Ionizing Radiations.

Ionizing radiations are high-energy radiations emitted from radioactive isotopes such as **cobalt-60** ***(gamma rays)*** or produced by mechanical acceleration of electrons to very high velocities and energies *(cathode rays*, *beta rays).*

Gamma rays have the advantage of being absolutely reliable, for there can be no mechanical breakdown; however, they have the disadvantages that their source (radioactive material) is relatively expensive and the emission cannot be shut off as it can from the mechanical source of accelerated electrons.

Accelerated electrons also have the advantage of providing a higher and more uniform dose rate output.

Electron Accelerators.

Electron accelerators are **of two general types, the linear and the Van de Graaff accelerators.** The principle of the linear accelerator may be followed from Figure 21-5.

-Very high-frequency microwaves (radar) collect electrons from a cathode and accelerate them as they travel through the vacuum tube, reaching almost the speed of light. The electrons are emitted and directed to the target at an energy range of 3 to 15 million electron volts (meV). Since energy potentials of 10 meV or higher may produce radioactive materials, linear accelerators of more than 9 meV are not normally used for sterilizing.

-The Van de Graaff accelerators are capable of energy potentials up to 3 meV. They utilize the force exerted on a charged particle by a high voltage potential in an electric field as a means of direct particle acceleration.

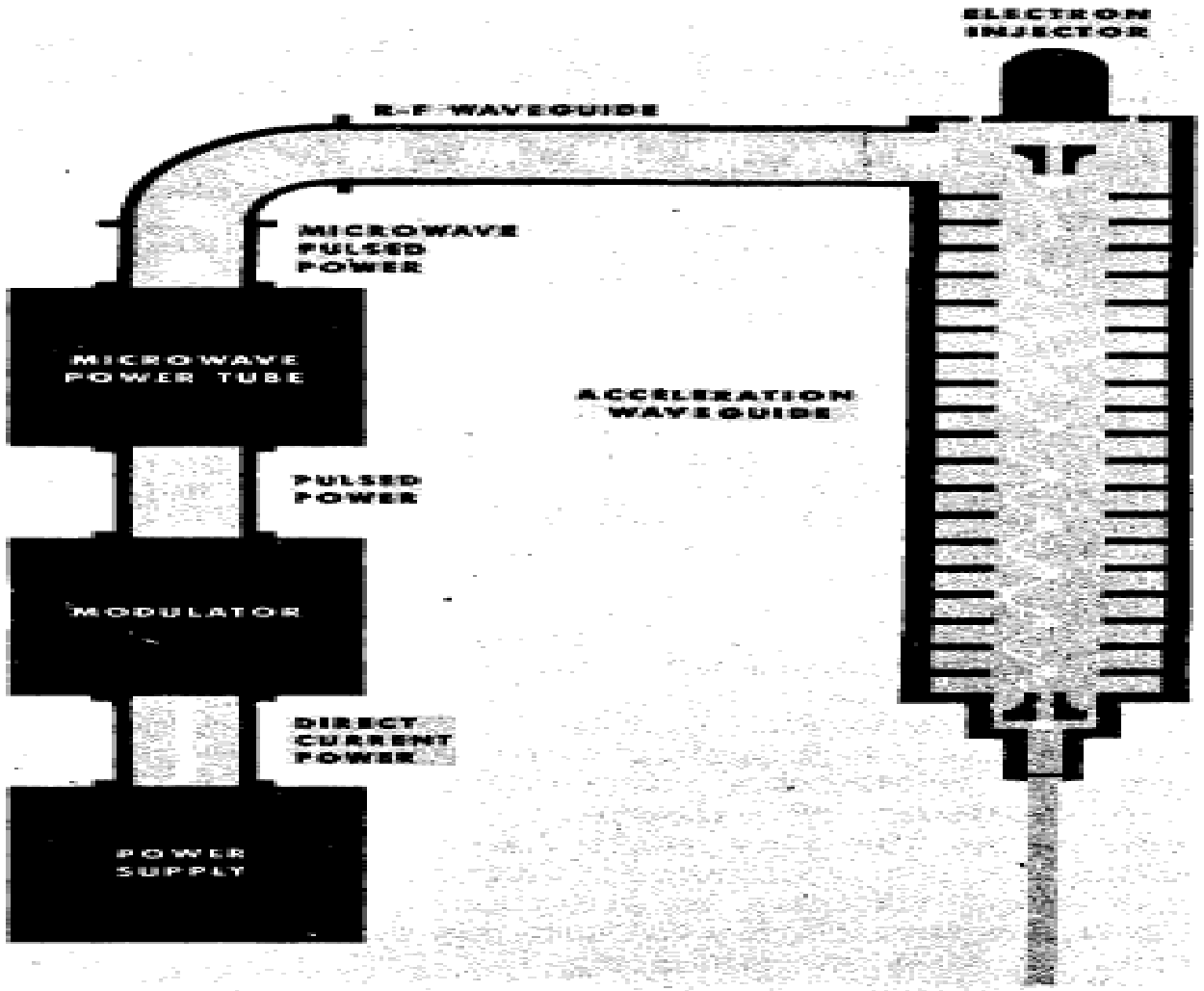

FIG. 21-5. *Operating principle of a linear electron accelerator. (Courtesy of High Voltage Engineering Corp.)*

Lethal Action and Dosage.

