration of this concentrated solution causes osmotic diuresis.

Mannitol (Osmitrol, Travenol). The intravenous administration of mannitol solutions results in osmotic diuresis. The solution is eliminated by the body almost entirely unmetabolized. Mannitol is of value in the prophylaxis of oliguria from tubular necrosis, in the treatment of cerebral edema, and in the promotion of diuresis. Dosage consists of 50 to 200 g as a 5%, 10%, or 20% solution. Twenty per cent solutions of mannitol are saturated solutions. A decrease in room temperature may cause crystallization of the mannitol. If this occurs, the injection should be warmed prior to its administration in order to place the mannitol back into solution. Administration of the 20% injection requires the use of a blood filter set to ensure against infusion of mannitol crystals.

Dextran 70, Dextran 40 (Macrodex, Pharmacia; Rheomacrodex, Pharmacia; Gentran, Travenol) (Fig. 8–6). Dextrans are polymolecular polysaccharides composed of glucose units formed by culturing a sucrose-containing medium. The average molecular weight of Dextran 70 is 70,000, and the average molecular weight of

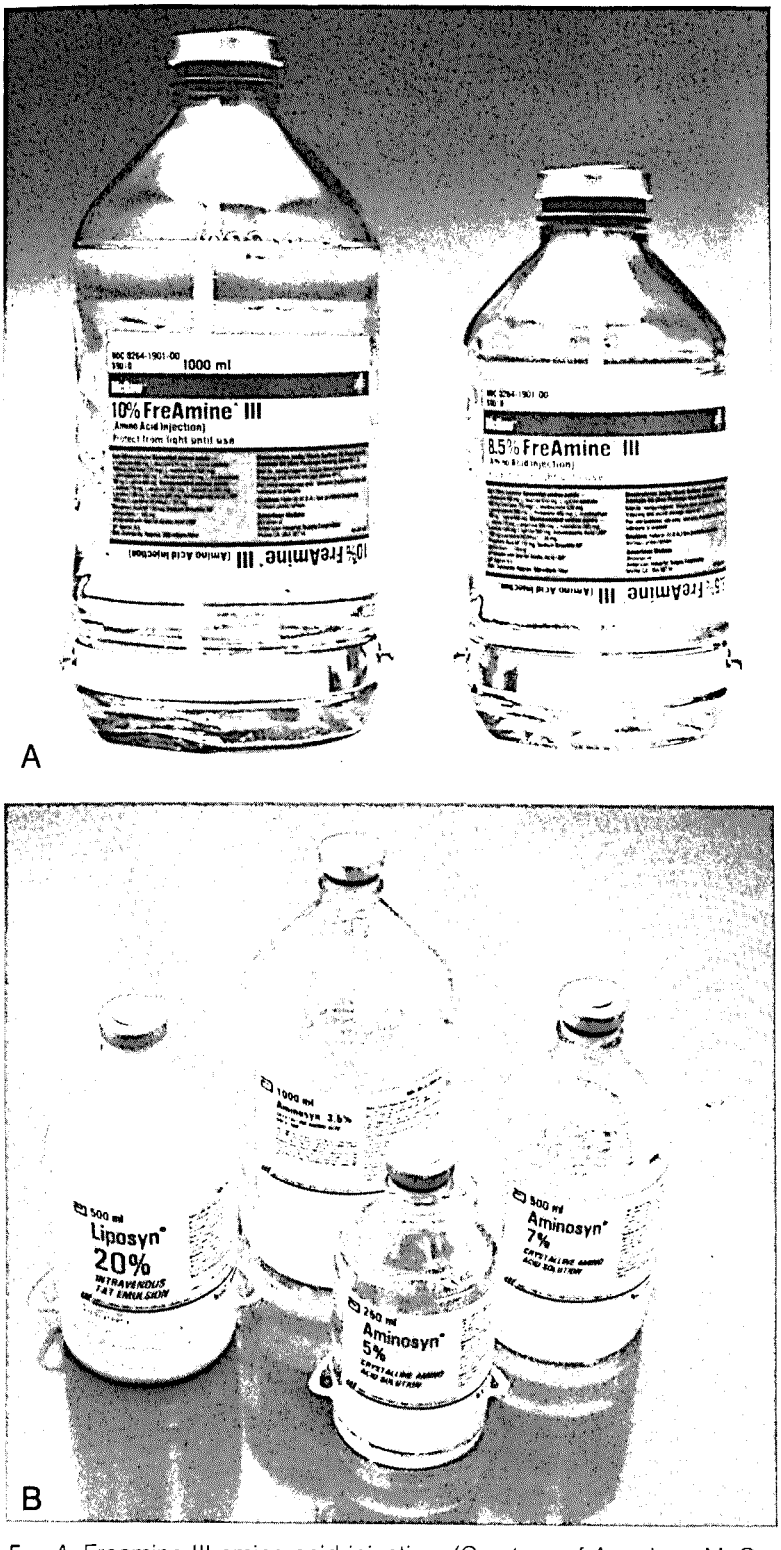
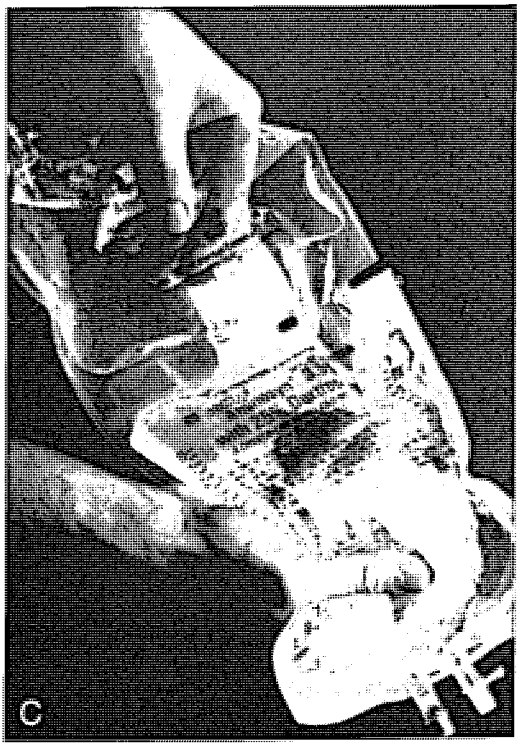
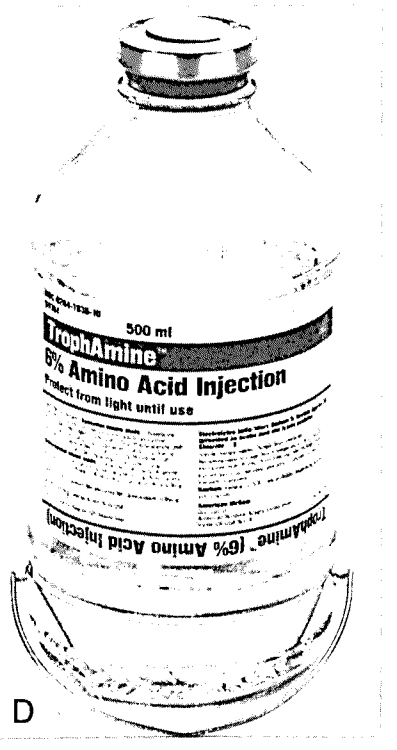
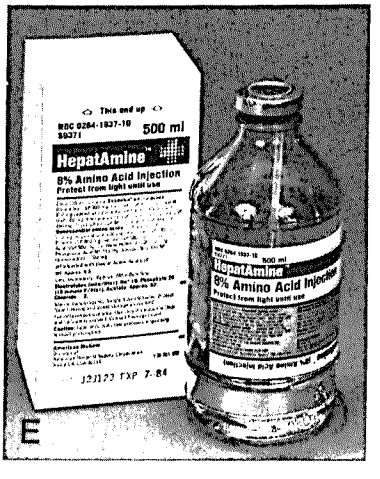


Figure 8–5. *A,* Freamine III amino acid injection. (Courtesy of American McGaw, Irvine, CA.) *B,* Total parenteral solutions (I.V. fat and amino acid). (Courtesy of Abbott Laboratories, North Chicago, IL.)







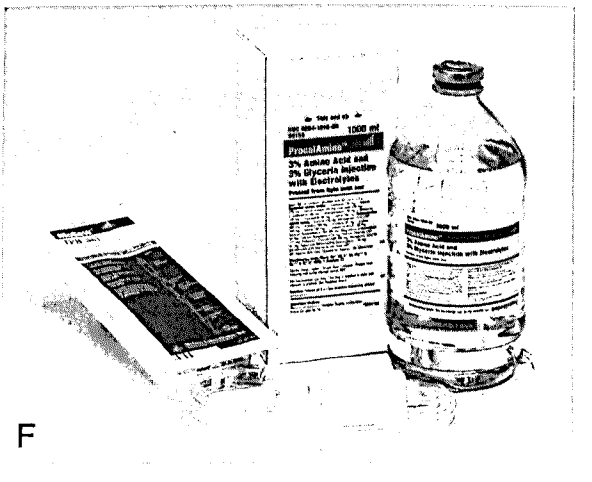


Figure 8–5. *C,* Dual-compartment container of Nutrimix, an Aminosyn and dextrose mixture. (Courtesy of Abbott Laboratories, North Chicago, IL.) *D,* TrophAmine amino acid injection. (Courtesy of American McGaw, Santa Ana, CA.) *E,* HepatAmine. (Courtesy of American McGaw, Irvine, CA.) *F,* ProcalAmine (TNP set). (Courtesy of American McGaw, Irvine, CA.)

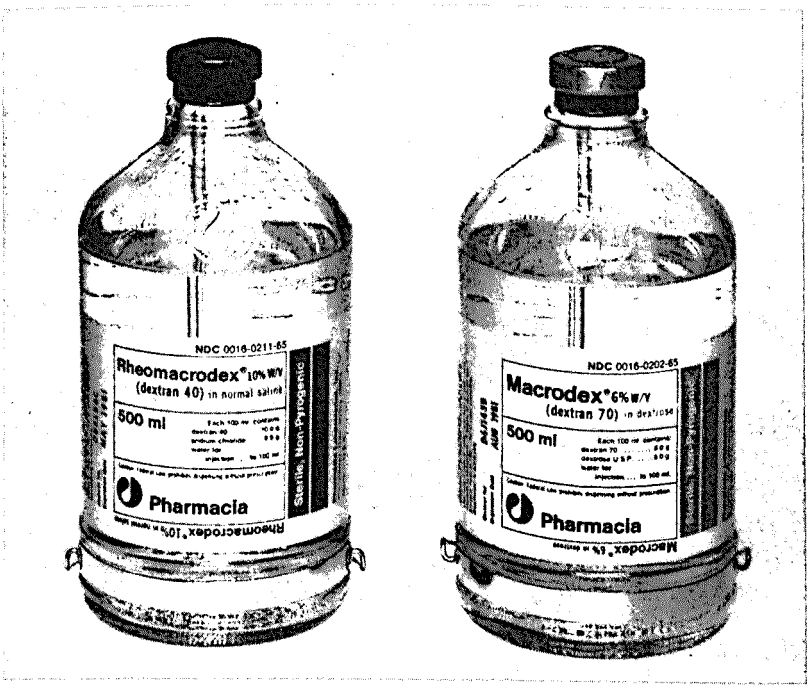


Figure 8–6. Dextran 40, Dextran 70. (Courtesy of Pharmacia Laboratories, Inc., Piscataway, NJ.)

Dextran 40 is 40,000. When administered intravenously, Dextran 70 is an effective plasma volume expander. It is used in the treatment of trauma, hemorrhage, burns, and surgical shock. Owing to its lower molecular weight, Dextran 40 has less effect as a plasma volume expander than has Dextran 70. It is used as a priming fluid in pump-oxygenators during extracorporeal circulation. Studies have also shown that Dextran 40 has value as a prophylactic agent against thrombus formation. The drug prevents rouleau formation of red blood cells.

Sodium Bicarbonate Injection. In addition to its availability in ampuls, vials, and prefilled syringes, sodium bicarbonate, 5% injection, is also packaged in 500-ml bottles. This solution is used to combat acidosis by supplying a ready source of bicarbonate ion, and it can be administered as an intravenous fluid. The pH of sodium bicarbonate solutions is in the area of 8. Although an uncomplicated compound, sodium bicarbonate has presented problems in manufacture and administration. It decomposes to sodium carbonate with the liberation of carbon dioxide; if this occurs, the bicarbonate ion is not available. Sodium Bicarbonate Injection is usually packed in large ampuls; removal of the contents is time-consuming and difficult. Its availability in vials increased its convenience. For a short time, the injection was available in convenient aluminum screw-cap-covered vials; however, this container was withdrawn because metal filings from the closure fell into the solution when the vial was opened. This infusion fluid is packaged in a Type 1 glass container sealed with a rubber closure and requires a special administration set. Sodium bicarbonate packaged in this manner has the disadvantages of requiring an additional intravenous site and being incapable of serving as a vehicle for other drug additives. The infusion

fluid is available in 500-ml containers as 1.4%, ⅙ molar, and 5% solutions. The injection has been made available in disposable prefilled syringes.

Sodium Lactate Injection (⅙ molar). Containing 167 mEq sodium and lactate ions per liter, this injection provides an immediate source of sodium for the elevation of bicarbonate level in severe acidosis. The lactate portion is metabolized by the liver into glycogen. This solution is used in the emergency treatment of metabolic acidosis.

Ammonium Chloride Injection (2.14%). Solutions are available containing 400 mEq per liter of ammonium and chloride ions and are used in the treatment of metabolic alkalosis and hypochloremia.

Large-Volume Solutions Not Administered Intravenously

Although solutions for irrigation and dialysis resemble intravenous fluids in many respects, they are not administered directly into the venous system. Their manufacture is subject to the same stringent controls as is that for intravenous fluids, but they may be packaged in containers that are larger than 1000-ml capacity and that are designed to empty rapidly.

Irrigation Solutions

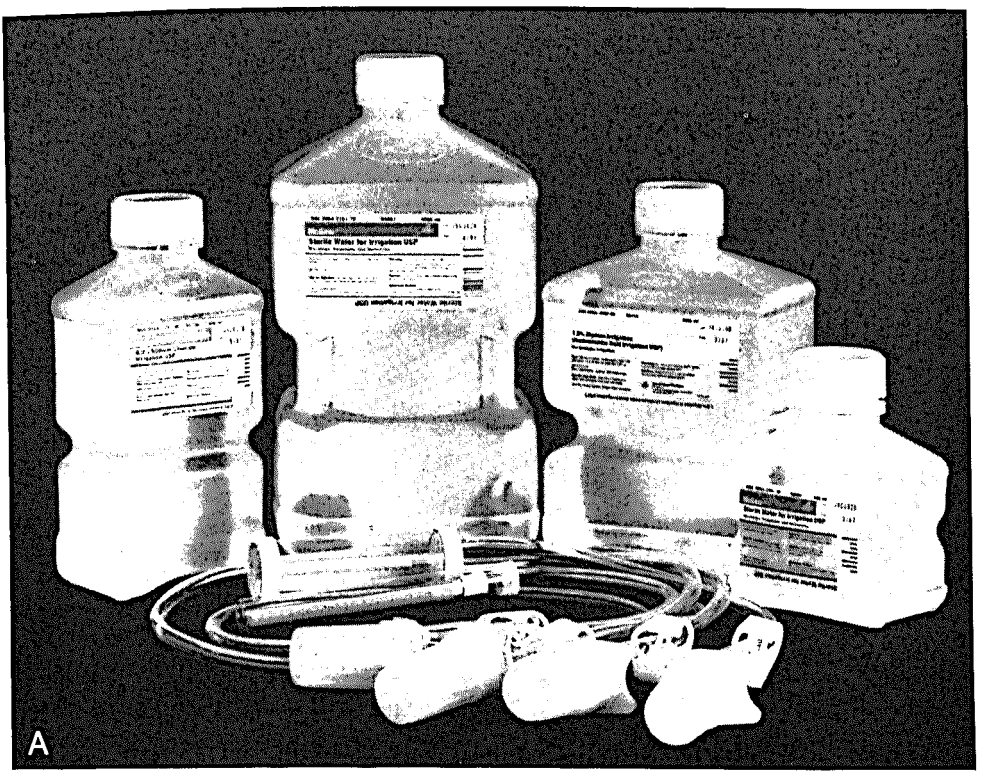
Surgical Irrigating Solutions (Splash Solutions). Surgical irrigating solutions (Uromatic, Baxter; Urogate, Abbott) are used to bathe and moisten body tissue (Fig. 8–7). They may be used topically for moistening dressings, for wound irrigation, or as soaking or washing fluids for instruments. Sodium Chloride for Irrigation and Sterile Water for Irrigation are commonly used for these purposes. They are available commercially in screw-cap containers known as "pour" bottles. More recently, irrigating solutions have become available in rigid plastic pour bottles (Uromatic, Baxter; McGaw; Aqualite, Abbott) (Fig. 8–8).

Urologic Irrigation Solutions. It is common for surgeons performing urologic procedures to use a considerable amount of irrigation solutions during operations (Fig. 8–9). The solutions help to maintain the integrity of the tissue, to remove blood, and to provide a clear field of view for the surgeon. Urologic solutions require an administration set and are used with Foley catheters by connection to a cystoscope. Sterile Water for Irrigation and Sterile Glycine Solution are commonly used. Antibiotics are sometimes added, as in the case of Neosporin G.U. Irrigant.

Glycine Solution. Glycine, a relatively nontoxic amino acid, is commonly used to eliminate the risk of intravascular hemolysis during transurethral resection. It is supplied as a 1.5% solution in Water for Injection and packaged in 1000-, 1500-, and 3000-ml pour bottles. Fifteen per cent solution concentrates are available for dilution. The 1.5% solution is slightly hypotonic. Glycine solution is nonconducting and does not cause dispersion of high frequency current and loss of electrosurgical cutting efficiency.

Sorbital Solution. Sorbital solution 3% is a nonhemolytic urologic irrigant used for transurethral resection.

Urologic Solution G (Suby's Solution). Urologic solution G is an infrequently used solution containing citric acid, magnesium oxide, and sodium carbonate, and is designed to provide a non-operative treatment for urinary lithiasis by dissolution of calculi within the urinary tract. It contains sufficient citric acid to give a pH of 4. With the aid of hydrogen ion, insoluble calculi composed of calcium carbonate or



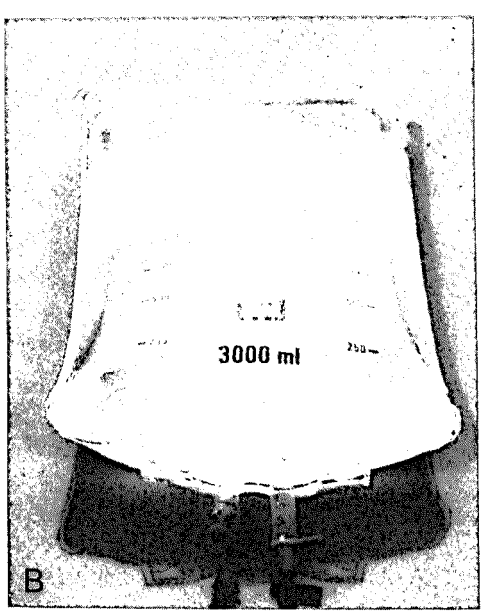


Figure 8–7. Surgical irrigating solutions. (*A*, Courtesy of American McGaw, Santa Ana, CA. *B*, Courtesy of Abbott Laboratories, North Chicago, IL.)

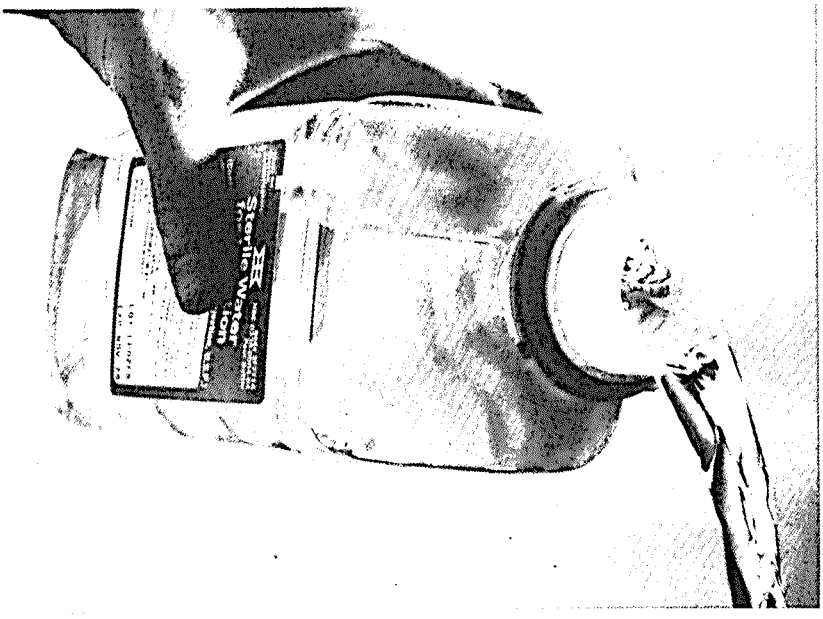


Figure 8–8. Plastic-pour bottle. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

phosphate are converted into soluble phosphoric acid. In addition, citrate ions combine with calcium ions to form soluble complexes.

Dialysis Solutions

Peritoneal Dialysis Solutions. Peritoneal dialysis solutions (Dianal, Baxter; Inpersol, Abbott) are not administered directly into the circulatory system, but rather into the peritoneal cavity (Fig. 8–10). Peritoneal dialysis is used to remove toxic substances normally excreted by the functioning kidney. In cases of poisoning or renal shutdown, or in patients awaiting renal transplants, dialysis is a lifesaving measure used to remove toxic substances, excessive body waste, and serum electrolytes. The composition of these commercially available solutions resembles that of potassium-free extracellular fluid. Solutions are available containing 1.5% and 4.25% dextrose and electrolytes. Solutions are made hypertonic to plasma with dextrose to avoid absorption of water into the intravascular compartment. By osmosis and diffusion, the peritoneal cavity behaves as a semipermeable membrane. Catabolites and other substances may be removed from the body. An incision is made on the linea alba (midline), and a trocar connected to a catheter attached to the container of the dialysis solution is inserted. The solution is permitted to flow into the abdominal cavity. The solution remains in the cavity for 30 to 90 minutes and is drained by a siphon. The procedure is repeated many times and may require 30 to 50 L of solution for daily treatment. Common additives to peritoneal dialysis solutions include tetracyclines, heparin, and potassium chloride.

