Radiation technology in surgery and the pharmaceutical industry: An overview of applications

Drugs, tissues, and other medical materials sterilized by gamma rays are being used for health care in many countries

by Glyn O. Phillips

Although drugs such as antibiotics can attack and destroy bacteria within the human body, they are not self-sterilizing. Pharmaceuticals, and/or their associated adjuvants (materials used to aid the delivery of drugs) can harbour bacteria, either from a primary source of origin or introduced during the production process. Their sterilization can present a problem since many such substances react with ethylene oxide to produce toxic chemicals and are unstable to heat.

The alternative — to manufacture in a sterile environment — is expensive. Radiation, therefore, has long offered an imaginative alternative, and it was initially pursued indiscriminately. Consequently, those expecting radiation treatment to be a panacea, applicable to all states and mixtures, were disappointed. The best results have since been obtained when the established principles of radiation chemistry were applied.

Like all chemicals, pharmaceuticals, and adjuvants, can undergo chemical changes under the influence of radiation. Thus each system must first be rigorously studied to examine the chemical changes induced and to establish the maximum tolerated dose. Further trials may then be necessary to endure long-term stability, and to demonstrate that there is no loss of potency or harmful pharmacological change produced by the selected dose. Fortunately, there is now extensive scientific literature documenting the effects of radiation on pharmaceutical systems. The main lesson is that irradiation should be carried out in the dry, solid state within an inert atmosphere to minimize damage. The presence of water and oxygen lead to reactive free radicals which promote secondary chemical changes.

Whichever sterilization or processing procedure is selected, the final product must conform to standards of safety, quality, and efficacy set by national regulatory bodies. Generally, this means that the producer must convince the regulatory authority that the treatment has not changed the potency of the drug, nor introduced harmful degradation products. Despite the inevitable prejudice against radiation, steady progress has been made in the use of radiation to sterilize pharmaceuticals, often because no alternative was available, or the alternatives were too costly.

Although some drugs are administered topically in the pure, dry form, formulations generally are devised for administering or delivery of the active ingredient. For this purpose, oils or ointments in a paraffin or polyethylene glycol base, for example, are frequently used. Thus, the radiation stability of such adjuvant materials must be considered as well.

Pharmaceuticals, raw materials, and wound dressings

Most solid pharmaceuticals that are irradiated dry show no significant loss of potency when irradiated to 25 kGy, which must be the starting point for any evaluation of the technology's applicability. *(See table on page 21.)* It has, therefore, proved possible to use gamma radiation to sterilize commercially parenteral antibiotic preparations. Heat can exercise adverse effects on vegetable oils, but preparations such as testosterone propionate, tetracycline ophthalmic oil suspensions, and physostiginine salicylate in an oil base are stable

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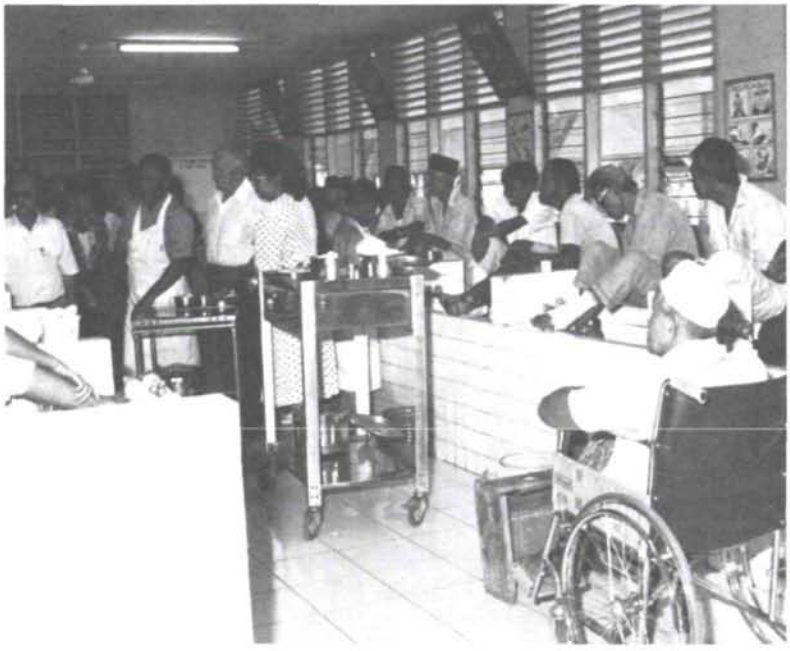

Patients at the Leprosarium, Sitanala Hospital, in Tangerang. Radiation sterilized amnion membrane has been used to heal their wounds. *(Credit: Newtech)*

Pharmaceutical products approved for sterilization by radiation

Regulatory bodies in a number of countries permit radiation sterilization of various pharmaceutical products. Below is a listing of approved products.