Ionizing radiations destroy microorganisms by stopping reproduction as a result of lethal mutations. These mutations are brought about by a transfer of radiation beam energies to receptive molecules in their path, the direct-hit theory. Mutations also may be brought about by indirect action in which water molecules are transformed into highly energized entities such as hydrogen and hydroxyl ions. These, in turn, bring about energy changes in nucleic acids and other molecules, thus eliminating their availability for the metabolism of the bacterial cell. Ionizing radiations differ from ultraviolet rays in their effects on matter primarily in that the former are of a higher energy level, actually producing ionization of constituent atoms.

Bacterial spores and viruses are generally four to five times more resistant than vegetating bacteria and molds.

Applications for Sterilization.

Accelerated electrons or gamma rays may be used to sterilize select products by a continuous process. Most other product sterilization procedures must be performed in batches.

A number of vitamins, antibiotics, and hormones in the dry state have been successfully sterilized by radiation. Liquid pharmaceuticals are more difficult to sterilize because of the potential effect of the radiations on the vehicle system as well as the drug.

Filtration.

Filtration may be used for the removal of particles, including microorganisms, from solutions and gases without the application of heat. Ideally, filters should not alter the solution or gas in any way, neither removing desired constituents nor imparting undesired components. This requirement essentially limits the types of filters currently employed to the polymeric types listed in Table 21-5A, B. Furthermore, almost all of those currently in use with parenteral solutions and gases are of the membrane type, that is, tissue-thin material removing particles primarily by sieving. When a filter does remove constituents from a solution such removal is usually due to the phenomenon of adsorption, which being a surface phenomenon, occurs during only the first portion of the filtration, that is, until the surface of the filter is saturated with the adsorbed molecule or ion. The most common attack on the filter itself is due to the solvent properties of the vehicle of certain parenteral products. Since the most common solvent for parenteral solutions is water, and the use of other types of solvents is limited, this usually is not a problem.

Moreover, the development of membrane filters composed of materials having **high resistance to most pharmaceutical solvents** has further reduced this problem since most of the membrane filters are disposable, the problem of cleaning after use is limited to the reusable filter housing and support screen.

These are usually made of **stainless steel or tough plastic polymers** that are cleaned rather easily.

Careful attention must be given, however, to **disassembly** of the housing and scrubbing to remove any residues that might **introduce** contamination in subsequent use.

Function of Filters.

The **pores, or holes**, through any filter medium consist of a **range of sizes**. For example, if a filter is designated as 0.2 micron porosity, the porosity most commonly used to effect sterilization, the maximum mean pore diameter is 0.2 micron, with many pores much smaller than this and a few larger. The latter may have diameters as large as 0.5 micron, but they are so few in number that the probability of a microbial spore (commonly rated as being 0.5 micron in diameter) finding those few pores is highly remote.

However, it must be recognized that there is a probability of this happening, even though remote. Therefore, it is no longer acceptable to consider such filters an absolute means of sterilizing a solution. To increase the probability of **achieving a sterile filtrate**, some researchers are proposing that the solution be passed through **a series of two 0.2-micron porosity filters**. Others have suggested that a 0.1-micron porosity filter be used, but this would greatly **reduce the flow rate**.

Since membrane filters function primarily by sieving, particles of any kind in a solution are **retained on the surface**.

If the content is relatively high, particles may **accumulate on the surface** and **plug the filter** so that the **flow of solution decreases and perhaps stops**.

To avoid this problem, when solutions have a high content of solids, particularly when the solids are deformable macromolecules, the solution can best be processed by **passing it through one or more prefilters**, the **first usually being a relatively porous depth filter.**

With depth filters, **particles may gradually migrate** through the filter if **filtration time is prolonged, if there is a high pressure differential, or if there is frequent fluctuation of the pressure.**

Liquid Flow Through a Filter.

The flow rate of a liquid through a filter is affected by the **size of the pores** through the filter, **the pore volume (the proportion of open space to solid matrix),** the **surface area of the filter, the pressure differential across the filter,** and **the viscosity** of the liquid.

Of these factors, the two most practical ways to **increase flow rate** is to **increase the surface area of the filter or the pressure differential across the filter.** There is a practical **limit to increasing the diameter of a disc filter**; thus, **if larger surface areas are required, a pleated filter in a cartridge form is often used.** In this way, a large increase in surface area may be achieved within a relatively small overall dimension of the filter unit.