Hemodialysis. Hemodialysis utilizes the same principles as peritoneal dialysis does. In this procedure, the blood leaves the artery via a polyethylene catheter and passes through a disposable dialyzing membrane unit. This unit is bathed in an ideal electrolytic solution simulating body fluids. One important difference with hemodialysis bath solutions is that their method of use does not require the solution to be sterile,

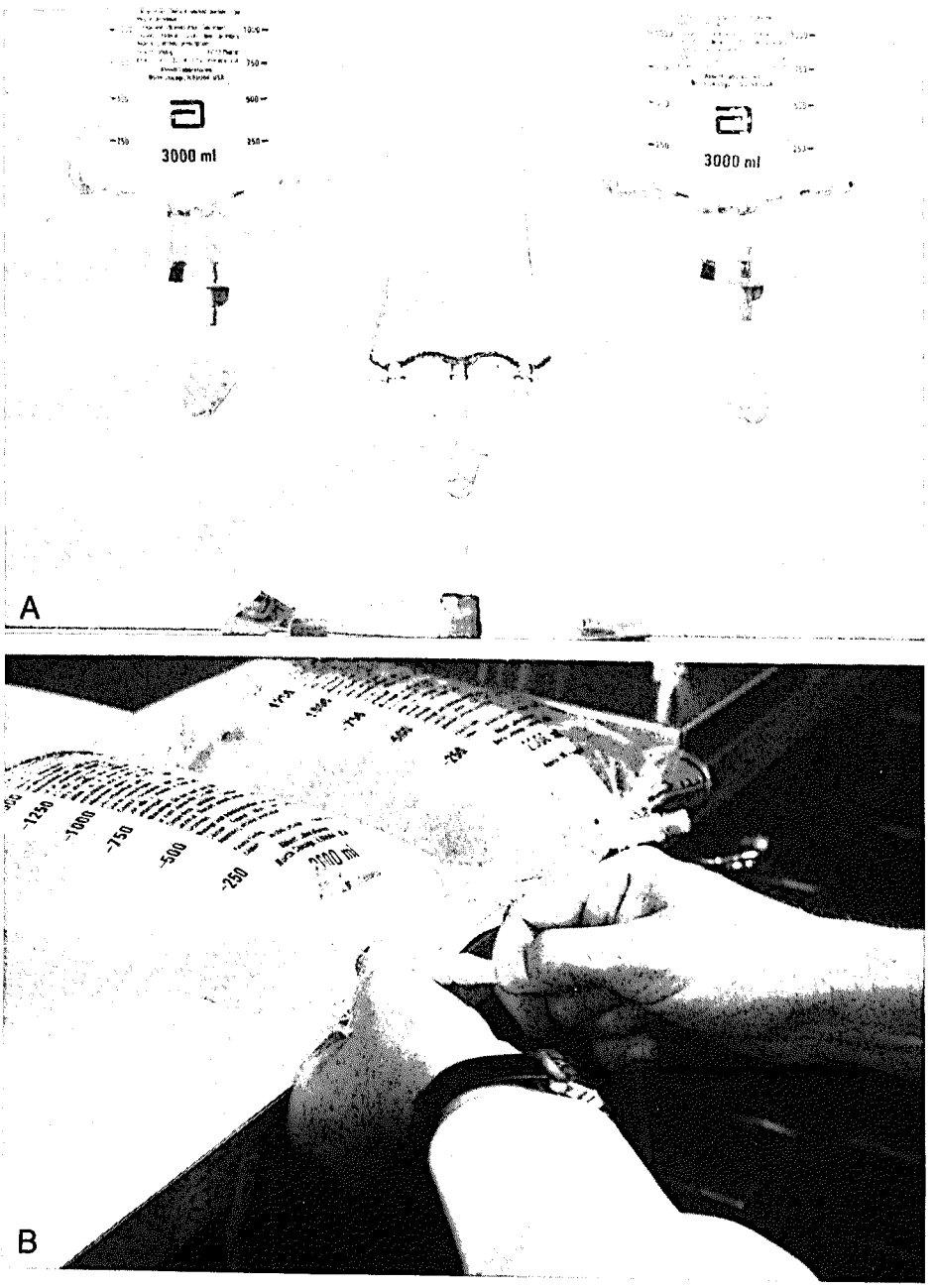
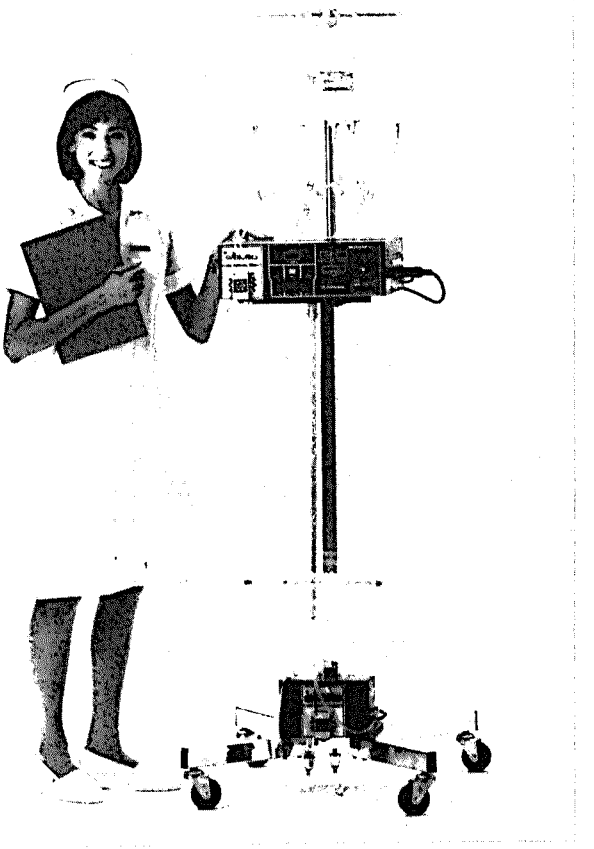


Figure 8–9. *A*, Urologic solution. *B*, Dialysis solutions. *C*, Microstar VCI Peritoneal Dialysis Cycler. (A, B, Courtesy of Abbott Laboratories, North Chicago, IL. *C*, Courtesy of American McGaw, Irvine, CA.)



C

Figure 8–9 (Continued).

pyrogen-free, or free of particulate matter. Concentrated solutions of electrolytes can be purchased and are added to water in a tank containing the disposable dialyzing membrane through which the blood is flowing. After cycling through the dialyzer, the blood enters the body by vein.

Intravenous Fluid Administration Systems

Systems for administering intravenous fluids were classified as either the open system (nonvacuum) or the closed system (vacuum). The open system, marketed by Abbott Laboratories, utilized a screw-capped bottle packaged at atmospheric pressure. A tamper-proof metal overseal with a tear-away tab was removed, the screw cap was removed, and the administration set was attached to the container. Because of problems of contamination with the open system, this type of packaging was removed from the market. Abbott Laboratories now manufactures a closed system container. All the presently available intravenous solutions packaged in glass are closed systems with a vacuum. Although there are variations in the types of sets used, all systems have common characteristics (Fig. 8–11) (Table 8–2).

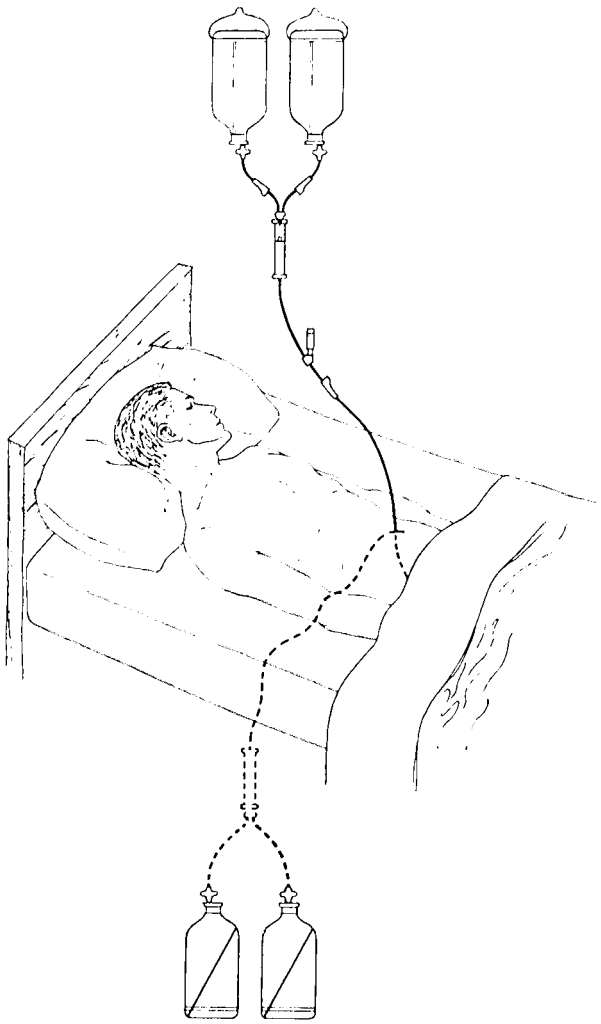


Figure 8–10. Peritoneal dialysis technique. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

All systems packaged in glass bottles require the entrance of air for operation. The vacuum present in the container after autoclaving must be released before the fluid can flow. These containers are Type II glass, with the exception of Sodium Bicarbonate Injection, which is packaged in Type I. All systems are for one-time use and all containers should be discarded after use. Intravenous fluids are packaged with approximately 3% excess in volume. The excess allows for priming the administration set and permits the labeled volume to be delivered from the container. The containers are graduated at 20-ml increments on scales that permit the volume in the container to be readily determined whether the bottle is inverted or in an upright position. A metal band around the container facilitates hanging it for use. Although these solutions are relatively stable, manufacturers date each solution to ensure proper rotation and to minimize stability problems resulting from prolonged or improper storage. Extreme temperatures are to be avoided during storage. Until 1971, all

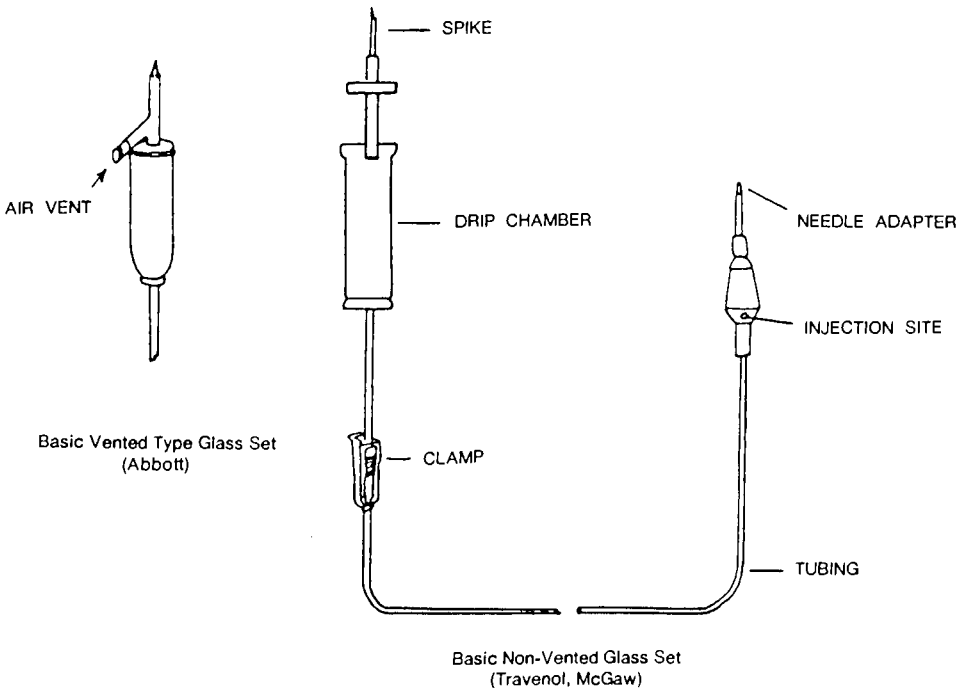


Figure 8–11. Basic intravenous fluid administration sets.

intravenous fluids in the United States were packaged in glass; plastic containers have been introduced by Baxter Laboratories (Viaflex), Abbott Laboratories (LifeCare), and McGaw Laboratories (Accumed), and are discussed later in this chapter.

Administration sets, or devices used to administer intravenous fluids, are disposable, sterile, and free of pyrogens and particulate matter. The basic sets contain a spiked plastic device to enter or pierce the rubber closure on the container. A sight, or drip, chamber is present to allow setting of the rate of flow; the sight chamber allows uninterrupted air-free flow. The chamber leads to a length of polyethylene tubing with an attached gum rubber injection port. At the tip of the port is a rigid plastic device that accepts the needle hub. A clamp-like device on the tubing pinches the internal diameter of the tubing to regulate flow.

Before the container is pierced, the contents should be inspected to ensure that they are clear and free from particulate matter; then the container is pierced asep-

TABLE 8–2. Intravenous Fluid Systems

System	Source
Glass, no air tube, vacuum, air filter on set	Abbott Laboratories
Glass, air tube, vacuum, no air filter	McGaw Laboratories Travenol Laboratories
Plastic, no air tube, nonvacuum	Travenol Laboratories (Viaflex)
Plastic, no air tube, nonvacuum	Abbott (LifeCare)
Plastic, no air tube, nonvacuum	McGaw (Accumed)

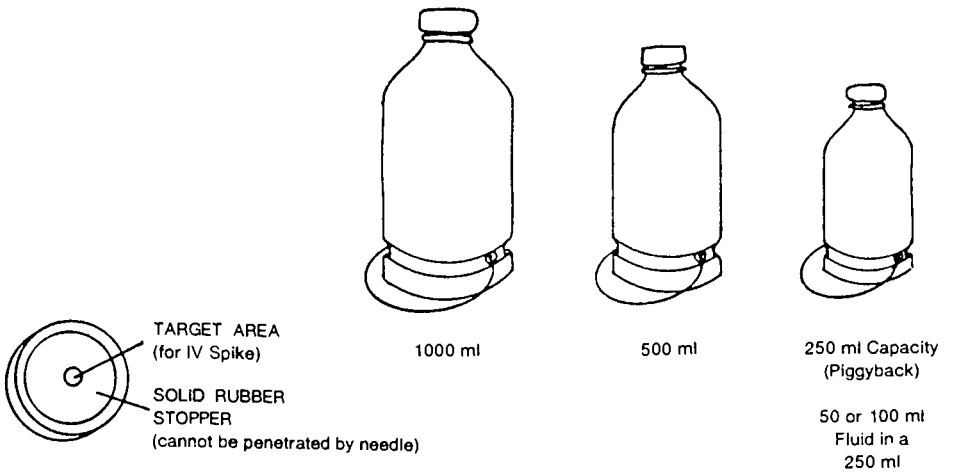


Figure 8–12. Abbott's intravenous glass container. The air venting is provided for in the intravenous set rather than the bottle. Thus, the bottles do not have integral air-venting tubes. Air enters the system through a bacteriologic air filter in the spike adapter of the intravenous set.

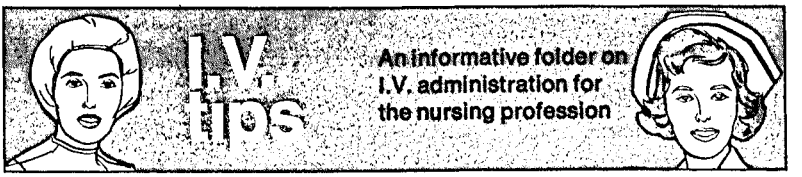
tically with the appropriate administration set. Air is removed from the tubing by pinching the sight chamber and allowing the fluid to flow until air is removed. When air has been removed, the pinched clamp is closed. The venipuncture is made, the pinch clamp is opened, and the rate of flow is regulated.

It is of extreme importance to check the container to ensure that it is not cracked. Fine hairline cracks are difficult to see; however, they present a real hazard. The fact that they do occur is indicated by a lawsuit involving the death of a patient due to septicemia from contamination of a cracked bottle.

Abbo-Vac (Abbott) System

The containers in the Abbo-Vac system have a vacuum and are closed with a solid rubber closure protected by a tear-off aluminum seal (Fig. 8–12). The set is equipped with a spike, which is forced through the solid closure. Air entering through a sidearm Teflon filter permits dissipation of the vacuum, and the solution is ready for use. As the solution leaves the container, air enters through the filter, producing a rising stream of air bubbles which indicates proper functioning. The Abbo-Vac set delivers 15 drops per ml.

Medication may be added to the system in a number of ways. By using syringe and needle, it may be added to the container fluid by insertion through the self-sealing rubber closure. With aseptic technique, medication may be added directly intravenously, if necessary, by injection through the gum rubber self-sealing injection site. Medication may also be added by use of a syringe with no needle attached by removing the Teflon air filter and injecting the solution into the intravenous fluid through the filter site and then replacing the filter. Additives packaged in convenience containers equipped with a spike may be used with these systems (Fig. 8–13). With either a Y-setup or secondary attachment, two containers may be set up simultaneously; however, secondary arrangements are not without hazards.



HOW TO USE ABBOTT'S NEW PINTOP VIAL

On your job you'll be encountering this helpful new Abbott additive container. It's called the Pintop Vial. The Pintop Vial makes it easy for you to add supplemental I.V. solution concentrates before setting up your I.V. bottles.

The Pintop Vial saves nursing time. For example, once you've plugged into the I.V. bottle, a 10 ml. fluid transfer is complete in less than two seconds!

The Pintop Vial is designed to be an important part of the Abbo-Vac® system. However, it is also compatible with other I.V. vacuum-container systems, and is also adaptable to syringe technique.

Examples of widely prescribed additives being supplied are *Potassium Chloride 20 mEq. (No. 4932), 30 mEq. (No. 4933), and 40 mEq. (No. 4934).* Your Abbott Hospital Representative will gladly give you the complete listing of medications available in the Pintop Vial.

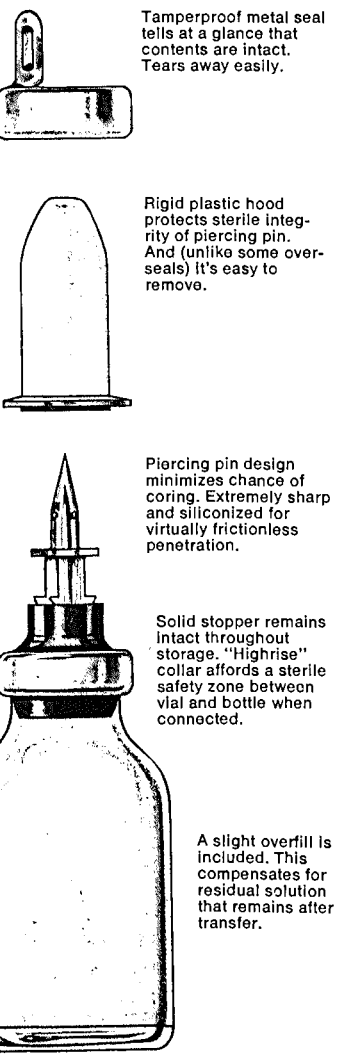


Figure 8–13. Pintop vial. (Courtesy of Abbott Laboratories, North Chicago, IL.)

Baxter and McGaw Systems

These systems differ basically from those previously described in that the rubber closures contain two openings (Fig. 8–14). One opening leads directly into a long plastic airway tube which permits air to enter the container above the solution as it is being administered. A second opening is present to receive the spike of the administration set. A thin rubber diaphragm maintains the integrity of the closure after removal of the aluminum tear-tab. The diaphragm is removed with a quick

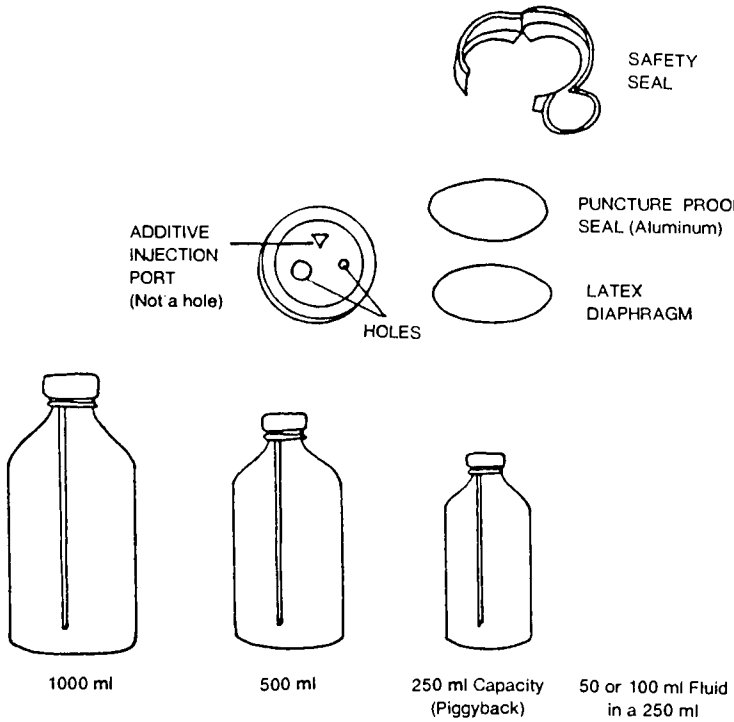


Figure 8–14. Travenol (Baxter) and American McGaw intravenous glass systems. LVP bottles have internal plastic venting tubes, which allow air to enter the bottles as fluid is infused into the patient.

snap, dissipating the vacuum. The administration set may now be plugged into the container. The container is inverted. The flexible sight chamber may need to be pinched to achieve a level of the fluid. The pinch clamp is opened to allow flow to remove air from the system. The pinch clamp is closed, the venipuncture is performed, and the flow rate is adjusted. The standard Baxter and McGaw sets deliver 10 and 15 drops per ml, respectively.

Medication may be added by means of a needle and syringe through a target area marked on the rubber stopper, or through the opening that receives the spikes of the administration set before insertion. If this is done with the diaphragm intact, this area should be swabbed with alcohol. Medication also may be added after the removal of the gum rubber diaphragm. If the administration set is not placed in the bottle immediately, additive caps should be used to protect the fluid from contamination. If necessary, medication also can be injected through the gum rubber injection port while fluid administration is in progress. Additives may be placed directly into the container during administration, using a needle and syringe, by penetrating the target area in the rubber closure.

Prior to dissipating the vacuum, additive solutions in convenience packages (Pin-top, Abbott) may be placed in the administration set opening and drawn into the container, utilizing the vacuum present (Fig. 8–13). A pumper-type convenience device may be used for sterile solids. The device is placed into the administration set opening; the infusion bottle is inverted; with pumping action, the infusion fluid is drawn into the device's container; and solution of the sterile solids is effected. The

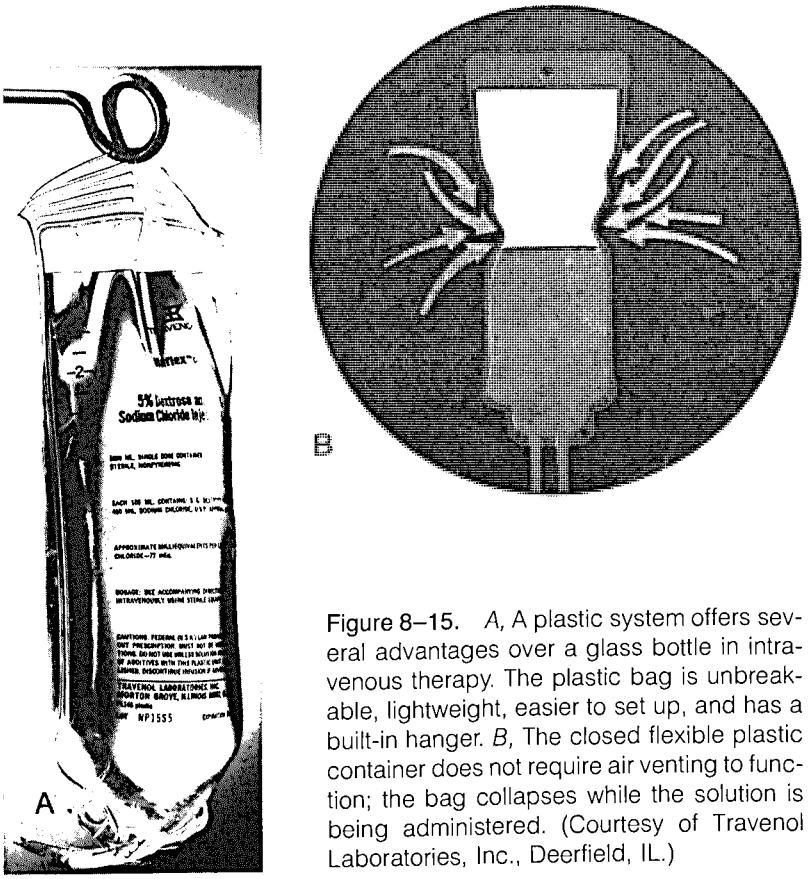


Figure 8–15. *A*, A plastic system offers several advantages over a glass bottle in intravenous therapy. The plastic bag is unbreakable, lightweight, easier to set up, and has a built-in hanger. *B*, The closed flexible plastic container does not require air venting to function; the bag collapses while the solution is being administered. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

infusion fluid container is placed in an upright position, and with a pumping action the contents of the device are forced into the intravenous fluid. Convenience devices may be left in place to indicate that a drug has been added, or the supplied supplemental label may be used.

Plastic Intravenous Fluid Containers

Owing to the large volumes of intravenous fluid administered to some patients, the particulate matter found in them has been of special concern. Sources of this particulate matter, as discussed previously, include the packaging components themselves. The glass bottle and the rubber closure of the standard intravenous fluid container can contribute particulates, not only from their improper preparation before use, but also from their potential reaction with the solution and the chemicals present.

In the search for other packaging material, plastic was suggested as an alternative. Reports from abroad indicated that its use for intravenous fluids did result in the reduction of particulate material. As discussed in Chapter 4, however, plastic packaging is not necessarily totally inert and can present problems, including the leaching of chemicals from the plastic by the solution, the absorption of substances from the solutions, and the permeability of the plastic to moisture transfer. These problems have to be considered for any plastic used as a packaging material, especially for solutions.

In the United States, several intravenous fluids are packaged in plastic (Viaflex,

Travenol) (Fig. 8–15). The plastic container or bag is prepared from transparent plasticized polyvinyl chloride. For shipment and storage, the plastic container is inserted and sealed in a tear-off, translucent, heavy-duty polyethylene case. The inner container or bag is designed with a plastic tab with an opening that permits it to be hung from an intravenous pole. On the opposite end are two sleeve ports. The plastic covering over one port can be removed to permit the insertion of the spike of the administration set. The other sleeve, with a gum rubber covering, permits addition of other medication to the intravenous fluid. When adding medication in this manner, the sleeve port should be milked to diffuse the added solution into the intravenous fluid. Adding medication through the sleeve port must be done with care to prevent the needle from puncturing the plastic. Since plastic material is not inherently resealing, puncturing it with a needle results in a hole.

The flexible plastic container functions physically by the forces of gravity and atmospheric pressure; as the fluid leaves the container, the bag collapses because it is not vented. Collapse of the bag precludes outside air from entering the container and eliminates the possibility of airborne contamination. In addition, the possibility of air embolism occurring from this collapsible system is reduced; however, the possibility of air embolism is greater when flexible plastic units are connected in a series of containers. Therefore, this type of hook-up is not recommended with plastic bags. Other advantages claimed for plastic packaging include reduction in breakage, economy in space during storage, simplified disposal, and reduction in weight and noise. Diagrammatic illustrations of flexible and semi-rigid plastic containers are shown in Figure 8–16.

The use of convenience devices with the plastic container requires an appliance designed to place a vacuum within the bag. This equipment is available commercially under the name "Viavac" and consists of a plexiglass chamber in which the bag is placed. When vacuum is applied to the chamber, the contents of convenience devices, as well as other forms of medication, can be added. Its use is designed for a centralized intravenous admixture location. Tamper-proof seals are available for the sleeve ports, once medication has been added to the intravenous fluids. When adding other medication to intravenous fluids packaged in plastic, the same precautions must be observed as with other admixtures, with consideration of compatibility and clarity. Provided continued progress is made in using plastics that have been shown to be nonreactive with the solutions, the trend in packaging intravenous fluids in the immediate future is toward the plastic container (Fig. 8–17).

LifeCare System (Abbott)

The introduction of the LifeCare plastic I.V. container system by Abbott Laboratories now makes two flexible plastic I.V. systems available in the United States (Fig. 8–18). LifeCare is similar in many respects to Travenol's Viaflex system. This flexible polyvinylchloride container has a resealable additive port on the upper side of the bag. This position reduces the potential for "welling" of additive medication in the outlet port and possible delivery of an undiluted bolus. It is also claimed to facilitate aseptic technique. Normal syringes or specially designed syringes can be used to inject medication into this port.

Additive caps are available to protect the port after the addition of medication or during transportation, and they also serve as indicators that additives are present. A "Vacu-add" unit can be utilized to create a vacuum in the LifeCare bag to facilitate transfer of additives from small volume parenteral containers.

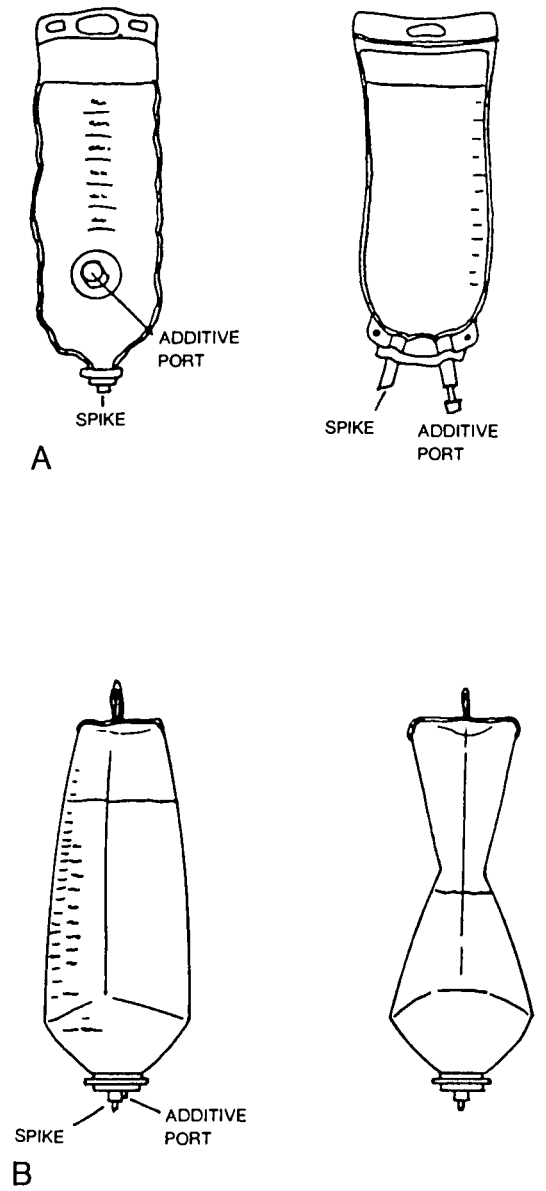


Figure 8–16. *A*, Abbott (LifeCare) and Travenol (Viaflex) supply nonvented polyvinylchloride flexible plastic containers. These containers require nonvented sets. *B*, McGaw (Accumed) offers a nonvented semi-rigid polyolefin plastic container.

Accumed System (McGaw)

Accumed (McGaw) plastic intravenous fluid administration system, utilizes a polyolefin plastic material (Fig. 8–19). This semi-rigid container has no plasticizer. The claim for virtually no extractibility or leachability is made. This plastic is also impermeable to vapor transmission. The system is not dependent on air and is programmed to produce predictable collapsibility and complete disposability. Combustible by-products of this container are water and carbon dioxide.

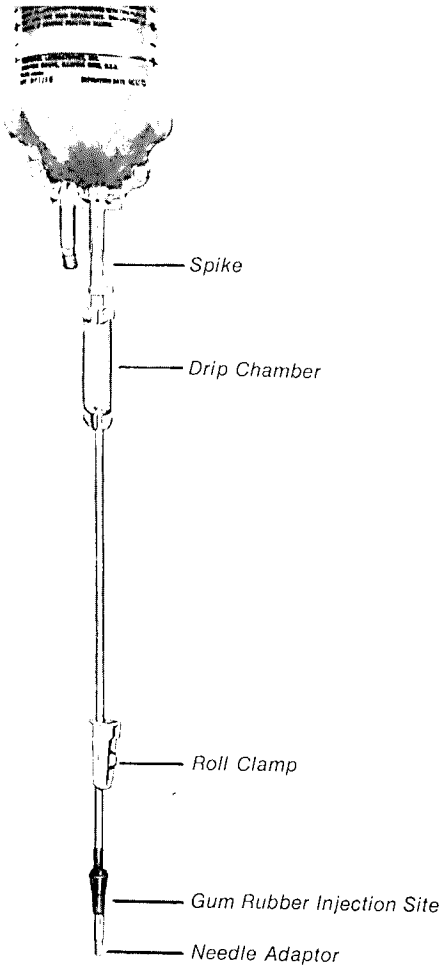


Figure 8–17. Basic intravenous administration set for flexible plastic container. (Courtesy of Travenol Laboratories, Inc. Deerfield, IL.)

Storage of Intravenous Fluids

Attention should be given to the storage conditions for large-volume solutions. Often, the storage of these solutions has low priority in hospitals. Overheated rooms and cold areas should be avoided because they accelerate discoloration, precipitation, and leaching.

In some instances, admixtures prepared several hours or more prior to administration are stored in a refrigerator. Refrigeration retards bacterial growth and drug deterioration. One study has shown that at reasonable administration rates a refrigerated admixture quickly approaches room temperature when the bottle is hung. It has been demonstrated that the incidence of cardiac arrest during massive blood replacement dropped from 58% to 7% when cold banked blood was warmed to body temperature prior to infusion.

Because infusions are packaged in single-use containers and no bacteriostatic agents are added, once they have been violated they should be used as soon as possible.

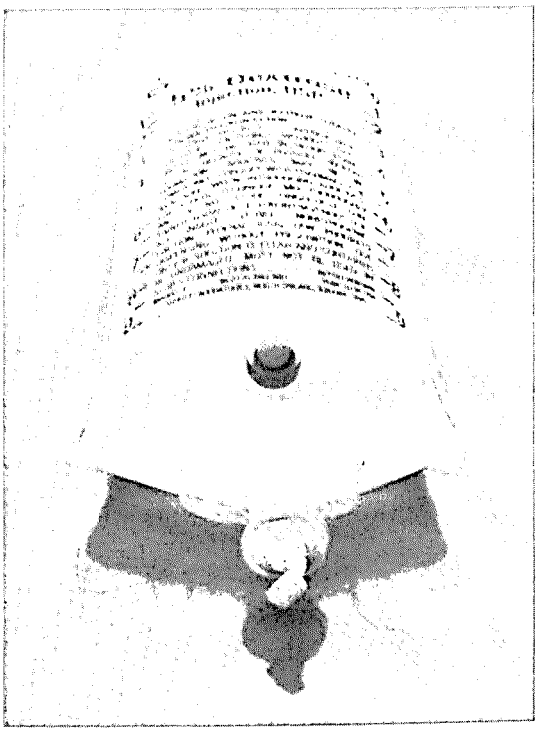


Figure 8–18. Plastic LVP bag. (Courtesy of Abbott Laboratories, North Chicago, IL.)

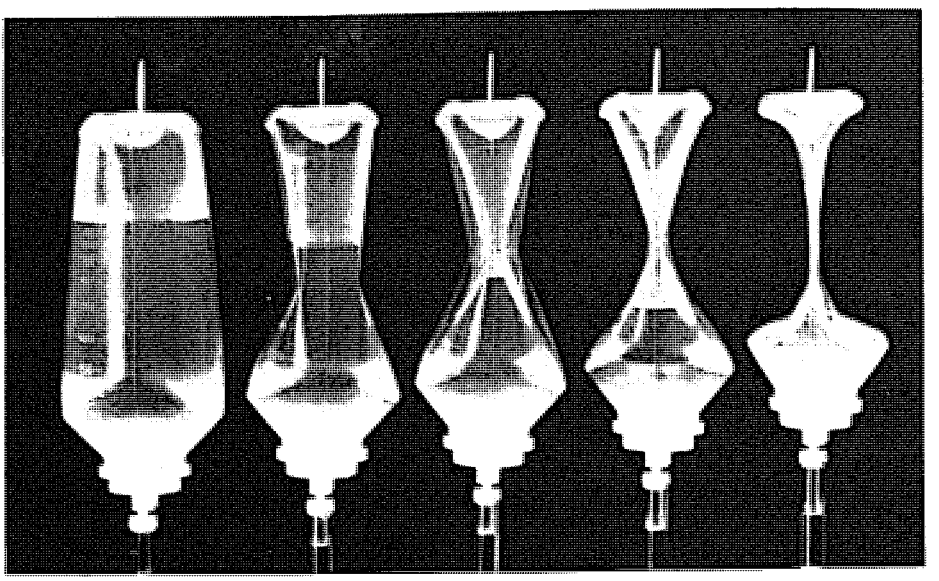


Figure 8–19. Accumed semi-rigid polyolefin containers. (Courtesy of American McGaw, Irvine, CA.)

Manipulated infusion fluids should always be used within 24 hours or be discarded. A more conservative recommendation is that I.V. mixtures be used within 1 hour after mixing, or if not, refrigerated and used within 24 hours. This safeguard minimizes contamination and does not allow sufficient time for incubation, if the solution inadvertently becomes contaminated.

Expiration dating on labels helps to rotate the stock of intravenous fluids in a manner that assures that the material will be used in order of its receipt. In addition, placing a 24-hour expiration date on an infusion that contains an additive lessens problems with stability.

Methods of Intravenous Administration

Drugs can be introduced intravenously in small or large volumes. An intravenous injection refers to a small volume of drug administered intravenously with a needle and syringe. Large volumes of solutions containing drugs given intravenously are administered in a variety of ways. Different methods are used to obtain the desired speed of achieving blood levels of the drug and to minimize the degree of irritation from the drug's administration. House staff availability, in addition to a particular hospital's policy as to what routes and classes of drugs may be administered by a nurse, can influence the methods of drug administration. The desire to achieve constant, prolonged blood levels also affects the mode of administration. The formulation of the injection that influences the manufacturer's recommendation as to the rate of injection is a factor to be considered. Except for Intralipid emulsion, only drugs in aqueous solution are given intravenously.

Drugs may be administered by the continuous or the intermittent technique. According to some authorities, either method of administration will be clinically effective in the majority of cases. Figure 8–20 depicts a "decision tree" for various modes of I.V. administration and lists various drugs and equipment that are to be explained in this chapter.

Continuous Therapy

Intravenous Infusion. A common method of administering drugs is to add the drug directly to an infusion container. The drug becomes diluted in the infusion fluid and is dripped slowly into the vein. This method permits the physician to accomplish fluid therapy and drug therapy simultaneously and achieves continuous, constant blood levels of the drug. In many instances, drug therapy is accomplished initially by intravenous push and then maintained slowly and constantly by intravenous infusion (Figs. 8–21, 8–22). A possible disadvantage of this method of therapy is delayed incompatibility occurring in the infusion container. The drug remains in contact with the vehicle for several hours or longer. If the solution is contaminated during preparation or administration, there is an additional disadvantage in not administering the solution immediately with an intravenous push; the consequences of administering a contaminated product are more severe as the organisms proliferate.

Hook-ups. Hook-ups (Solution Series Set, Baxter; Secondary, Abbott; I.V. Series Set, McGaw) allow fluid to be added or solutions to be changed while the infusion continues (Fig. 8–23). A tube with a clamp is connected to the two containers. The air vent in the primary container is closed, and the air vent in the second container is opened, allowing the second container to empty first.

This type of hook-up has several disadvantages. An unintended increase in flow

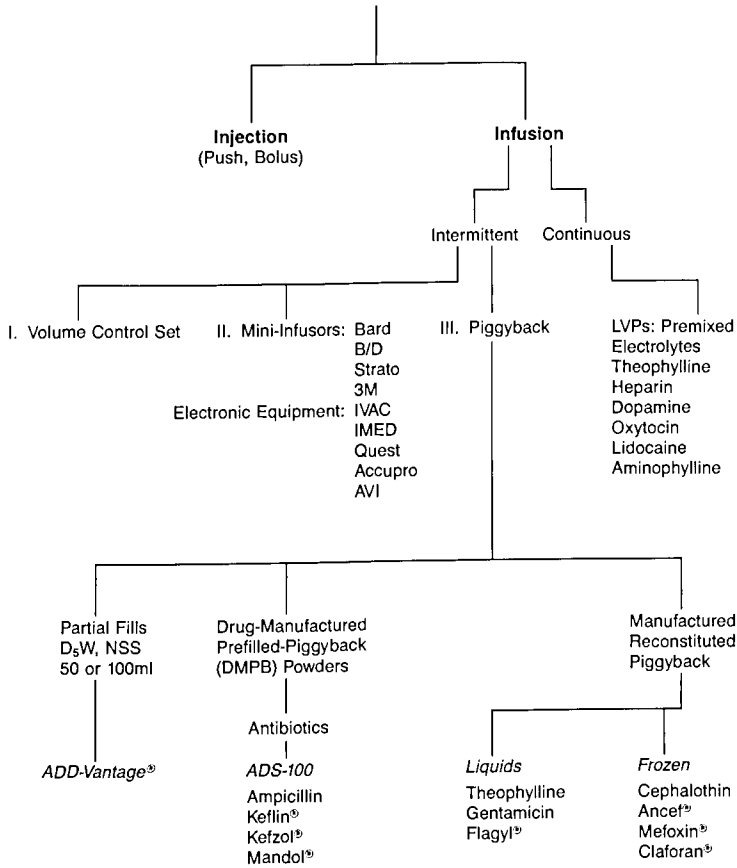


Figure 8–20. Decision tree for various modes of intravenous administration.

if not noticed, will cause a double volume of fluid to be infused, which may produce circulatory overload. Physicians and nurses may have varying opinions as to the order of emptying. A layering effect may take place with solutions and drugs of varying viscosities, which may increase or decrease administration time. This type of I.V. administration should be avoided.

Intermittent Therapy

In intermittent therapy, the drug is given at spaced intervals. Three possibilities for handling intermittent therapy have been suggested: (1) use of a mini-bottle with the already hanging administration set; (2) injection of the solution slowly by needle and syringe directly into a vein or injection site of an already hanging large-volume administration set (true intravenous push); or (3) addition of the drug to a predetermined volume of fluid in a volume-control device.

Piggyback Method. The piggyback method refers to the intermittent intravenous drip of a second solution, the reconstituted drug, through the venipuncture site of an established primary I.V. system (Figs. 8–24, 8–25). With this setup, the drug can be thought of as entering the vein on "top" of the primary I.V. fluid (hence, the designation "piggyback"). The piggyback technique not only eliminates the need for another venipuncture but also achieves drug dilution and peak blood levels within

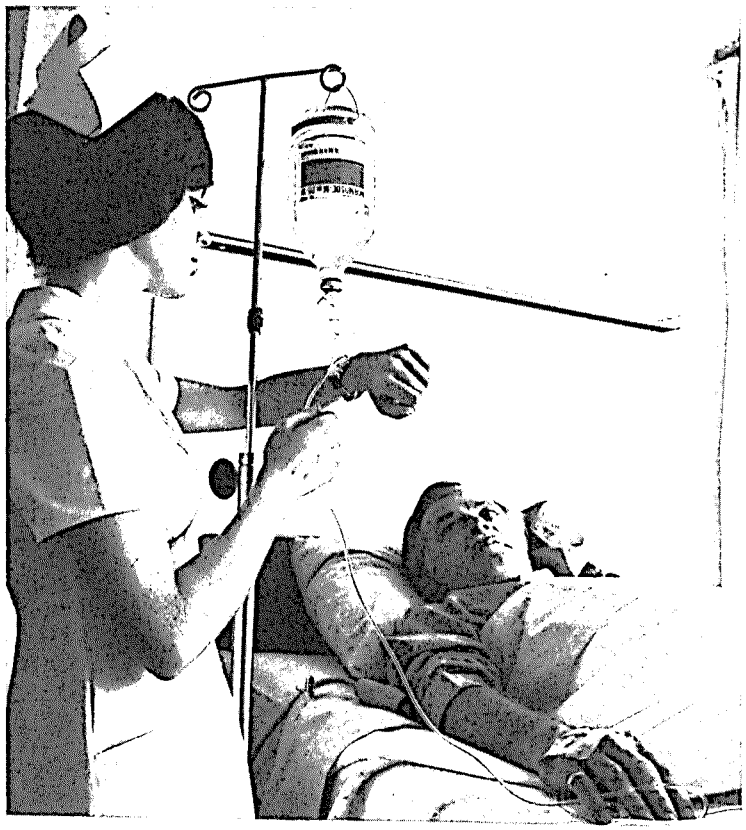


Figure 8–21. Administration of intravenous fluid to obtain continuous flow. (Courtesy of Abbott Laboratories, North Chicago, IL.)

a relatively short time, usually 30 to 60 min. Drug dilution helps to reduce irritation, and early high serum levels are an important consideration in serious infection requiring aggressive drug therapy. These and other advantages have served to popularize the piggyback method of I.V. therapy, especially for the intermittent administration of antibiotics. At present, two possibilities exist for piggybacking.

Piggyback administration may be accomplished with any basic administration set, but the nurse must reestablish flow of the primary fluid after infusion of the piggyback drug solution. Special administration sets can be used; however, they contain pressure-sensitive valves that sense when the piggyback drug container is empty; at that point, the primary flow begins automatically, owing to a height (gravitational pull) difference between the primary fluid and piggyback drug containers (Fig. 8–26). Automatic piggyback administration sets are supplied by Abbott (Automatic Drug Delivery System), McGaw (IV Additive Set), and Travenol (Continu-Flo Set).