Within the **limits of the physical strength of the filter and its housing**, the pressure differential can be increased to several hundred pounds per square inch. In pharmaceutical practice, however, the pressure differential used is **rarely more than 25 to 30 pounds per square inch.**

Usually, **positive pressure is applied** on the liquid upstream of the filter, but a **vacuum may** be drawn downstream of the filter. In the case of a vacuum, the maximum differential achievable is one atmosphere, or approximately 15 pounds per square inch.

Furthermore, the **negative pressure** in the filtrate chamber makes it **difficult to prevent the ingress of contamination from the environment.**

Therefore, for filtrations designed to render solutions sterile, it is preferable to apply pressure upstream of the filter using a gas filtered to be free from microorganisms. Any leakage that may occur in such a system causes loss to the outside without contamination of the sterile filtrate.

Solutions having a **high viscosity normally have a slow flow rate**. In most instances, the rate can be **increased by warming the solution**, thereby reducing its viscosity provided the warming does not have an adverse affect on the solution. As previously mentioned, the flow rate through a filter also depends on the relative pore volume of the filter. All filters must have a solid matrix that forms the framework for the pores.

The lower the amount of solid matrix is in proportion to the pore spaces, the higher are the pore volume and the flow rate.

Types of Filters.

Since the filter membranes are designed to be used once and then discarded, they are disposable; further, filter housings composed of plastic polymers, which are also intended to be disposable, are becoming increasingly available. Thus, all after-use cleaning is eliminated. In addition, the membrane filter is sealed into the housing by the manufacturer, so that the risk of leakage is minimal. Membrane filters are usually in the form of discs or pleated cylinders (cartridges). They range from 13-mm discs (approximately 0.8 cm^2) to 20-in. or longer cartridges (approximately 0.84 M2). The housings are usually of stainless steel or of various plastic polymers.

A few years ago, it was rather common practice to use filters that were reusable, such as diatomaceous earth, sintered glass, and unglazed porcelain. Because of the problems of adequate cleaning between uses and of testing, current applications of these filters are limited.

Chemical Processes of Sterilization

Gas Sterilization

Gas sterilization is not new. Such gases as **formaldehyde and sulfur dioxide** have been used for sterilization for many years. **These gases are highly reactive chemicals, however, and are difficult to remove from many materials after exposure.**

Therefore, their usefulness is limited.

Two newer gases, ethylene oxide and beta-propiolactone, have fewer disadvantages than the older agents and therefore have assumed importance in sterilization.

Ethylene Oxide.

Ethylene oxide (EtO) is a cyclic ether ($[CH_2]_2O$) and is a gas at room temperature. Alone, it is highly flammable, and when mixed with air, explosive.

Admixed with inert gases such as carbon dioxide , or one or more of the fluorinated hydrocarbons (Freons) in certain proportions, ethylene oxide is rendered nonflammable and safe to handle.

As a gas, **it penetrates readily such materials as plastic, paperboard, and powder.**

Ethylene oxide dissipates from the materials simply by exposure to the air. It is chemically inert toward most solid materials. **On the other hand, in the liquid state, as compressed in cylinders, ethylene oxide dissolves certain plastic and rubber materials and requires particular care in handling.**

Mechanism of Action.

Ethylene oxide is believed to exert its lethal effect upon microorganisms by **alkylating essential metabolites, affecting particularly the reproductive process**. The alkylation probably occurs by **replacing an active hydrogen on sulfhydryl, amino, carboxyl, or hydroxyl groups with a hydroxyethyl radical**. **The altered metabolites are not available to the microorganism, and so it dies without reproducing.**

Application.

Alkylation may also occur with drug molecules in pharmaceutical preparations, particularly in the liquid state. Therefore, ethylene oxide sterilization of pharmaceuticals is **limited essentially to dry powders of substances shown to be unaffected. It has extensive application, however, to plastic materials, rubber goods, and delicate optical instruments**. **It has also been found that stainless steel equipment has a longer useful life when sterilized with ethylene oxide instead of steam.** The effective penetrability of ethylene oxide makes it possible to sterilize parenteral administration sets, hypodermic needles, plastic syringes, and numerous other related materials enclosed in distribution packages of paperboard or plastic.

Beta-propiolactone.

Beta-propiolactone ($[CH_2]_2OCO$) is a cyclic lactone and **is a non-flammable liquid at room temperature**. It has a low vapor pressure, but since it is bactericidal against a wide variety of microorganisms at relatively low concentrations, no difficulty is experienced in obtaining bactericidal concentrations of the vapor.

It is an **alkylating agent and therefore has a mode of action against microorganisms similar to that of ethylene oxide**.

The penetrability of beta-propiolactone vapour has been found to be poor. Therefore, its principal use appears to be the sterilization of surfaces in large spaces, such as entire rooms.