Prefilled Partial-Fill Containers (Underfills, Mini-bottles). Commercially supplied partial-fill containers used for piggybacking are 250-ml capacity infusion bottles of bags underfilled with 50 or 100 ml of 5% D/W or normal saline solution. The drug to be administered is first reconstituted in its original parenteral vial and then added by needle and syringe to the "underfill," which receives an administration set complete with needle. The needle of this piggyback delivery system is inserted into the

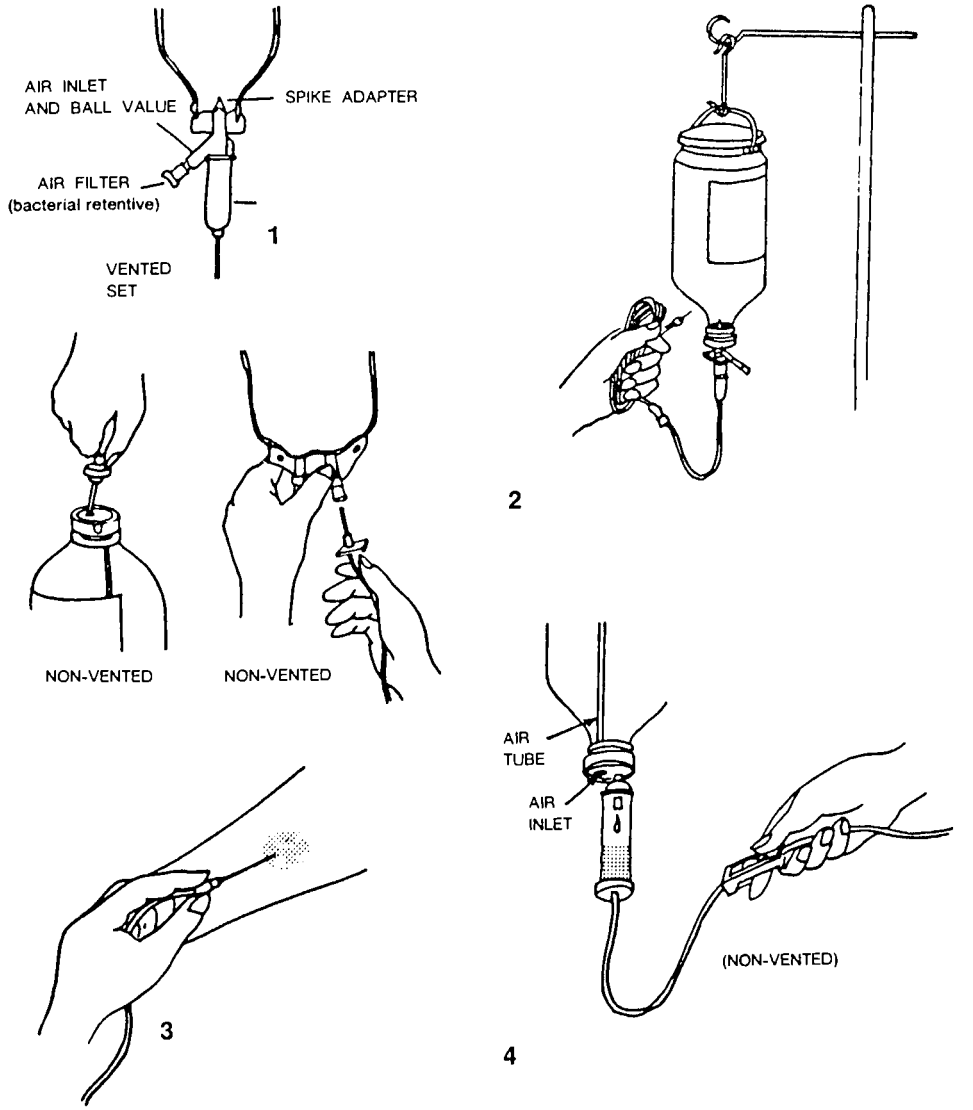


Figure 8–22. Process of starting LVP infusion continuous therapy. *1*, Spike adapter of intravenous set is inserted into stopper of LVP container (bottle or plastic). *2*, LVP container is hung on stand at bedside, and air is purged from the intravenous set by opening clamp until fluid comes out of needle. Set is then clamped off. *3*, Venipuncture is made by intravenous team, or floor nurse. *4*, Infusion rate is adjusted by slowly opening and closing clamp until desired drip rate, viewed in drip chamber, is obtained. The usual running time is 4 to 8 hours. (Usually, 125 ml is delivered in 1 hour.) Set is calculated to deliver 10, 15, 20, 50, or 60 drops per ml, depending on manufacturer.

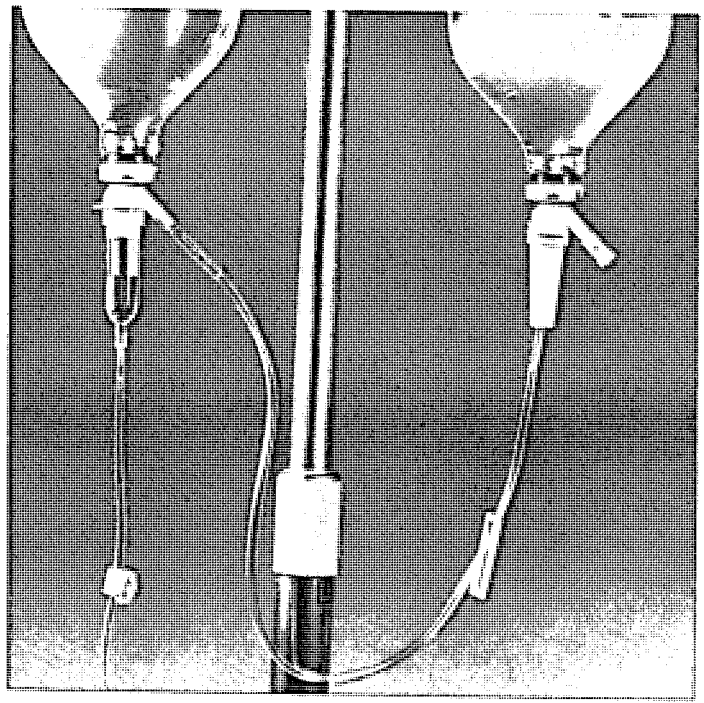


Figure 8–23. Secondary hook-up provides a means of adding more fluid or of changing fluid without interrupting infusion. (Courtesy of Abbott Laboratories, North Chicago, IL.)

Y-site or gum rubber injection port of a hanging primary infusion set. Flow of the primary intravenous fluid is stopped while the drug solution in the partial-fill container is administered (30 to 60 min). After the drug solution has been totally infused, the primary fluid flow is reestablished. When the next dose of drug is required, the piggyback procedure is repeated, replacing the prefilled partial-fill container and, in some cases, its administration set as well.

Prefilled Piggyback Units (Manufactured Prefilled Drug Containers). A more recent innovation by which piggybacking can be accomplished is the piggyback unit, a mini-bottle (100-ml capacity) prefilled with a specific amount of dry drug. Several manufacturers (Beecham, Lilly, Roerig, Smith Kline Corp., Wyeth, Bristol) have already introduced mini-bottles prefilled with various antibiotic products; each manufacturer's container is provided with either a plastic bag or a plastic hanger for direct suspension from an I.V. pole as the piggyback solution is administered through the resealable gum rubber injection site or Y-type facility of an existing I.V. system. Reconstitution of drug in a piggyback unit requires only the addition of a small volume of compatible diluent. Since the drug is reconstituted in and administered from the same bottle, no drug transfer is involved; transfer syringes and additional I.V. containers are not necessary. Prefilled piggyback units, therefore, offer greater ease in handling and considerable reduction in inventory costs than do either prefilled partial-fill containers or volume-control sets, for which prior reconstitution and subsequent transfer of the drug to be administered are essential.

Direct Intravenous Push (Bolus). In direct intravenous push the solution of the drug is placed into a syringe and administered in a short period of time directly into

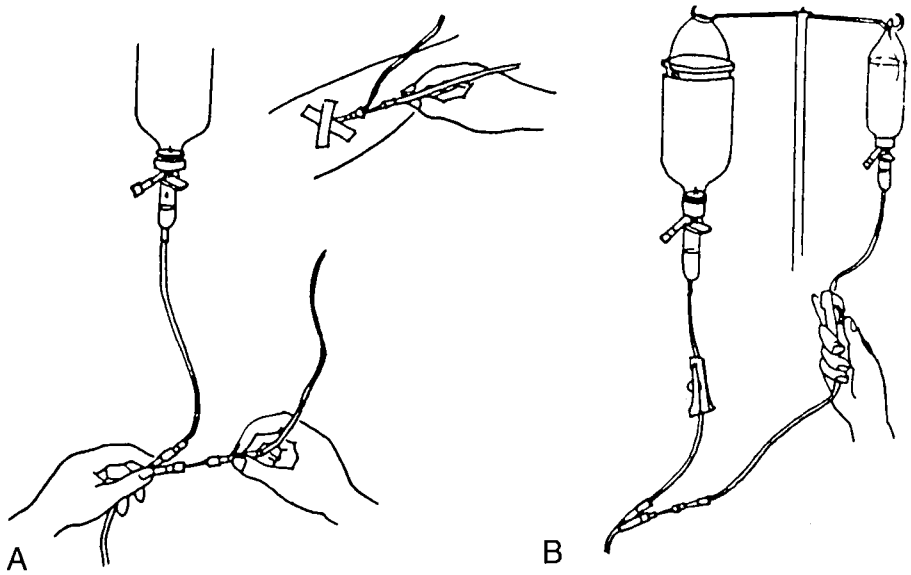


Figure 8–24. Process of starting piggyback infusion. *A*, The secondary set is purged of air, and its needle is inserted into a Y injection site of the primary set, or into the injection site at the end of the primary set. *B*, The piggyback infusion is started. Once it is completed, the primary fluid infusion will be restarted.

a vein (Fig. 8–27), or through the gum rubber injection site of the administration set (Fig. 8–28). The injection time is a matter of minutes and varies with different drugs according to the manufacturer's recommendations. Many drugs given by direct intravenous push are diluted further with the vehicle, using a larger syringe, to reduce the irritability of the drug on the vein. Table 8–3 lists the recommended times for a number of drugs.

The determination of which method and at what speed a drug may be given I.V. is associated with the physicochemical properties of the drug and bioavailability factors. Not all drugs may be pushed I.V. Those drugs that can are usually diluted sufficiently to minimize toxicity. Almost always, drugs pushed I.V. have recommended injection times established by the manufacturer. For example, phenytoin and diazepam injections must be given by I.V. push. When these drugs are diluted and given by other I.V. methods, the instability of the drugs causes precipitation. Therefore, they must be pushed at a specified rate that is slow enough to prevent toxicity. In contrast to phenytoin and diazepam, because of its toxicity, gentamicin may not be given by push, but must be given well diluted (1 mg/ml) and must be administered piggyback or by volume-control method over a period of at least 1 hour to minimize renal and ototoxicity and neuromusuclar blockade. Many drugs can be given I.V. by push or diluted in volume-control or piggyback units. Such is the case with ampicillin; however, direct I.V. push in less than 100 mg/min may cause seizures. The package insert for furosemide has been revised. Ototoxicity[1] is usually seen when the drug is given rapidly by push to patients with renal impairment. This is particularly associated with large doses and often when it is combined with other ototoxic

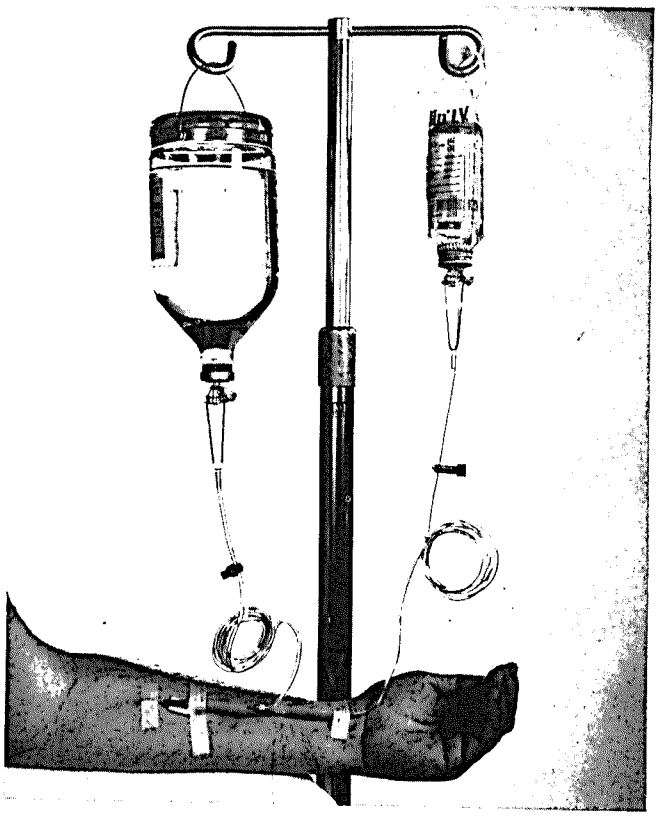


Figure 8–25. Piggyback infusion technique. (Courtesy of Abbott Laboratories, North Chicago, IL.)

drugs. An infusion rate of not more than 4 mg/min is suggested (formerly 10 mg/min).

On occasion, manufacturers suggest I.V. push but may not give definite injection time recommendations. Diazoxide (Hyperstat) is particularly unusual in that it must be pushed I.V. in less than 30 seconds. This is done in order to prevent the drug from becoming inactivated by plasma proteins. One publication[5] suggested administration in 10 seconds. When drugs are given by the I.V. push method, the manufacturers' recommendations must be followed. Grotting et al.[6] published I.V. push rates of cancer chemotherapy drugs. A publication by Rapp et al.,[7] "Guidelines for the Administration of Commonly Used Intravenous Drugs," is also most valuable. The rationale and procedures for intermittent and direct I.V. push were reviewed by Godwin.[8] "How to Develop an I.V. Push Service" was published by Grotting et al.[9] A manual for the preparation and administration of drugs for I.V. is available through the Canadian Society of Hospital Pharmacists.[10]

Volume-Control Sets. Volume-control sets (Metriset, McGaw; Soluset, Abbott; Buretrol, Baxter) are calibrated plastic fluid chambers used as measuring devices in conjunction with intravenous bottles (Figs. 8–29, 8–30). These devices permit administration of drug solutions in precise quantities. Drugs in solution are added directly through the gum rubber injection port or the volume-control unit into a predetermined volume of fluid from the primary intravenous fluid. Four reasons have been

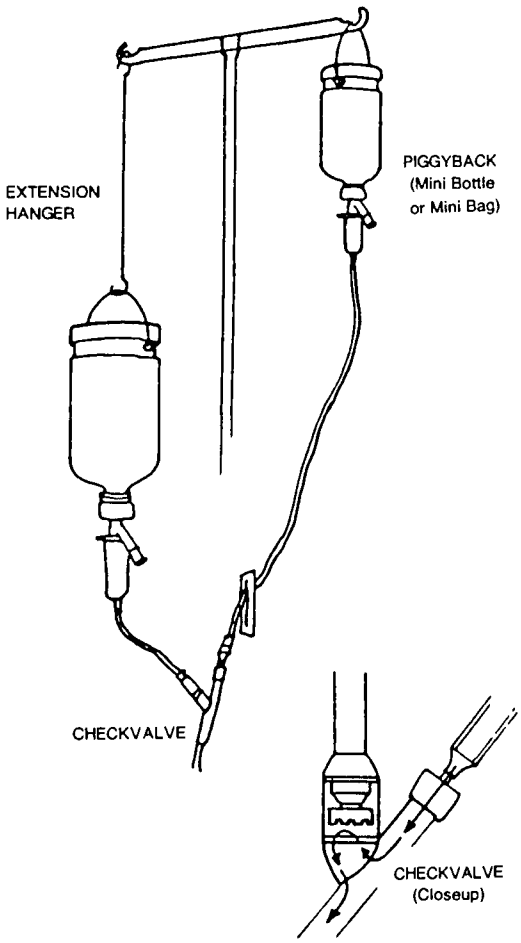


Figure 8–26. Automatic piggyback set with built-in checkvalve.

suggested for using a volume-control set: (1) the chamber provides a means for critical measurement of infused fluid; (2) the chamber provides a vehicle for intermittent intravenous medication therapy, as opposed to continuous therapy; (3) unstable drugs may be administered quickly in a minimum volume of fluid; and (4) the chamber limits the volume of fluid that may be infused accidentally. Many potential problems exist with these devices because of their misuse, overuse, and abuse in hospitals.

Volume-Control Sets Versus Piggyback Method. The previously discussed disadvantages of volume-control sets and the microbiologic hazards (i.e., nosocomial infections as a result of bacterial colonization) associated with these devices have been repeatedly documented by numerous investigators.[11-13] The National Coordinating Committee on Large Volume Parenterals (NCCLVP) states that "volume-control sets (Buretrol, Soluset, Volu-trol) should not be used for the routine administration of intermittent drug therapy in adults." The same NCCLVP panel "does not recommend volume-control sets as devices for injections of intermittent IV medication ... (but) does recommend the use of partially-filled bags or bottles for this."

Prefilled partial-fill containers have many advantages over volume-control sets: Underfills are easier and faster to use, so nurses can better meet the demands of crowded work schedules; they are properly labeled for one-time unit-dose use only,

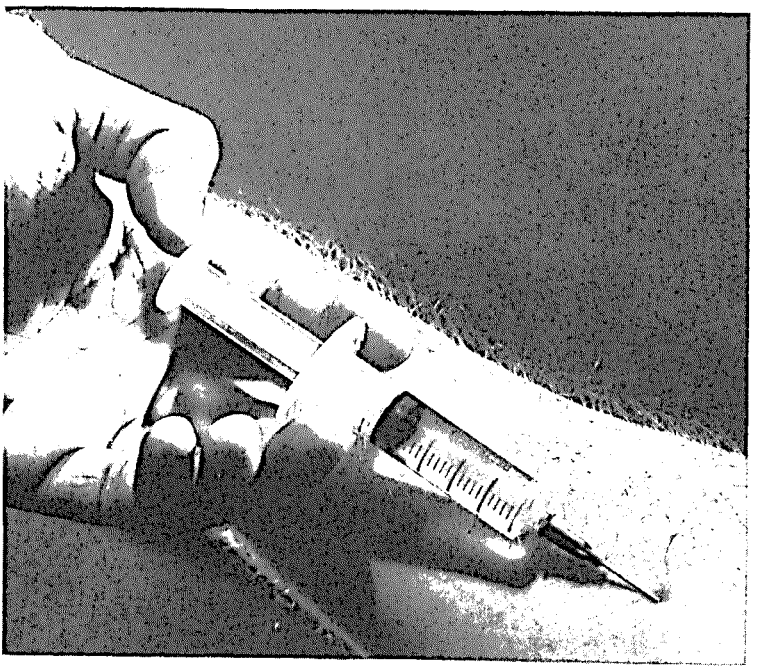


Figure 8–27. Direct intravenous push administered directly into vein. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

lessening the chances of medication error, admixture incompatibility, and solution contamination; and they foster use of the proper diluent in the right amount.

All the aforementioned features apply equally well to prefilled piggyback units, which provide even greater convenience, economy, and patient safety in I.V. therapy than partial-fill containers. In obviating the need for transfer of reconstituted drug, easy-to-use piggyback units improve the quality of patient care through reduced potential for solution contamination. Self-contained reconstitution and administration capabilities also eliminate expenditure for parenteral drug vials, transfer syringes, and the more costly partial-fill containers; this reduced inventory with proven dollar savings in turn releases shelf storage needed for other purposes. In short, prefilled piggyback units truly represent a new dimension in unit dose; that is, a unique, sophisticated packaging for direct administration of drug.

Flow Rates of Intravenous Infusion Fluids

The rate of flow of intravenous fluids is determined by the prescribing physician whose judgment is based on a variety of factors, such as the patient's body surface area and age, and the composition of the fluid to be administered. The rate of administration and total volume are often limited by the patient's ability to assimilate the fluid. Patients with congestive heart failure or pulmonary difficulties can react adversely to infusion fluids. Extreme caution is exercised when administering fluids to patients with any degree of renal impairment.

The physician may want rapid or slow infusion, depending on his objective. He may want fluids, or perhaps his interest is in administering electrolytes. His primary interest may be in the administration of a drug and not necessarily with fluids. The

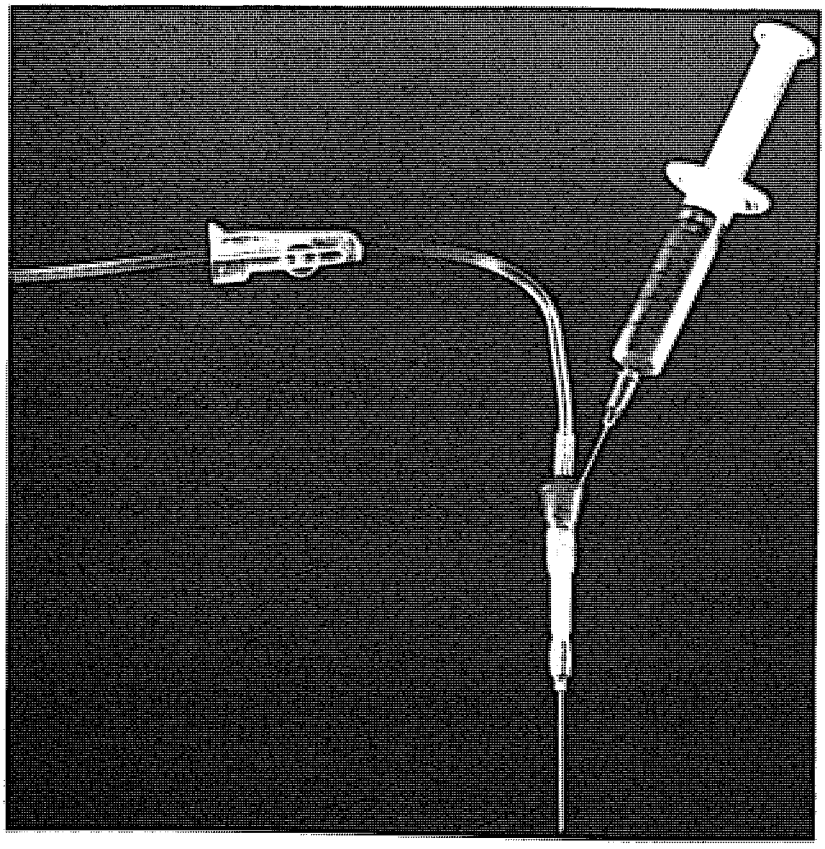


Figure 8–28. Direct intravenous push administered through gum rubber injection site of administration set. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

usual or normal flow rate of low-viscosity isotonic solutions (5% D/W, normal saline, Ringer's lactate) is approximately 125 ml/hour or 1 L every 8 hours. This amounts to 2 ml/min. Highly hypertonic solutions such as hyperalimentation solutions are administered at a rate not exceeding 1 L every 8 hours or 3 L every 24 hours. Only in exceptional cases (blood loss, shock, or administration of anesthesia) would the rate be in excess of 1 L every 1½ hours. This amounts to 11 ml/min. Often, orders are written as "KVO" (keep vein open), in which case, the rate of administration would be slow. The objective is to keep the intravenous fluid running in anticipation of future therapy. Gravity-fed intravenous flow rates below 10 ml/hour reduce pres-

TABLE 8–3. Recommended Push Times for Certain Drugs

Injection	Concentration	Time
Valium	5 mg/ml	Not less 3 mg/min
Keflin	100 mg/ml	Not less 200 mg/min
Ancef	100 mg/ml	Not less 200 mg/min
Aminophylline	500 mg/20 ml	Slowly
Dilantin	50 mg/ml	Not less 1 minute
Hyperstat	15 mg/ml	Within 10–30 seconds

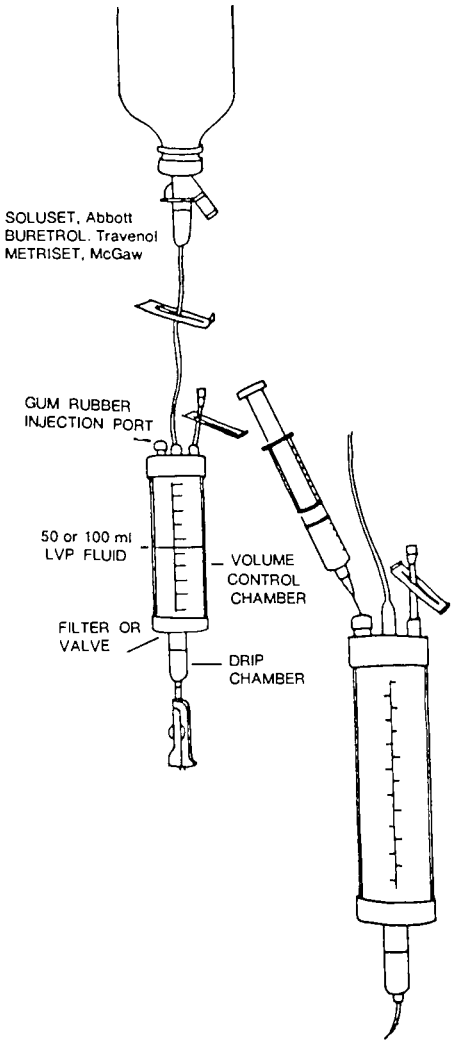


Figure 8–29. Intermittent infusion system for antibiotics and other drugs.

sure to the point at which blood will regurgitate through the needle and tubing, and a clot may form. When solutions are administered too rapidly, speed shock occurs. Side reactions caused by rapid infusion vary with the drug. Nomograms are used to calculate body surface area (Fig. 8–31).

The physician, having decided on the volume to be administered, may prescribe his order in one of several ways: (1) 1000 ml every 8 hours, (2) 1000 ml at 50 ml/hour, (3) 30 drops (gt)/min, or (4) KVO with 5 D/W.

Gravity Flow

To administer fluids from an intravenous container by gravity, the container must be supported above the patient in order for the solution to flow. The inverted container with the administration set in place is hung approximately 1 meter above the patient. Flow will not begin until the pinch clamp is opened and air is allowed to enter the container. For a plastic infusion container, however, air is not required in order for the solution to flow. As the solution leaves the container, it drops into a drip chamber (sight chamber). By collecting in this chamber, the solution can flow

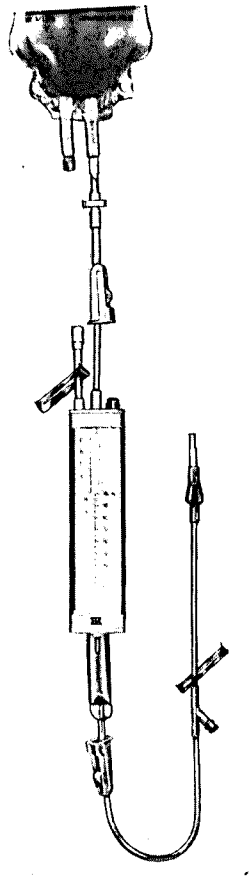


Figure 8–30. Buretrol volume-control set permits the administration of intravenous fluids in limited amounts and precise volumes. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

without allowing air to enter the length of administration tubing. The rate can be adjusted by counting the drops that enter the drip chamber. The clamp on the tubing is then adjusted to regulate flow (Fig. 8–32).

To determine the rate of flow requested, one must know the number of drops per milliliter delivered by the administration set being used; this varies with the commercial source. For example, if a set delivers 10 drops/ml and 1000 ml are to be infused over 480 minutes, then 1000 ml ÷ 480 = 2.08 ml/min × 10 gtt/ml = 20.8 gtt = 21 gtt/min. If 50 ml/hour are to be infused, 0.83 ml/min × 10 = 8.3 gtt = 8 gtt/min. All manufacturers of intravenous fluids distribute calculators and charts for determining rates of flow (Fig. 8–33).

A needle is attached to the needle adaptor and the administration set is cleared of air by allowing the solution to fill the tubing. The clamp is closed and the venipuncture is made. The desired rate is now regulated. When stainless steel cannulas are used for intravenous administration, an 18- to 21-gauge, 1½-in. needle is commonly used. Smaller scalp-vein needles are being used with increasing frequency, as are plastic needles.

Positive Pressure

The majority of infusion fluids are administered by the gravity method. Medical emergencies do arise, presenting situations in which fluids must be administered

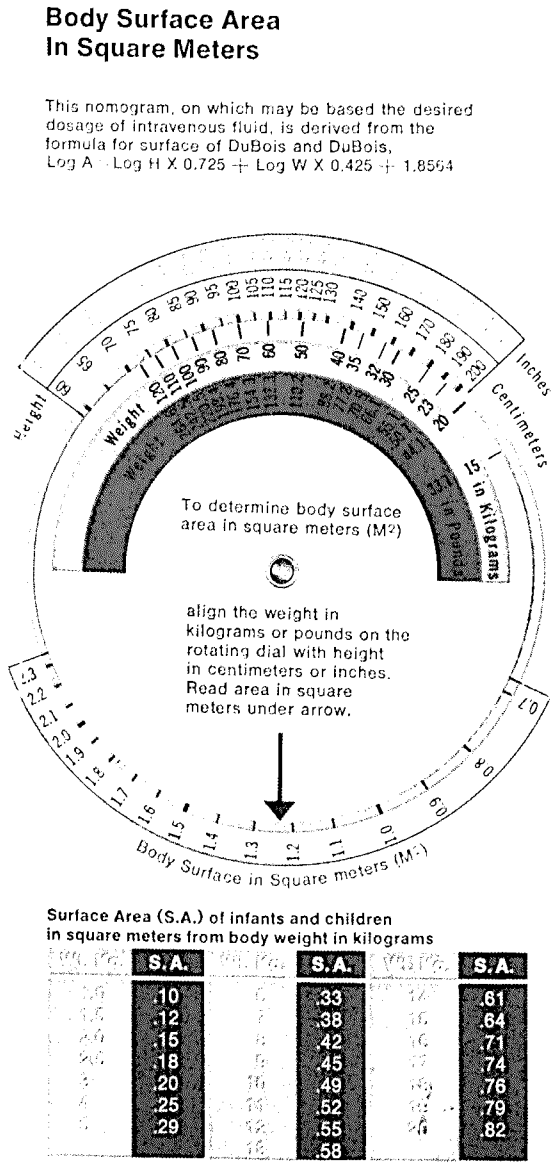


Figure 8–31. Nomogram used to calculate body surface area. (Courtesy of Abbott Laboratories, North Chicago, IL.)

rapidly. For example, rapid infusion of blood is necessary in hemorrhage. Positive pressure administration sets that enable external pressure to be applied for rapid administration are available (Fig. 8–34).

Inaccuracies in Intravenous Flow Rates

Intravenous systems and administration sets are not precision devices. Fortunately, precision is not always required in the administration of I.V. fluids. When accurate and precise flow rates are required, however, other methods must be followed (see Pumps and Controllers, p. 158).

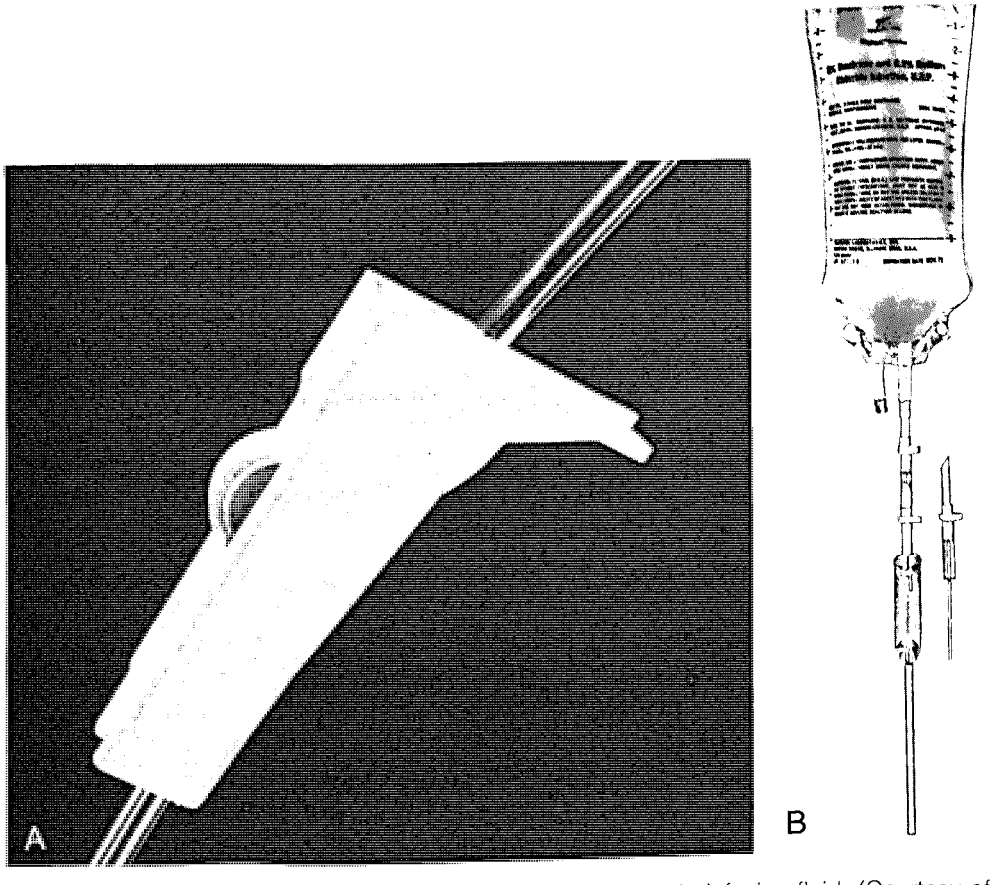


Figure 8–32. *A*, Abbott Cair Clamp used to regulate flow in infusion fluid. (Courtesy of Abbott Laboratories, North Chicago, IL.) *B*, Administration set adapter for reducing drop size to $\frac{1}{50}$ ml inserted into drip chamber of administration set. Set delivers 50 drops per ml, enabling the patient to receive a slow infusion. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

Accurate infusion rates ensure patient safety and drug efficiency. Inaccurate rates are contrary to rational drug therapy and can lead to delayed or toxic response in the patient, increased risk of phlebitis and thrombophlebitis, pulmonary edema, speed shock, and metabolic problems.

Gravity-flow I.V. systems are affected by the following factors, which may alter the flow during administration:

Volume.[14,15] Flow rate problems begin immediately upon arrival of the I.V. bottle into the hospital: (1) The liter container has, as a minimum, a recommended excess of 2 to 3%; (2) additives may be used at least 50% of the time. In the case of hyperalimentation, these additives may account for an additional 50 ml or more. Most often, these excesses in volume are not considered when flow rate calculations are made.

Variations in Size of Drip Chamber Orifice.[16,17] To be consistent and reproductive in flow, the orifices of the different drip chambers must be identical. Mass-produced

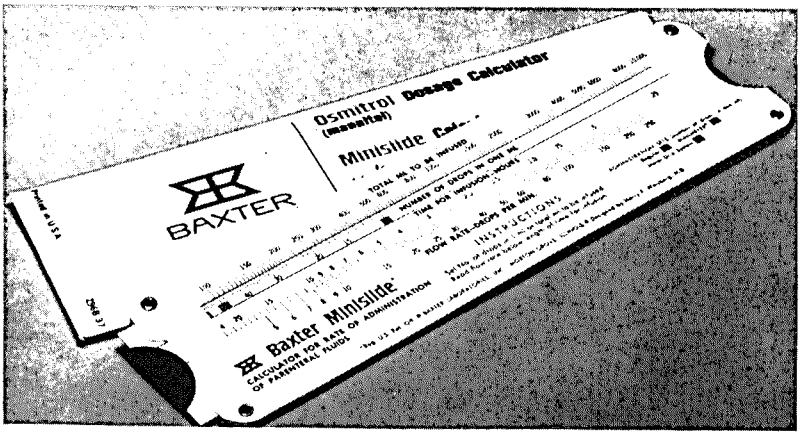


Figure 8–33. Calculator for determining rate of flow for a given volume of fluid over a set period of time. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

administration sets are not precision instruments; therefore, some variances can be expected in flow.

Viscosity of Solution.[18,19] When a manufacturer states that an administration set delivers a specified number of drops per milliliter, viscosities of the various solutions have not been considered. The sets are calibrated for distilled water.

Twenty drops of 5% D/W will not deliver into a patient's vein the same volume as 20 drops of hyperalimentation solution. The viscosity of the solution will affect the size of the drop (and hence the volume) as it forms and leaves the orifice of the drip chamber. For example, parenteral hyperalimentation solutions have a greater specific gravity and form smaller sized drops than do other I.V. solutions.

Plastic (Cold Flow).[18–20] Adjusting the rate of flow with a screw or roller clamp causes distortion of the plastic tubing. The nurse, leaving the administration set after flow rate is adjusted, has only to return in minutes to find the adjustment off 100% owing to changes in the bore diameter of the plastic tubing (cold flow).

Fonkalsrud et al. reported on the design of a new clamp.[20] In this study, the decrease in flow rate over the first hour was over 50%; whereas, the newly designed clamp (ARDL), a roller-type clamp, allows the tubing to be compressed at the edges. Thus, the area of tubing through which the fluid flows is under less stress. This clamp is patented by Abbott Laboratories under the name of CAIR (constant accurate infusion rate) clamp. A number of publications suggest that Silastic tubing may cause a lesser degree of error.[19]

Slipping of Clamps. To some small degree, the possibility exists for the force of gravity to reposition a set clamp. The result of the pull of gravity, of course, affects the rate of flow, and can result in a runaway I.V. injection.

Final Filters.[21] The use of final filters in the I.V. system may cause flow rates to decrease or even cease, depending on the degree of particulate matter blocking the filter surface.

Patient's Blood Pressure and Movements.[22] One study has shown clearly that body movements and blood pressure during I.V. therapy can affect the rate of flow.

Extravasation. Infiltration causes a decrease in flow rate because of the increased resistance to flow of the subcutaneous tissue.

Movement of Patient for Diagnostic Test. Often flow is interrupted by non-nursing

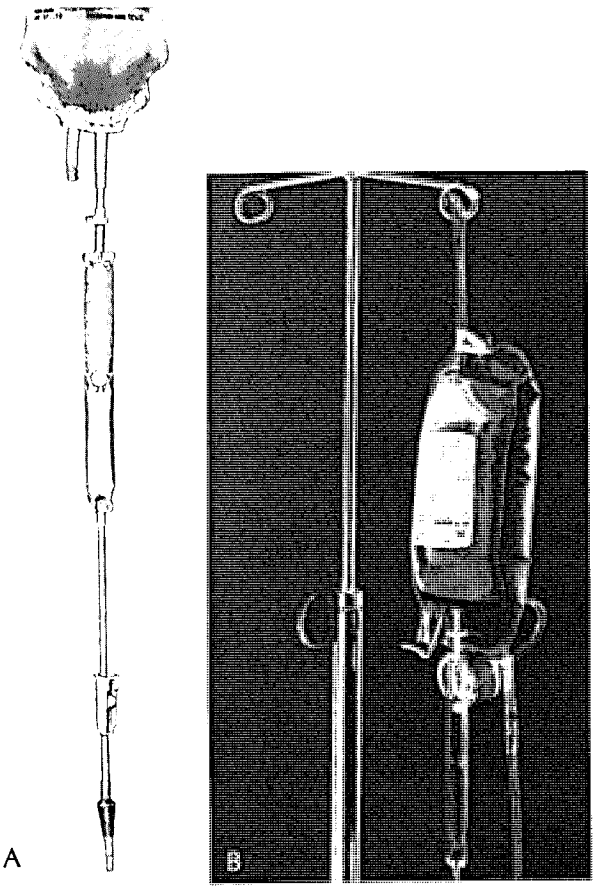


Figure 8–34. *A*, Positive pressure set permits fluids to run by gravity with a pressure unit available for rapid infusion should an emergency arise. *B*, Blood cuff with external pressure provides rapid infusion of blood. (Courtesy of Travenol Laboratories, Inc., Deerfield, IL.)

personnel, or changed when patients are subjected to testing. Frequently, the established flow rate is not readjusted to the pretest rate. Additionally, when patients are transported, the solution container should be maintained at the same height, or the speed of the solution should be readjusted to the prescribed rate of flow.

Height of I.V. Container. I.V. fluids flow because of gravity. Any change in gravity caused by raising or lowering the container alters the rate of flow. Once the rate has been established, changes in the height of the container in relation to the patient will alter fluid flow.

Clot Formation.[18] Clot formation in the lumen of the cannula may alter or completely stop flow. Clot formation may occur when increased venous pressure results from blood pressure cuffs or restraints above the needle.

Kinked Tubing. Flow may be interrupted by patients lying on tubing. Complete blockage may occur if tubing is completely kinked. An innovation used to prevent kinked tubing of venipuncture sets has been developed.

Pressure Changes in I.V. Container.[18,20] As fluid is administered to the patient,

pressures within the container change. This changing head pressure causes changes in rates in flow.

Rate of Flow.[16,23] An increase in drop rate results in the formation of larger drops. Rapid rates mean drop size can increase as much as 25%.

Obstructed vents and airway tubes on I.V. fluid can alter flow.

Shunting in the drip chamber[18,24] may cause drops to flow down the side of the drip chamber instead of dripping clearly.

Changes in needle position[25] may push the bevel of the needle against or away from wall of vein.

Temperature and Nature of Solutions.[25] Stimulation of vasoconstriction resulting from cold (blood) or irritating solutions may cause venous spasm with resultant changes in flow.

Trauma to Vein.[25] Injuries such as phlebitis or thrombosis reduce the lumen of the vein and decrease flow.

Y-sets and Multiple Solutions.[25] The rates should be reestablished when the patient receives two solutions simultaneously.

Demoruelle et al.,[26] in an extensive study of administration set flow rates, showed a percent change in flow rate at the end of the first hour of flow for 7 different sets to have a range of − 63.1% to a + 50.5%. They suggested that the United States Pharmacopeial Convention establish standards for administration sets:

1. The average volume of fluid delivered should be within ± 10% of the theoretical volume.
2. The maximum number of flow rate adjustments necessary in 24 hours should be 10.
3. The maximum change in flow rate at the end of the first hour of operation should be ±33%.

Pumps and Controllers. Several manufacturers have developed pumps and controllers. When accurate constant flow rate is critical, as for hyperalimentation solutions, pediatric therapy, or special drug therapy, mechanical devices are essential. The extensive use of infusion pumps in one hospital has been reported.[27] Several excellent evaluations of pumps have also been published.[28,29]

Manufacturers of I.V. systems have redesigned clamps and explored the development of more precise flow devices in an effort to achieve greater accuracy and efficiency in I.V. flow rates.

Flow Control in I.V. Therapy

Administration Sets

Currently, about 160 million I.V. administration sets are used to administer about 400 million I.V. fluids. They are *sterile, pyrogen-free,* relatively *inexpensive,* and basically simple to use. Their major drawback is lack of accuracy. With most I.V. fluid administration, some degree of error can be tolerated; however, when *accuracy* is required in I.V. administration such as TPN, drug therapy, and pediatric therapy, other methods must be considered. With *intra-arterial* therapy, methods other than gravity must be used.

Who Needs Control I.V. Flow?

Accurate infusion rates ensure patient safety and optimum drug efficacy; they promote physician compliance and conformance and ensure the desired drug

sponse. Inaccurate rates are contrary to rational drug therapy and fail to comply with the physician's treatment. Inaccurate flow rates can

1. lead to delayed or toxic patient response to drug therapy or I.V. therapy,
2. increase the possibility of phlebitis and thrombophlebitis,
3. complicate infiltrations,
4. cause pulmonary edema, which may lead to impaired renal and cardiac function,
5. cause speed shock,
6. create metabolic problems.

One of the primary functions of an I.V. therapist is to *maintain constant accurate flow rate.* This is a difficult order when one considers the problems confronted by the nurse. The demands of the work load from physicians, patients, and administration, and of laboratory, dietary, and other clinical activities make it difficult to meet the above requirement. Above all, the nurse can be defeated from the very start by the myriad of mechanical and physical problems associated with current I.V. delivery systems, which have already been discussed.

Although a variety of infusion pumps and controllers are used in hospitals across the country, only a limited number of publications attest to their desirability. This is understandable considering their recent appearance in hospitals. The use of pumps with heparin,[30–32] parenteral hyperalimentation,[33–36] lidocaine,[37] and oxytocin[38] has been reported. Their use with hyperalimentation of the newborn[39] and in aircraft[40] has also been reported. Several publications[41–43] reported on the use of I.V. controllers, and one publication[44] described the utility of pumps in reducing the volume of fluid infused. Several excellent evaluations[45,46] of various pumps have been published, including one[47] concerning inspection and preventive maintenance of infusion pumps.

Pumps

Turco[48] stated "Disadvantages of pumps are extra cost and personnel training required for their use, in addition to bedside clutter and electrical hazards." Kopezynski[40] commented "consequently a simple form of treatment such as I.V. infusion is apparently to be made more complicated for the medical crew member with the introduction of a new form of equipment. This problem cannot be avoided; however, it is not serious enough to prevent acceptance of this device." Martinez[39] found pumps satisfactory when used for parenteral hyperalimentation of the newborn; however, when used in adults for whom less nursing care was available, the lack of consistency and accuracy and the absence of safety features created many problems. Some of these problems, such as air embolism despite the use of filters, I.V. solution bags running dry, and clotted catheters, were catastrophic. Monahan and Webb[44] suggest that with the use of pumps infiltration can be more serious than the gravity flow system, i.e., the hazard of air emboli is more significant. In a survey,[49] users of infusion pumps reported a variety of problems including "inaccurate flow rate and volume delivered, nonconstant flow rate, a lag time between change of setting and change of drop rate, inadequate alarms, complexity of operation, placing tubing in wrong way, possibility of contamination with use of syringe pumps, air in cassette of a small piston pump, possible damage to blood being pumped, possible overload of fluid if device fails, required use of special tubing, possible damage to tubing if the pump head is dirty, patients may 'play with the pumps,' change the settings, and turn off the alarms and others." Emergency Care Research Institute (ECRI)[50]

reported on one type of pump and the electrical hazard it presented if not grounded properly. Electrical hazards can also be present with the use of electrosurgical equipment.[51] ECRI[52] reported on the potential shock hazard associated with a battery charger of one pump. Bubble formation in a roller type pump has been reported;[53] the source of air was the pumping element material. Insertion of Luer connectors into pump chambers[54] has precipitated rupture. Croke et al.[55] reported on pseudoarrhythmia as a result of a defective infusion pump and ECG monitor; a defective pump connecting pin caused artifact. ECRI set an error limit of 10% for delivery of fluid to the critically ill; however, in several studies[45,46] of 9 infusion pumps, 6 had an error rate of greater than 10%.

Many of the problems or potential problems in pump technology were resolved by the manufacturer as they were reported.

ECRI[45,46] has evaluated infusion pumps in their application to hyperalimentation and listed 26 factors of performance and safety criteria.

Robinson et al.[56] reviewed a pharmacy-based infusion pump program and outlined plans for use, quality control, selection, economic justification, and revenue generation. An excellent review[57] of I.V. pumps described a nurse's viewpoint of the various pumps available.

Rapp et al.[58] reported on the cost savings and safety of electronic infusion control. Emergency Care Research Institute completed an in-depth evaluation of infusion controllers.[59] Kelly et al.[60] attempted to classify electronic controllers and pumps according to the type of drug used and the clinical condition of the patient. This paper presented a logical method for instrument selection. A recently published sourcebook[61] on control-drug delivery presents the potential complications and problems associated with electronic equipment as well as the proper use and selection of the equipment in hospitals. An annual buyers guide[62] of pumps and controllers has been published; which illustrates all those available and their specifications.

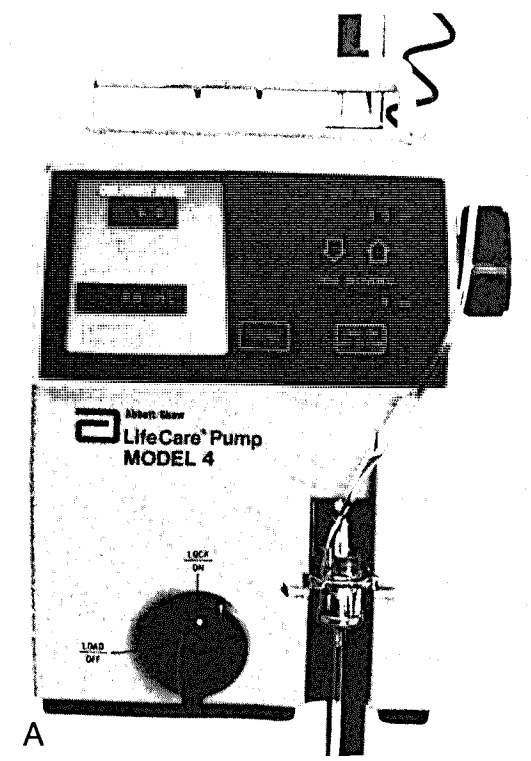
We have seen a proliferation of pump devices for the general administration of I.V. fluids (Fig. 8–35). Although pumps have been available for many years for intra-arterial pressure infusions, we are led to believe that they should also be used for general I.V. use. Eliminating the consideration of pumps for pressure infusions where they are an absolute necessity, the major claim for them is a greater degree of accuracy (most manufacturers claim accuracy ± 2%). This degree of accuracy, however, has been questioned. Other advantages claimed by some pump manufacturers are savings of nurses' time and the detection of infiltrations or occlusions and air.

In general, two pumping mechanisms are employed: piston-cylinder and peristaltic.

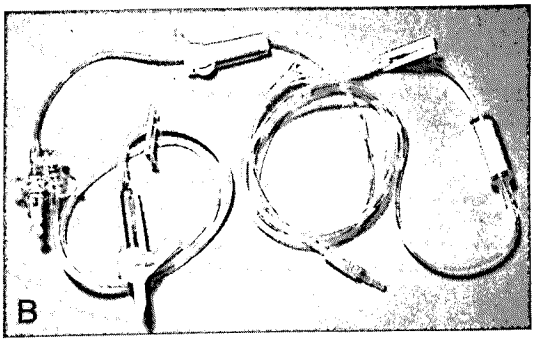
1. Piston-Cylinder. Movement of a piston in a cylinder produces a pressure sufficient to expel the fluid contents of the cylinder. Moving diaphragm pumps are also included here. The terms "syringe pump" and "volumetric pump" are often used to describe devices having this pumping action.

2. Peristaltic. Movement of the wall of the pumping chamber as a result of an externally applied force produces a pressure sufficient to expel fluid contents of the pumping chamber. The lumen of the tubular pumping chamber is totally or nearly totally occluded by the external force; as the point of occlusion moves along the tube, the fluid is propelled by the resultant increases of pressure.

The peristaltic pumping mechanism can be further classified in two subdivisions: *rotary* and *linear.* In rotary peristaltic pumping, the tubular pumping chamber is arranged in a somewhat semicircular shape and the point of contact, usually provided



A



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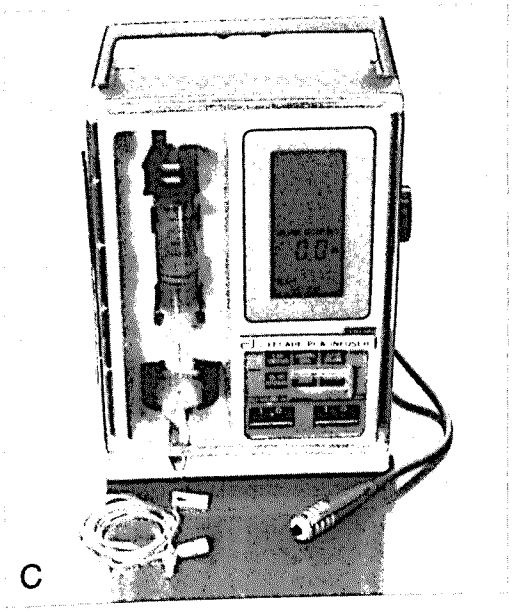

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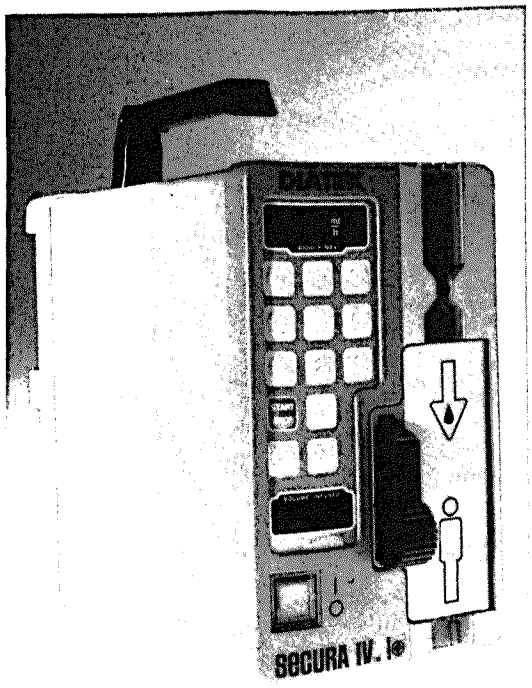

D

Figure 8–35. Infusion pumps. *A*, Abbott/Shaw LifeCare Model 4 pump. *B*, Administration set for Abbott/Shaw LifeCare Model 4 pump. *C*, Diatek Secura I.V. pump. *D*, Abbott LifeCare PCA Infuser (patient control analgesic pump). *E*, Cormed Ambulatory Infusion Pump. (A, B, D, Courtesy of Abbott Laboratories, North Chicago, IL. *C*, Courtesy of Diatek Corporation, San Diego, CA.

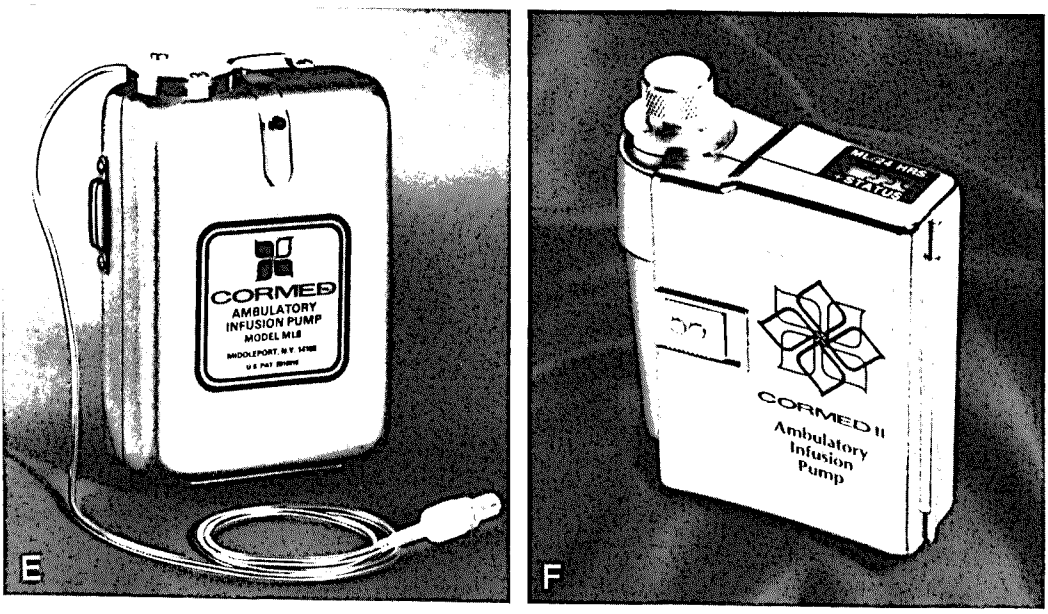

Figure 8–35. *E, F,* Courtesy of Cormed Inc., Medina, NY.)

by a roller, moves around the semicircular pumping chamber, making contact with the chamber at the beginning of the semicircle and breaking contact at the opposite end, thus propelling fluid through the pumping chamber. In some rotary peristaltic pumps, the lumen of the pumping chamber is occluded by forcing the tubing against a stationary, semicircular backing plate. In other designs, the lumen is occluded by forcing the roller against one side of the tubing and allowing tension in the tubing to provide the resistance necessary to allow occlusion. In linear peristaltic pumping, the tubular pumping chamber is straight and the point of contact moves along the pumping chamber. Most of these pumps have a row of "fingers," which sequentially press the tubing against a stationary backing plate; thus, a wave-like motion of the wall propels fluid through the pumping chamber.

Controllers

Many individuals are not able to differentiate between pump devices and controllers. Controllers work on the concept of gravity and exert no pressure; they count drops electrically or extrude volumes of fluid mechanically and electronically (Fig. 8–36). They are less complex than pump devices and usually less expensive. They have no *moving components*, which could mean fewer maintenance problems. They are generally less sophisticated, but they achieve ± 2% drop rate accuracy (as stated by the manufacturer) in a gravity-type I.V. flow. They present difficulty with the administration of viscous solutions such as blood or oral alimentation. With one company, IVAC, any standard administration set can be used; the Burron Epic requires a special set that contains a chamber housing a ball bearing that electronically and magnetically determines the movement of the ball. It would seem logical that controllers that cost less, require less training, have fewer problems mechanically, and achieve reasonable accuracy (± 2% drop rate as stated by manufacturer's bro-

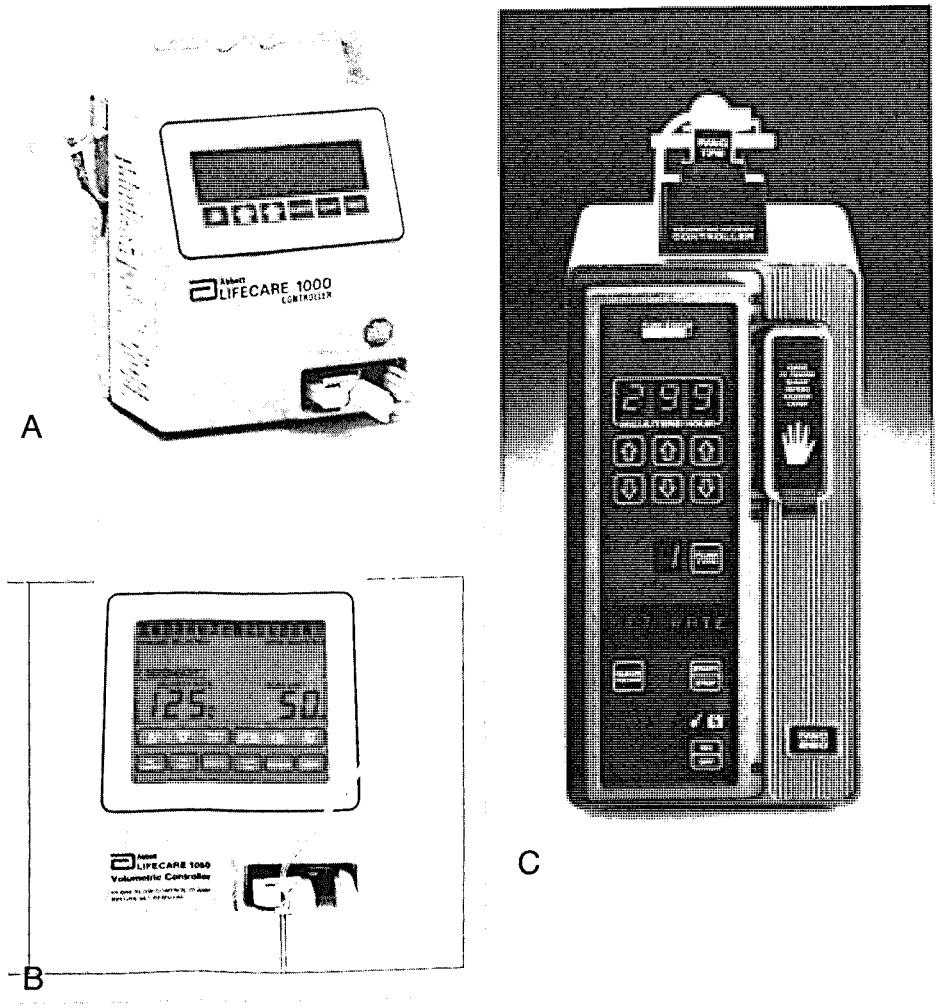

Figure 8–36. Controllers. *A*, Abbott LifeCare 1000 Controller. *B*, Abbott LifeCare 1050 Volumetric Controller. *C*, IVAC 260 Volumetric Infusion Controller. (*A*, *B*, Courtesy of Abbott Laboratories, North Chicago, IL. *C*, Courtesy of IVAC Corporation, San Diego, CA.)

chure) be the device of choice. This could be the case with uncomplicated therapy when some degree of inaccuracy can be tolerated with minimal safeguards.

Requirements of Ideal Pumps and Controllers

These devices should be

1. Mechanically sound.
2. Mechanically reliable. Flow rate should be accurate within ± 10%, repeatable, and constant.
3. Of a maximum output pressure that will not damage injection site or cause extravasation.
4. Equipped with battery option when power failures occur.
5. Compact.

Table 8–4. Some Currently Marketed Drug Pumps and Controllers

Device/Manufacturer	Model No./Name	Operation Principle
Volumetric Pumps		
American McGaw	Accu Pro	Linear peristaltic
Abbott	IID	Cassette (piston)
Abbott	Model 3	Cassette (piston)
Critikon	2100A	Rotary peristaltic
Diatek	Secura IV	Linear peristaltic
IMED	922/927/928	Cassette (syringe)
IMED	960/965	Cassette (syringe)
IMS	MVP-1	Miniature Volumetric Pump
IVAC	530 Non-volumetric	Linear peristaltic
IVAC	630	Cassette (syringe)
IVAC	1500	Cassette (syringe)
Omni-Flow	4000	Piston diaphragm
Sigmamotor	5000	Linear peristaltic
Travenol	6000	Rotary peristaltic
Travenol	8000	Cassette (piston)
Valleylab	5000B	Cassette (hydraulic)
Valleylab	6000/6006	Cassette (hydraulic)
Variable Pressure Pumps		
AVI	Guardian 1Q	Dual-chamber rolling diaphragm
IVAC	560	Linear peristaltic
Sigmamotor	7000	Linear peristaltic
Controllers		
Abbott	1000	Gravity
Anatros	Rateminder Volumetric	Gravity
Anatros	Rateminder II	Gravity
Centaur	Guardian II	Gravity
DNA	Flo-Control	Gravity
IMED	350	Gravity
IMED	380	Gravity
Infusor (Cutter)*	Volumetric	Gravity
IVAC	230	Gravity
IVAC	260 Volumetric	Gravity
Quest	1001 Volumetric	Gravity
Travenol	3000	Gravity
Enteral Nutrition Pumps		
Biosearch	Enteral Feeding Pump	
Chesebrough-Pond's Inc.	Kangaroo 220	
IVAC Corp.	Keofeed	
Ross Labs	Flexiflo	
Syringe Pumps		
Auto Syringe Inc. (Travenol)	AS2F, AS3B, AS5A	Portable syringe
Harvard (Bard Med Systems Div.)	2720 Series	Portable syringe
Harvard Mini Infuser (Bard Med Systems Div.)	100, 150, 200	
Mobile Infusion Pumps		
Cormed Inc.	Mobile Infusion Pump ML 6–4, 6–6, 6–8, 6–10	
Pacesetter Systems Inc.	Micromed Portable	Insulin infusion pump
Implantable Pumps		
Infusaid Corp.	Implantable Pump	
Ommaya CSF	Implantable Pump	

*Distributed by Cutter under contract with Quest.

6. Portable.
7. Reasonably priced.
8. Easy to operate.
9. Constructed to permit cleaning and sterilizing.
10. Equipped with alarm to signal depletion of I.V. solution and stop pump.
11. Equipped with other alarms to detect malfunction, battery depletion, infiltration, and excessive output pressure.
12. In compliance with all electrical safety standards for hospital use.

Table 8–4 provides a partial list of drug pumps and controllers that are currently available.

Suppliers of Pumps and Controllers

Abbott Laboratories
Abbott Park
North Chicago, IL 60064

American McGaw
Division of American Hospital Supply Corporation
2525 McGaw Avenue
Irvine, CA 92714

Anatros Corporation
1922 Junction Avenue
San Jose, CA 95131

AVI, Inc.
1118 Red Fox Road
St. Paul, MN 55112

Bard Med Systems Div.
C.R. Bard Inc.
87 Concord Street
North Reading, MA 01864

Biosearch Med. Products
35 Industrial Parkway
Somerville, NJ 08876

Centaur Sciences Inc.
180 Harvard Avenue
Stamford, CT 06902

Chesebrough-Pond's Inc.
33 Benedict Place
Greenwich, CT 06830

Cormed, Inc.
P.O. Box 470
591 Mahar Street
Medina, NY 14103–9990

Critikon, Inc.
1410 N. West Shore Blvd.
Tampa, FL 33607

Cutter Medical
Berkeley, CA 94710

Diatek Corporation
5720 Oberlin Drive
San Diego, CA 92121

DNA Medical Inc.
3385 West 1820 South
Salt Lake City, UT 84104

Heyer-Schulte del Caribe, Inc.
P.O. Box 1386 Rod 402 N
KM 1.2
Anasco, Puerto Rico 00610

IMED Corporation
9925 Carroll Canyon Road
San Diego, CA 92131

IMS
311 Rt. 46 West
Fairfield, NJ 07006

Infusaid Inc.
1400 Providence Highway
Norwood, MA 02062

IVAC Corporation
10300 Campus Point Drive
San Diego, CA 92121

Omni-Flow
4 Henshaw Street
Woburn, MA 01801

Pacesetter Systems Inc.
12884 Bradley Avenue
Sylmar, CA 91345

Quest Medical, Inc.
3312 Wiley Post Road
Carrolton, TX 75006

Ross Labs
Columbus, OH 43216

Sigmamotor, Inc.
14 Elizabeth Street
Middleport, NY 14105

Travenol Laboratories, Inc.
1425 Lake Cook Road
Deerfield, IL 60015

Valleylab
5920 Longbow Drive
P.O. Box 9015
Boulder, CO 80301

Selection of Infusion Devices

Many hospitals that have acquired infusion devices have failed to develop an organized approach to the utilization of such devices. Often, infusion devices are chosen for specific purposes. Later, as the devices become commonplace in the institution, they are used in a greater variety of ways. As with any new procedure, there may be some justification for trial and error experimentation, but an organized approach for the use of devices will allow full and effective usage of the equipment in the safest manner possible.

It is no small wonder that some confusion currently exists regarding the selection of the appropriate device. A rapidly growing technology has produced shifts in thinking among the users as to the choice of device for a particular use. It is generally accepted that most infusion device problems originate from a poor understanding of the device on the user's part rather than from the instrument itself. Those contemplating the selection and purchase of instruments should give immediate consideration to at least the following:

a. Infusion devices introduce technological complexity and demand a greater degree of user understanding.
b. Personnel must be trained in the use of the equipment.
c. Apparent operational costs (the cost of the devices and sets) may increase. Total institutional cost may actually decrease, however, because problems associated with conventional I.V. therapy are often reduced or eliminated.
d. The equipment must be maintained.
e. In a rapidly changing technical area such as infusion devices, the equipment can soon become outdated.
f. There may be a limitation on the number of infusion devices any one institution is capable of purchasing. Therefore, patient selection is a factor for consideration.

Justification for Infusion Devices

As reported in the literature, infusion devices

Provide accurate and timely delivery of fluids and drugs.
Can change the flow rate when needed.
Provide controlled limitation of fluid intake.
Minimize the number of I.V. infusion checks required of the nurse.
Reduce infiltration rates.
Reduce the occurrence of infusion phlebitis.
Reduce the cost of I.V. therapy.
Save nursing time.
Allow intra-arterial administration of drugs.
Reduce the incidence of runaway I.V.s, plugged needles, and empty bottle conditions.
Reduce the incidence of dehydration caused by insufficient fluid replacement.
Permit accurate small-volume delivery of drugs and fluids.
Permit accurate large-volume delivery of drugs and fluids.
Simplify I.V. therapy.

Enable the hospital staff to meet pharmaceutical companies' recommendations on many selected drugs, e.g., nitroprusside, streptokinase, dopamine.
Reduce the incidence of infection by maintaining catheter patency and by avoiding occluded catheters.
Avoid gastric distension, emesis, and aspiration in enteral nutrition.
Permit the administration of a constant rate of flow of vasopressin, counteracting volume depletion while bleeding is controlled in life-threatening hemorrhage from peptic ulcer.
Permit patients to undergo arterial infusions of chemotherapeutic agents directly into the target organ while leading a more normal life.

Committee for Instrument Selection

A hospital committee for the selection of proper infusion devices should be established.[63] The committee should have representation from nursing service, biomedical, medical staff, anesthesia, purchasing, and administration. The nursing service representatives should include nursing specialists from the intensive care, emergency room, and medical and surgical units; if enteral instruments are utilized, representation from the dietary department is needed.

The committee should define the problems associated with I.V. therapy in the institution. Incident reports can be a source of information. Reports of phlebitis, infiltrations, restarts, inaccurate drug delivery, and other related I.V. problems often can help determine the type of infusion equipment needed.

Once the problems experienced in the institution are pinpointed, input regarding solutions to the problems can be gathered. Careful consideration of the following factors might help identify needs:

Requirements for rate control with high pressure.
Requirements for rate control without high pressure.
Pressure required for arterial lines.
Capabilities of pumps and controllers.
Intensity of drug therapy, type of patient, and length of hospital stay.
Hospital mix of equipment.
Small-volume infusion delivery needs.
Hospital occupancy rate.
Average daily I.V.s
Number of pediatric beds.
Special care beds.
Who monitors I.V.s: floor nurse or I.V team.
Consultation with other institutions for information and experiences.

The committee may invite a manufacturer to give a presentation. At the presentation, consideration should be given to such equipment factors as:

Simplicity of operation.
Weight.
Ease of use.
Hospital compatibility of instrument.
Hazards associated with instrument.
Cost considerations; lease versus purchase.

Company ability to respond to service, inservice programs for life of the instruments.

Once the equipment has been purchased, inservice of equipment throughout the hospital is performed. Responsibility for and control of the equipment must be established; control may be a nursing service, I.V. team, or pharmacy responsibility. Responsibility for maintenance, cleaning, and care of the equipment must be established.

Criteria For Using Infusion Devices

General Use

When a greater degree of accuracy is desired than is achievable using gravity-fed manual clamp methods:

When positive pressure is required to override vessel pressure, such as with intra-arterial therapy, or additive resistances in the I.V. line.
When significant morbidity is associated with drug extravasation.
Where a danger of fluid overload exists.
For complicated drug dosage regimens.
When there is a specification from a pharmaceutical manufacturer.
When instrumentation provides an effective method of risk reduction.

Nutrition

Total parenteral nutrition.
Enteral alimentation: stomach or jejunum.
I.V. fat.
Vitamin/mineral preparation.
Pediatric formula.

Fluid Administration

Critical care fluid management.
Pediatric fluid management.
Restricted fluid situations.
Blood and blood products.
Controlled clinical trials.
General electrolyte administration.

Drug Therapy

Continuous drug therapy.
Chemotherapy.
Intra-arterial infusions.
Oxytocic agents.
Regional heparinization.
Antiarrhythmic agents.
Pressor agents.
Bronchoactive agents.
Hypoglycemic agents.
Anticoagulants.

Cardiovascular drugs.
Neonatology drug therapy.
Corticosteroids.
I.V. anesthetics.
Anti-infective agents.
Muscle relaxants.
Antihypertensives.

Other Uses

Closed wound irrigation.
Keep-vein-open (KVO) for central lines, e.g., cardiac catheter, intra-arterial infusions.
Peritoneal dialysis.

Home Use

Parenteral and enteral nutrition.
Insulin therapy.
Oncology therapy.
Antibiotic therapy.

Patient Complications

Restarts.
Infiltration morbidity with drug extravasation.
Runaways.
Phlebitis.
Fluid overload.
Complicated drug dosage regimens.

On some occasions, not enough infusion instruments may be available for every potential use. The following priority list may be used for determining which drugs or nutritional products receive priority to be administered via an infusion instrument. When such an occasion arises, infusion instruments will be removed from patients receiving the drugs/nutrition, starting at the bottom of the list (e.) with the oral alimentation group.

a. Drugs administered by constant infusion that require frequent dose adjustments and have a small therapeutic:toxic ratio. These drugs must be administered by an infusion pump or controller: dobutamine, dopamine, isoproterenol, lidocaine, nitroglycerin, nitroprusside, procainamide, ritodrine, and vasopressin. Improper infusion rates for these drugs may become life-threatening within minutes.
   When it is necessary to remove an infusion pump from a patient for a higher priority infusion, the intravenous infusion bottles should contain no more than a 6- to 8-hour supply of solution. They should be labeled with the appropriate rate and time for the infusion.
b. Drugs that are administered at a fixed hourly rate that, when properly used, may have the dose changed every few hours. Improper infusion rates may be life-threatening within hours. These drugs include aminocaproic acid, antineoplastics, heparin, insulin, morphine, naloxone, oxytocin, streptokinase, I.V.

solutions given via Hickman catheter, and total parenteral nutrition via a central line.

c. Drugs that are administered at a fixed hourly rate that, when properly used, may require a dose adjustment every few days. Due to drug toxicity, the use of an infusion pump is strongly recommended. Aminophylline falls into this category.
d. I.V. fluids administered to patients with severe fluid restrictions.
e. Oral alimentation preparations that are administered at a fixed hourly rate that, when properly used, may require a rate change every few days. If administered without an infusion pump, the immediate threat to the patient is minimal.

Standardized Concentration For Drugs Administered By Constant Infusion

Standardized concentration of drugs used for instrumentation can simplify procedures and help minimize errors. An example from one hospital is reproduced below.[64]

> Various concentrations of drugs are frequently prescribed for the administration of drugs by constant infusion. This leads to confusion when the rates of infusion must be changed.
>
> The following drugs given by constant infusion, and their recommended concentrations, have been approved by a hospital staff committee. These concentrations can be changed if the clinical situation requires a more concentrated solution. Charts indicating flow rates for each concentration are available from the department of pharmacy. A similar list should be adopted in each hospital as a safety and quality assurance measure.
>
> aminophylline 1 g/250 ml and 1 g/500 ml
> dobutamine 250 mg/ml
> dopamine 400 mg/250 ml
> isoproterenol 1 mg/250 ml
> lidocaine 1 g/500 ml and 2 g/500 ml
> heparin 20,000 units/L and 30,000 units/L
> morphine 50 mg/250 ml
> insulin 50 units/500 ml
> nitroprusside 50 mg/250 ml and 100 mg/250 ml
> vasopressin 100 units/250 ml
> ritodrine 150 mg/500 ml
> epinephrine 2 mg/250 ml
> norepinephrine 4 mg/250 ml
>
> The department of pharmacy provides constant flow charts for all of these standard drug solutions to expedite dosage calculation as well as changes in flow rate.

The following are the Recommendations of Practice for the National Intravenous Therapy Association as they relate to infusion devices.

Mechanical Controlling Devices

> Mechanical controlling devices are used to provide minimal deviation from the prescribed medical order in the delivery of solutions and/or medications, thus reducing the risk of possible I.V. complications.

Recommendations For Infusion Devices

a. Delivery of all aspects of I.V. therapy shall be controlled with minimal deviation from the prescribed rate ordered.
b. The use of gravity-feed mechanical devices (I.V. controllers) is advocated for the majority delivery of I.V. therapy.
c. The use of pressure-feed mechanical devices (I.V. pumps) is recommended for controlling I.V. delivery when a specified accuracy of I.V. delivery is mandatory due to patient risk.
d. I.V. pumps should maintain I.V. delivery without stringent deviation from the prescribed medical order, and their accuracy or deviated limit (plus or minus) shall be stated by the manufacturer.
e. All I.V. electronic devices shall be routinely cleaned and checked for possible malfunctions.
f. The use of electronic mechanical controlling infusion devices shall be prioritized and stated by hospital policy in the I.V. Policy and Procedures Manual.
g. The registered professional I.V. nurse shall be proficient and knowledgeable in the use of mechanical controlling devices within the health care facility.
h. Operating instructions for electronic mechanical I.V. controlling devices shall be affixed to the device.
i. Audible and visible alarms to detect air, deviated flow, occlusion, and any other deviations placing the patient at risk shall be integrated within the mechanical infusion device.
j. If the mechanical controlling device is battery operated, the life and potency of the battery should be ascertained and changed accordingly.
k. Mechanical electronic controlling devices should be patient tamperproof.

Future Trends For Infusion Devices

The quality of patient care has been improved by the increasing use of sensitive infusion devices. With proper use of these devices, flow rates can be maintained, and parenteral and enteral nutrition can be safely conducted. Technical advances have come quickly in the field of electronic infusion devices, and progress shows no sign of slowing. Research is being done on closed-loop infusion, where drug response or body chemical concentrations is coordinated by the infusion device. The future promises ever-greater safety and efficiency.

Plastic Medical Components

Early experiments with parenteral packaging material utilized such materials as pigs' bladders and goat skins. The disadvantages of these materials are obvious.

Glass appeared to solve the packaging problems for parenteral products. Glass is a relatively inexpensive, clear, stable material that can be shaped, sterilized, sealed, and handled; however, it is still far from being the ideal container. Breakage, disposability, weight, and increased cost have led to the increased development and use of "plastic" for parenteral packaging. "Plastic" is a term used generally to describe a variety of compounds of high molecular weight that can be molded to shape, hardness, and clarity.

Devices and Materials Used in Parenteral Medical Practice

Plastic devices used for parenteral medical practice include

1. Disposable syringes (polyethylene, polypropylene, polycarbonate).
2. I.V. solution administration sets (polyvinylchloride [PVC]).
3. Plastic I.V. catheters (Teflon, polypropylene).
4. Blood containers (polyvinylchloride).
5. I.V. solution containers (polyvinylchloride, Viaflex, LifeCare, polyolefin, Accumed).
6. Irrigating solutions, (polyolefins, polyethylene, polypropylene) (McGraw, Travenol, Abbott).

Plastic components, like rubber formulations, may contain a variety of additives to enhance the quality desired for their use. The basic polymer (plastic) may contain *plasticizers* to give flexibility to the package, as in the LifeCare or Viaflex containers. *Antioxidants* are added to prevent discoloration. Plastic devices are produced with heat and pressure, which may result in the need for *stabilizing agents. Fillers* may be added to enhance the formulation. *Antistatic agents* are sometimes needed to prevent clinging of the material. *Colorants* may be necessary for some devices. *Lubricants* are added to facilitate removal from the production molds.

Some common plastic materials used in medical devices are listed below:

Polyethylene. Various densities are available (low, medium, high). A relatively inert, opaque material containing no plasticizer. A common ingredient of plastic syringes.

Polypropylene. Similar to polyethylene, it is relatively inert. Many grades are sterilizable. A common ingredient of plastic syringes.

Polyvinylchloride. Available in a variety of formulations. Available in a relatively clear, inert, sterilizable container. When 30 to 40% of a phalate ester is added to the formula, this product can be flexible. Polyvinylchloride formulations are used to manufacture plastic I.V. bags (Viaflex, LifeCare). All I.V. tubing administration sets are polyvinylchloride formulations.

Polystyrene. An inexpensive, rigid clear type of plastic material; however, not very inert. Will react with paraldehyde and other materials. Has a low melting temperature and cannot be heat sterilized.

Nylon. A stable, inert, generally opaque material. Can be made and used where hardness is necessary (e.g., spike I.V. sets, filters in blood sets).

Polymethylmethacrylate (Lucite). A relatively expensive, stable, hard material used to make needle adaptors on I.V. sets.

Polyolefins (polyethylene and polypropylene). A mixture of two compounds produces a rigid or semi-rigid formulation. Contains no plasticizer. Available in use for McGaw, Travenol, and Abbott irrigation containers. Currently available in McGaw I.V. container (Accumed).

A common I.V. administration set may combine a variety of plastic components tailored to suit a particular need. For example, an administration set contains a nylon spike, a Lucite Y-site, a polyvinychloride tube, and a polypropylene clamp.

Medical Considerations of Plastic Containers for Parenteral Use

Numerous factors are involved in considering plastic material for parenteral use: vapor transmission, sterilization qualities, texture, clarity, weight, aging, ease of production, ease of destruction, ultimate method of use, inertness, chemical reac-

tivity of the plastic material with the drug, binding, leaching and, probably most important, biologic safety. Medical uses of plastic materials are increasing at an accelerated pace as a result of the many advantages of plastics, such as disposability, lightness, cost. Current technology, however, does not permit the formulation of the ideal container (whatever that may be) for a particular medical use. Usually, a compromise of one or some of the desired qualities and attributes must be made.

A new concept in the packaging of intravenous fluids, Viaflex, was introduced into the United States in 1971 by Travenol Laboratories. Abbott Laboratories introduced a similar container, LifeCare. These soft, flexible plastic bags have some advantages over the traditional glass containers. The most outstanding feature of this type of container is its ability to respond to normal outside atmospheric pressure, with the result that no venting is required. Because of its rigidity, a glass container must be vented to allow solution to flow. The closed system of bags may mean that the threat of contaminating air entering by the usual methods is eliminated. Hansen and Hepler[66] studied glass systems and the Viaflex and concluded that the Viaflex system offered significantly better protection against contamination by airborne microbes than did other systems. Paretz et al.,[67] however, found the incidence of contamination with Viaflex containers to be 5 times greater than that with glass (6.9% for Viaflex, 1.3% for glass). The source of contamination was unclear but "touch" appeared to play an important role. The possibility of air embolism is significantly reduced in the use of flexible plastic containers; however, the possibility of air embolism is greater when flexible plastic units are connected in a series of containers. Therefore, this type of hook-up is not recommended.

Flexible containers are nonbreakable; however, accidental punctures can create a point of entry for microorganisms.[68] Additions of drugs through the additive port with a needle can cause puncture of the plastic.[69] Flexible plastic containers are lighter and consume less space than glass. They are thought to be easier to handle and dispose of, although this point has been questioned.[69,70] Some workers suggest that the lack of rigidity presents problems when manipulation is required. Studies have shown that plastic I.V. containers have less particulate matter than do glass containers.[71] Other studies have shown generation of colloidal-sized material after agitation and unusual manipulation. Needham and Luzzi[72] have identified this material as di-2-ethylhexylphthalate (DEHP), although the labeled maximum of 5 ppm was not exceeded.

Incomplete mixing of drugs[73] added to intravenous solutions is more likely to occur with plastic bags than with glass. This poor mixing is in part a result of pooled drug at the injection site, and the manufacturer has taken steps to correct this. Proper mixing precautions are noted in the manufacturer's brochure. Significant amounts of some drugs may be adsorbed to the bag. A number of drugs are known not to be adsorbed, but for many the amount of adsorption is unknown.[73] The Medical Letter commenting on flexible plastic I.V. bags noted that they are convenient but they can adsorb some drugs out of solution and may introduce chemicals into solution, and summarized that plastic containers have not proven to be more reliable than glass in protecting against contamination of I.V. fluids. The reader is referred to the last published review of plastic containers.[70]

I.V. Teams

In past years, intravenous therapy was generally uncomplicated, consisting chiefly of supplying simple fluids to fasting patients. With better understanding of fluids

and drug therapy and parenteral nutrition, intravenous therapy has become increasingly complex. A better understanding of the problems associated with intravenous therapy (e.g., contamination, particulation) has also enlightened medical care workers so that specialized expert training is required for those who administer injections. This has led to the development of specialized groups: the American Association of I.V. Therapists and the National Intravenous Therapy Association. The sole concern of these groups is to provide expert patient care in intravenous therapy. To accomplish these goals, educational meetings, journal publications, the *American Journal of I.V. Therapy and Infusion*,and the official publication of the National Intravenous Therapy Association (NITA) have been utilized. The concept of intravenous teams has evolved from these specialty groups. Sophisticated medicine requires sophisticated I.V. therapy. The initiation and justification for I.V. teams have been reported by Kelly et al.,[74] Kimmell,[75] and Godfrey.[76] Willett[77] describes the development of an I.V team in a small hospital. The nature of parenteral medication will require the growth and proliferation of I.V. teams in the future. The complex legal and ethical nature of parenteral therapy will demand that specialized groups of trained individuals perform intravenous therapy.

National Coordinating Committee on Large Volume Parenterals

The National Coordinating Committee on Large Volume Parenterals (NCCLVP), a group cosponsored by the U.S.P. and the FDA, is financed by an FDA contract. This committee was established in 1971 to deal with problems of concern in large-volume parenterals. Those concerns were, in part, precipitated by a national outbreak of contaminated I.V. fluids.[78] Representation on the committee was drawn from many national organizations, including the four manufacturers of LVPs. The initial research was to determine the problems. The bibliography and literature review on the ecology of LVPs in hospitals was completed in August, 1973.[79] A master list describing 167 problems associated with LVPs was generated from a national sample of 26 hospitals. Identification of the component procedures and techniques used by hospital personnel in preparing and administering LVPs was also established by this committee, as were guidelines to the type of personnel and training for those who give LVPs in hospitals. From the list of 167 problems, 39 were targeted as top priority. Four expert working subcommittees dealt with these problems: Microbial and Pyrogenic Contamination; Particulate and Chemical Contamination; Incompatibilities and Stability, Delivery, and Recall; and the Dissemination of Information and TPN. A list of 35 top priority problems and recommendations was published.[80]

Other important accomplishments of the NCCLVP were the development and publication of a document entitled "Recommended Methods for Compounding Intravenous Admixtures in Hospitals."[81] This detailed set of procedures[81] was sent to all hospitals with the purpose of instructing how to compound and administer LVPs so that the quality built into the product by the manufacturer is maintained all the way to the bedside. A third document produced and published was a "Recommended System for Surveillance and Reporting of Problems with Large Volume Parenterals in Hospitals."[82] This is an early-warning system of procedures that is designed to detect problems of LVPs immediately and to transmit the alert to FDA, CDC, and state and local health authorities. It interphases with the Drug Product Defect Reporting System.

The committee also developed "Test Methods for Particulate Matter in LVPs."

An expert panel recommended the standards that became official in the first supplement to *U.S.P. XIX*. A report[83] approved by the Subcommittee on Incompatibilities and Instabilities of the NCCLVP discussed recommendations to hospitals, manufacturers, pharmacists, physicians, and FDA and/or USP concerning the problems associated with incompatibilities. Additional discussion included problems with formulation, administration, and packaging material. The literature concerning incompatibilities was also presented. Two additional documents were published concerning labeling and testing of LVPs.[84,85]

Trends and Developments in I.V. Delivery Systems

The hospital pharmacy's potential involvements in the dissemination of parenteral products can be envisioned using one of three different scenarios. Deciding which roles the hospital pharmacist will play in the process of delivering parenteral drugs suitable for a patient's needs—whether the roles are related to the parenteral drug's procurement, storage, accounting, distribution, preparation or manufacture—is dictated by many factors, including the presence and amount of trained personnel and the space in which to store and mix the drug products; the hospital administration's commitment to such pharmacy functions as the intravenous admixture service; and the availability of adequate pharmacy programs and services and the willingness of the hospital's pharmacists to participate in the manipulation of parenteral drugs.

The final product—the parenteral drug that is injected or infused into the patient—must be appropriate in its concentration, dilution, and rate.

Three Scenarios

Procurement, Storage, Accountability, Distribution

In this, the scenario of minimum involvement, the pharmacist is required to purchase, properly store, maintain adequate records, and ultimately distribute the drug to the nursing unit, where it will be injected by either a nurse or a physician.

In this scenario, the nurse is charged with removing the sterile dosage form from an ampule, vial, or syringe (a solution ready for injection). Alternatively, the dry parenteral would have to be reconstituted by the nurse, who would select the diluent and its concentration.

In some situations, the nurse may be required to perform further manipulations of the parenteral drug.

The parenteral drug may require only a limited amount of manipulation; for example, with a unit-dose syringe, the nurse would be required to simply remove the needle's sheath and administer the injection.

Although the type of system outlined in this first scenario is considered undesirable by professional organizations and most pharmacists, this type of parenteral distribution still exists in some hospitals in the United States.

Procurement, Storage, Distribution, Preparation

Hospital pharmacists in this distribution scenario present to either the nurse or physician the completed parenteral dosage form, which is ready for injection. It therefore requires only a minimal amount of manipulation by the nurse or physician.

The hospital pharmacy department must be dedicated to and capable of handling and preparing parenteral products in order for this scenario to be justified.

It requires technical knowledge, skill, adequate personnel, proper equipment, and a hospital administration supportive of such centralized pharmacy areas as I.V. admixture and reconstitution services.

According to one survey, over 54% of the general hospitals in the United States reported conducting an I.V. admixture service, and over 66% of specialized hospitals reported that they had such a service.[86]

Of all the survey's respondents, fully 89% said they purchased as many drugs in unit-dose packages as possible. The survey also disclosed that, of the hospitals with more than 500 beds, the average number of I.V. admixtures performed and dispensed on a weekly basis was over 1000, and reconstituted I.V. piggyback containers numbered over 2000 per week.

The preparation of parenteral drug products may be as simple as drawing the parenteral drug into a syringe from an ampule or vial or as complex as preparing a total parenteral nutrition (TPN) solution. The hospital pharmacy must be capable of handling all preparation situations.

The heart of such a distribution system is the pharmacy's program of I.V. admixtures and piggybacking.

In this scenario, the hospital pharmacist requires syringe prefilling and reconstitution programs, and may well require freezing abilities.

Bulk and As-Needed Parenteral Manufacturing

Some hospital pharmacies offer a manufacturing service that prepares the parenteral dosage forms. In this scenario, the pharmacy starts with the raw chemicals needed to mix the parenteral drug and transforms them into a final sterile product.

Manufacturing can be done in smaller amounts of a unit or two to satisfy parenteral drug needs as they arise, or in large-bulk groups consisting of many units for long-term needs.

Whether a hospital pharmacy should manufacture its own parenteral drug products depends on several factors. To cite several examples, does the medical staff require certain drug products that are not commercially available, or do they require unavailable dosage strengths of existing products? Are the proper manufacturing equipment and personnel available, and does the hospital pharmacy possess the appropriate knowledge of manufacturing techniques?

The need for this type of function in hospital pharmacies has waned in recent years because of the increasing commercial availability of numerous parenteral dosage forms.

In 1976, infusion devices accounted for $185 million in sales. Such sales amounted to $585 million in 1982. By 1988, device sales may amount to $1 billion or more.[87] Further innovations in packaging systems will increase this growth. Although hospitals have experienced a trend toward cost containment and pressure has been placed on hospitals to hold the line on costs, this has had and will continue to have a minimal effect on the expansion of I.V. therapy. As much as 70 to 80% of hospital costs are labor costs. Thus, significant pressures in the cutting of material costs (i.e., those costs reflected in goods and supplies) will offer only insignificant savings. Cost constraints will have to be achieved through systems that reduce labor. The onus on the I.V. manufacturers will be to refine the I.V. systems (both electronic and mechanical) and I.V. packaging in an effort to reduce labor costs. Drugs will be packaged in systems that will reduce any necessary manipulations in hospitals to a minimum.

I.V. drug delivery systems have attracted the attention of almost every major

pharmaceutical firm as well as members of the medical device industry. Intense research in this field enforces the belief that new uses and methods of administration will be found for established drugs. A better understanding of pharmacokinetic and pharmacodynamic principles of drugs has opened the door to the development of new concepts in I.V. delivery systems. Newer delivery systems can provide

For the Patient:

Round-the-clock administration of drugs and nutritional formulas.
Continuous pain relief.
Reduced dosage and frequency of administration.
Reduced cost through decreased labor.
Increased convenience and safety.

For the Manufacturer:

New uses for approved, established drugs.
Reduced regulatory approval time.
Increased revenue.
Maintenance of current revenue and market shares.

The medical staffs of most hospitals recognize the problems associated with intravenous drug administration and impose limitations on their nursing personnel regarding the administration of drugs by I.V. push. This limitation has led to the hospital-wide use of various types of intermittent infusion devices—such as volume-control units, minibags and minibottles—for the administration of scheduled intravenous medications. This in turn has satisfied the requirement for dilution and prompted hospitals to allow their nurses to give intravenous medications. This has also resulted in clinical decision-making by the nurses and pharmacist concerning which medications can be given effectively while using such intermittent infusion devices.

A review of intermittent drug administration systems is in order. With the advent of antibiotics, particularly cephalothin, volume-control units gained wide hospital use in the 1960s and 1970s. These devices provided a method for intermittent drug administration.[7]

In 1971, Duma et al.[11] noted the hazards associated with these devices. Henry and Harrison[12] also noted problems associated with these devices.

The early 1970s saw the introduction of the minibottle and, eventually, minibag containers (underfills, piggyback containers). These containers supplied diluent of D_5W and normal saline in 50-ml or 100-ml containers. They allowed dilution and preparation of the drug by pharmacists.

Minicontainer diluents offered many advantages. McAllister et al.[88] reported on the safety of minibags over in-line burettes. Paxinos et al.[89] studied volume-control sets, piggyback systems, and a combination of the two of intermittent I.V. therapy. They concluded that the piggyback system is safe and effective, although costly. They found that an alternate system they devised (a combination volume-control unit and piggyback) was safe, effective, and less costly than the piggyback systems alone.

In 1975, the National Coordinating Committee on Large Volume Parenterals (NCCLCPs)[81] stated "The use of volume control sets is discouraged for intermittent drug therapy in adults."

Grey[90] compared methods and costs preparing I.V. piggyback solutions for diluent use in piggyback containers and noted that manufacturer's prefilled drug containers offered significant cost savings.

Several manufacturers responded to the hospital pharmacist's needs by supplying a variety of antibiotics in manufacturer's prefilled piggyback glass containers. In addition, drug manufacturers supplied bulk prefilled containers to accommodate I.V. reconstitution and admixture programs.

In an evaluation of ampicillin, Gibbs[91] noted that, for hospitals using glass systems, the prefilled 1-g piggyback bottle was best; for hospitals using I.V. bags, the 10-g "bulk" container was best. Hand et al.[92] also reported on the cost effectiveness of manufacturer's prefilled piggyback containers.

Paxinos et al.[93] studied the contamination rates and costs associated with the use of four intermittent infusion systems. They noted that the piggyback using the minibag was the most expensive; the piggyback with the Buretrol was the least expensive; and the piggyback using the drug manufacturer's prefilled piggybacks was the most efficacious.

Yarborough et al.[94] compared four admixture procedures for intermittent therapy. This group found no significant differences in the contamination rates between systems (1.3 to 2.5%). They also noted that no system worked best in all categories, and that hospital considerations affect the final choice of a system.

Dreiman[95] compared six methods of preparing piggyback doses of cephalothin and considered labor, equipment, and material costs for each of the six methods studied. The personnel cost proved the lowest for partial-fill bottles and drug prefilled manufacturer's bottles. Material costs were lowest for both manufacturer's prefilled bottles using a pressure infusor and for partial-fill bottles with the Pharm Aid fluid dispensing system. The preferred systems, however, included the drug manufacturers prefilled bottle, using the pressure infusor, as well as gravity flow method in conjunction with the drug manufacturers prefilled bottle.

Lu et al.[96] studied a new vacuum-filling method for reconstitution of most drug-manufacturers prefilled containers and noted that the vacuum diluent method was both effective and safe.

Fraterigo et al.[97] studied the accuracy and efficiency of three methods of preparing piggyback admixtures.

1. Pharm Aid fluid dispensing system
2. Valleylab I.V. Formulator
3. Viavac vacuum unit

This group noted that the I.V. Formulator required the least amount of time. The cost was nearly identical for all three systems, however, and no one system was best for all situations.

Pohorylo et al.[98] studied the time and cost associated with four methods of filling piggyback bottles.

1. Traditional vacuum method
2. Wheaton Unispense Model II
3. Valleylab I.V. 6500 Formulator
4. Instafil Method

This group concluded that for small batches the Instafil method was best, and for larger batches methods 2 and 3 were best.

Markowsky et al.[99] compared six methods for preparing cefazolin sodium for intermittent injection.

1. Manual Syringe and Stopcock
2. Multi-Ad System

3. Wheaton Unispense
4. Valleylab I.V. Formulator
5. Faspak ADS-100
6. Prefilled Manufacturer's Piggyback Bottles (DMPB)

Systems 1 through 4 used bulk 10-g vials added to partial fills, and systems 5 and 6 used DMPBs. It was concluded from this study that the Faspak ADS-100 system achieved the lowest personnel cost and the DMPB system achieved the lowest annual cost.

The decade from the 1970s through the early 1980s explored using methods other than volume-control units for intermittent I.V. drug administration. The partial-fill diluent piggyback containers were accepted and became widely used. Over 100 million piggyback containers are used yearly in the United States today. Introduction of powdered DMPBs in the early 1970s along with bulk containers expedited I.V. piggyback administration.

Large-Volume Parenterals (LVPs) With Manufactured Additives (Premixes)

In the late 1970s, the industry recognized the need to add simple electrolytes during manufacture. It has been estimated that considerable amounts of LVPs contain potassium chloride (40 to 60%). With over 300 million units of LVPs used yearly in the United States, millions of small-volume parenterals (SVPs) with potassium chloride had to be added to LVPs.

Turco[100] studied the cost and time required to add KCl to LVPs using three systems:

1. Ampule KCl—needle and syringe.
2. Vial transfer and needle method.
3. Pintop method.

The Pintop method proved the most convenient and the fastest, but was also the most expensive.

In a second study, Turco[101] studied a comparison of manufacturer's "premixed" and "non-premixed" potassium chloride LVPs and noted that the purchase of "premixed" KCl solutions from the manufacturer proved the most logical choice so long as the medical and nursing staffs can be taught to recognize the contents of the container.

Premixed LVPs containing KCl have gained wide use. Other LVP premixes have become available, e.g., lidocaine, heparin, theophylline, and dopamine (Fig. 8–37).

Premixed drug solutions and containers offer significant advantages to hospitals: They are less demanding of time, and they have less potential for error and contamination. It is significant that drug and fluid manufacturers have combined efforts to achieve optimal packaging for hospital use.

An innovation in prefilled I.V. piggyback containers has been the introduction of ready-to-use plastic containers of solutions that require no manipulation or dilution and thus are ready for direct intravenous infusion. The antibiotic metronidazole (Flagyl, Searle & Co.) is marketed in ready-to-use Viaflex plastic I.V. containers from Travenol Labs.

I.V. Flagyl was originally introduced in 500-mg vials of lyophilized drug requiring reconstitution and buffering. Later it was introduced in 100-ml ready-to-use glass containers and, eventually, in Viaflex containers.

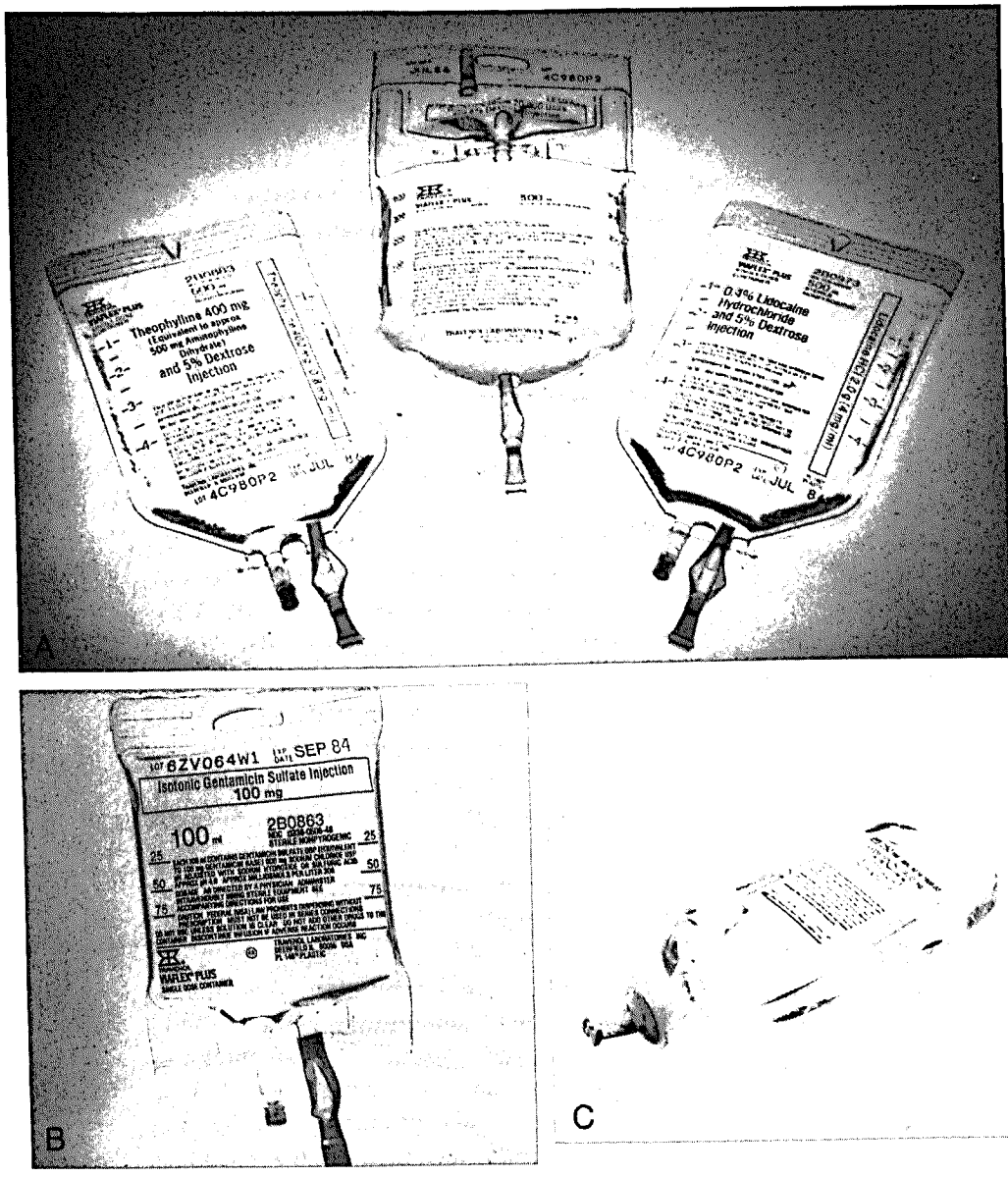

Figure 8–37. Premixed LVPs. (*A*, *B*, Courtesy of Travenol Laboratories, Inc., Deerfield, IL. *C*, Courtesy of Abbott Laboratories, North Chicago, IL.)

In early 1982, Travenol announced agreements to package I.V. drugs produced by Schering, Bristol, SmithKline, Hoechst-Roussel, and Merck in Viaflex containers. These provide additional ready-to-serve antibiotics in convenient packaging and, more importantly, will serve to generate systems for premixing oncolytic drugs.

Frozen Premixes

Currently underway by Travenol is the delivery to hospitals of frozen drug products packaged in polyvinylchloride containers. These frozen products are stored in a

freezer in the hospital's pharmacy and thawed and used when needed. Available are frozen cefazolin (Ancef), cephalothin, cefoxitin (Mefoxin), cimetidine (Tagamet), and cefotaxime (Claforan) (Fig. 8–38).

Under new agreements reached with the drug manufacturers, Travenol will package premixed solutions of Hoechst-Roussel's Claforan (cefotaxime sodium). These third-generation cephalosporins will be distributed by Baxter Travenol to hospitals in frozen form. Double-bag Viaflex has been introduced by Travenol, offering the convenience of incompatible drugs in liquid form.

Faspak/ADS-100 System

Eli Lilly supplies a non-PVC plastic piggyback container, named "Faspak," which contains the dry, powdered form of certain drugs (Keflin, Kefzol, Mandol, and ampicillin), which upon reconstitution with the appropriate diluent, allows direct administration of the diluted drug. This avoids a transferring step that normally takes place when reconstituting a powdered drug. To help in the reconstitution step, a specialized dilution pump named the ADS-100 system is supplied.

The package design eliminates the need for transferring between containers after reconstitution, and the Faspak acts as a final delivery container.

Abbott/ADD-Vantage System

Introduced in 1985, the Abbott ADD-Vantage system has two parts: a plastic I.V. bag sold by Abbott that is filled with solution, and a separate glass vial of powder or liquid drug sold by a drug maker. The vial is encased by a plastic cover that is removed prior to use. The user locks the vial holding the drug into a chamber at the top of the plastic bag and mixes the drug and solution by externally removing the vial's stopper. Abbott claims ADD-Vantage saves both labor and material costs and minimizes drug waste. Beecham, Wyeth, Upjohn, Lilly, Burroughs Wellcome, and Roche have already made or will soon make available vials designed for the ADD-Vantage system (Fig. 8–39).

Mini-Infuser Pumps for Intermittent I.V. Drug Delivery

A novel concept in intermittent drug delivery, introduced several years ago, was the Bard-Harvard Mini-Infuser System. This instrument was designed for the administration of antibiotics and other medications delivered intermittently in 40 minutes or less. This battery-generated, lightweight instrument uses standard disposable syringes and microbore disposable extension sets. Different models are available, depending on volume-to-be-delivered selection. This instrument provides accuracy, constant flow, convenience, and safety for intermittent drug delivery.[102–104]

Introduced and designed for intermittent I.V. drug delivery, Becton Dickinson's 360 infusor allows drug delivery intermittently over 60 minutes or less in a volume dilution of up to 50 ml. This instrument is currently undergoing hospital evaluations.

Abbott Laboratories, IVAC Corporation, and Pancretec, Inc. all manufacture syringe pumps as well. AVI, Inc. makes a syringe device called Medifuse, which uses a constantly applied force, instead of the usual battery power, to propel the syringe plunger.

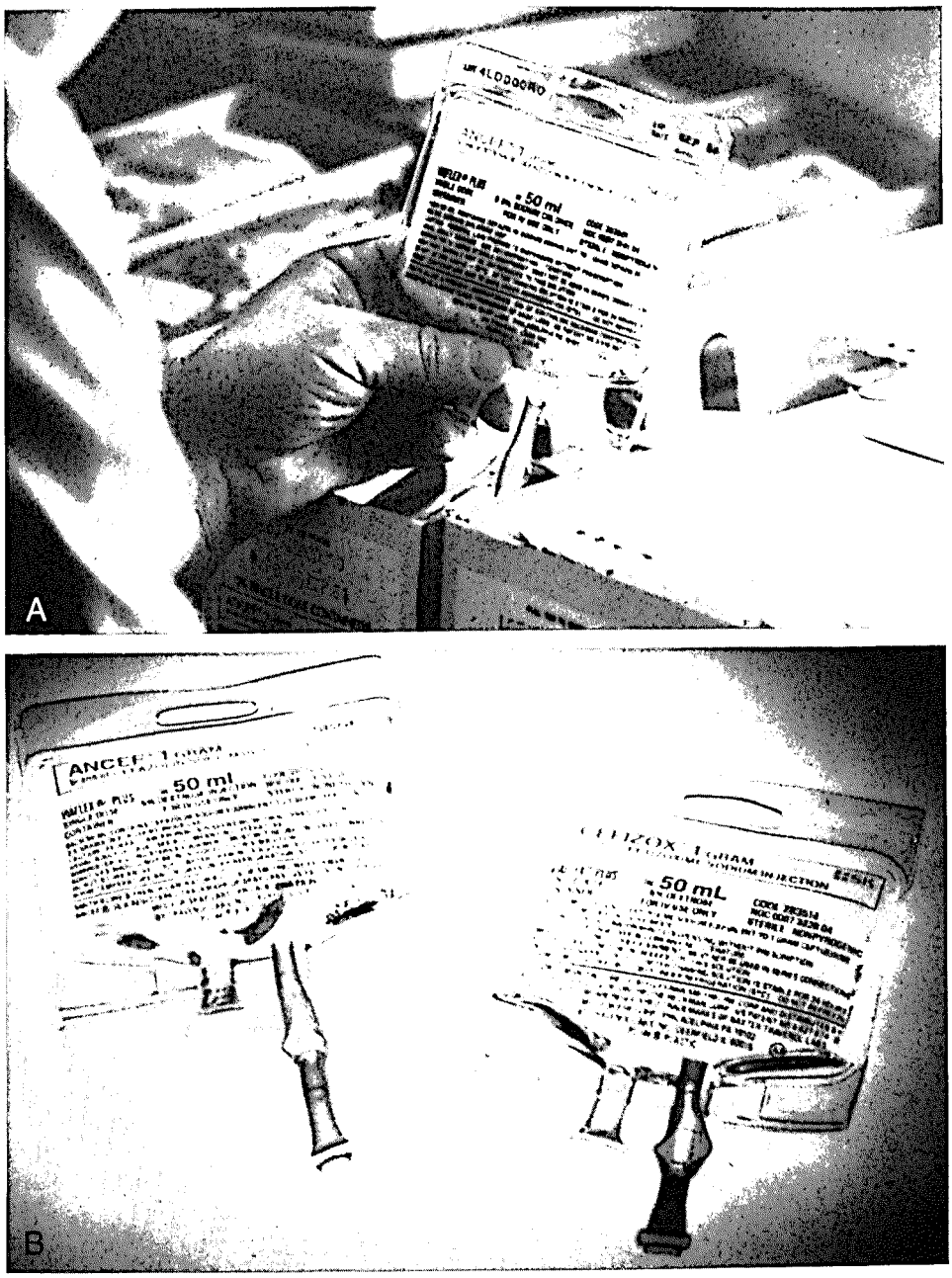

Figure 8–38. *A, B,* Frozen premixes. (Courtesy of Travenol Laboratories Inc., Deerfield, IL.)

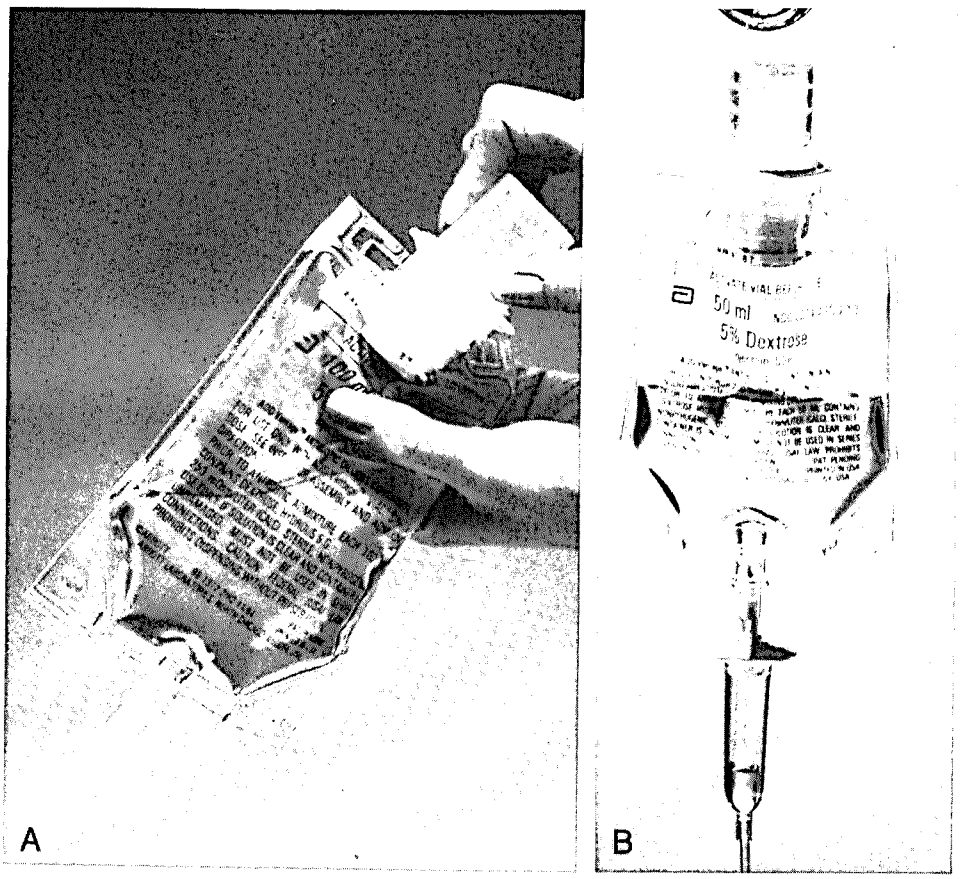

Figure 8–39. *A*, Abbott ADD-Vantage system. *B*, System in use. (Courtesy of Abbott Laboratories, North Chicago, IL.)

Larger Electronic Equipment

We have recently seen the introduction of electronic equipment for automated administration of intermittent secondary medications (piggyback). Four manufacturers supply this equipment as part of a system that uses an electronic pump.

These systems allow the programming of the secondary infusion (piggyback); at the time of completion, the systems automatically revert back to the desired primary fluid flow rate. These devices save time, offer nursing convenience, and reduce intravenous sites lost as a result of dry secondary bottles (if no check valve set is normally used), and also reduce the possibility of the primary solution infusing at the secondary rate. One system can limit the volume infused from the secondary container, introducing the possibility of cost savings by compounding the secondary container to contain more than one dose. These systems also reduce the need for using multiple electronic equipment devices. These instruments can increase the precision of drug administration and allow optimal interpretation of serum drug level concentrations.

The suppliers of the equipment discussed in this section are as follows:*

*Manufacturers' addresses can be found in the earlier section, "Suppliers of Pumps and Controllers."

IVAC Multi Dose System Model 460 (Controller)
IVAC Corporation
IMED 380 Piggyback Controller
IMED Corporation
Rateminder II Secondary Infusion Monitor (SIM) (Controller)
Anatros Corporation
Quest 1001 Intelligent Infusor (Controller)
Quest Medical, Inc.
McGaw/AccuPro (Pump)
American McGaw
Omni-Flow 4000 (Pump)
Omni-Flow

Patient-Controlled Analgesia

Electronic patient-controlled pumps have been introduced by Bard, Abbott Labs, and Pharmacia, and are being clinically evaluated by Becton-Dickinson.

ADD-Vent I.V. Medication Delivery Systems

Add-Vent can be used with gravity or in conjunction with the Quest Medical 2001 Infusor. It requires a basic 10 to 60 ml plastic syringe as the drug reservoir. After preparation of the drug, the syringe is placed in a plastic minisack that is hung from the I.V. pole. The Luer Lok syringe is placed into the connector on the Add-Vent set, allowing the fluid to run by gravity without the need for a syringe pump to depress the plunger.

Travenol Infusor

The Infusor is a continuous infusion system. Drug is injected into the infusor, which then inflates a balloon reservoir, creating constant internal pressure. As the reservoir deflates, medication is delivered through an orifice of controlled size that regulates the infusion at a constant rate of 2 ml/hr. When infusion is completed, the empty infusor is discarded. Rates of drug administration can be varied from 1 to 24 hr/infusor, depending on the solution concentration.

Reconstitution and Admixture Services

Several companies supply reconstitution and admixture services for hospital pharmacies in certain areas of the United States.

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