AUSTRALIA: Gaviscon; ispaghuyla husk; lubricating cream; lyophillized reagent kits of calcium-glucanate and DTPA for preparing technetium-99m radiopharmaceuticals; neomycin, polymixin, and bacitracin (separately or combined as a dusting powder); normal saline (for perfusing kidney transplants); opthalmic oil suspension of physostigmine salicylate; opthalmic ointment of mercuric oxide and sodium sulphacetamide; sutures.

INDIA: Absorbable gelatin sponge; catalin sodium tablets; fluorescein sodium strips; normal saline (for kidney perfusion); ophthalmic ointment in paraffin base in collapsible aluminium tubes (atropine sulphate; chloramphenicol; gentamycine sulphate; hydrocortisone and neomycin; tetracycline hydrochloride) and in soft gelatin capsules (chloramphenicol; gentamycine sulphate); prickly heat powder (antifungal containing boric and salicylic acids); raw materials (bella donna dry extract; ergot powder; papain; Rauwolfia serpentina powder); Ringer's lactate sodium; silver sulphadiazine; skin ointment in PEG base (neomycin sulphate; hydrocortisone acetate; alpha-chymotrypsin); sutures; veterinary products (quinapyramine prosalt).

INDONESIA: Herbal medicines; medicated dressings containing framycetin sulphate.

ISRAEL: Tetracycline hydrochloride ophthalmic ointment.

NORWAY: Chloramphenicol ointment.

UNITED KINGDOM: Atropine sulphate eye ointment 6%; chloramphenicol eye ointment; chloramphenicol ear ointment; chlorhexidine burn dressing; chlortetracycline eye ointment 1%; contact lens saline aerosol; corticosteroid ophthalmic ointment; Debrisan; neomycin ophthalmic ointment; sulphacetamide sodium eye ointment 6% tetracycline eye ointment 1%; tetracycline ophthalmic oily suspension 1%; tetracycline powder for i.m injection; tetracycline powder for i.v. injection; tetracycline topical ointment 3%; veterinary products.

UNITED STATES: Antibiotics; botanicals; chlortetracycline opthalmic ointment 1%; eye drops; eye ointments; injectables; pigments; steroids; Sutilains ointment USP; talc; tetracycline ophthalmic ointment 1%; veterinary products.

Source: Dr. Brian Read, Nordion International Inc., Canada.

to radiation. Various types of ophthalmic ointments have long been routinely sterilized by radiation. *(See box.)*

Raw materials. Radiation also is extensively used for the decontamination of naturally occurring excipient materials. Gum Arabic, a natural gum exudate from the African Acacia senegal tree is widely used as a tableting, coating, and encapsulating agent for the active ingredient. The natural product, as delivered to the processor, inevitably has a high microbial load. Radiation has been shown to be an excellent method to decontaminate Gum Arabic, without degradation, loss of functionality, or viscosity. For this gum, radiation is now favoured by the pharmaceutical industry, though not completely by the food industry where Gum Arabic is widely used as an ingredient and additive. Such up-

grading to acceptable microbial levels of bulk natural commodities is now an increasing application of radiation. (The European Commission is now poised to accept this process for food.)

A variety of other materials or thickeners can be sterilized without significant induced chemical change, if suitable irradiation conditions are selected. These include sodium carboximethyl cellulose, gelatin, starch, liquid paraffin, lanolin, and white soft paraffin.

Wound dressings. Wound-healing materials having a carbohydrate base also are regularly sterilized by radiation. One of the most well-known is Debrisan, a cross-linked dextran. It is produced as dry porous beads with highly hydrophilic properties. When poured on the secreting wound, Debrisan swells and seals the wound. The wound exudate with its associated bacteria is drawn into the three-dimensional macromolecular network, thus cleansing the wound. It reduces inflammation and edema, prevents crust formation, and keeps the surface soft and pliable. Debrisan can also be prepared as a paste with organic alcohols which are stable to radiation.The merit of the sterilization process is that the final dry product or paste can be processed in the packaged form. For packaged chemical wound and burn dressings, radiation is a valuable method of sterilization.

	Dose (kGy)	Loss of potency (%)
Chlortetracyline	17.9-100	0
Oxytetracyline	17.9-100	0
Chloramphenicol	17.9	0
Tetracyline hydrochloride	80	0
Streptomycin hydrochloride	25	0
Sodium benzyl penicillin	25	0
Phenoxymethyl penicillin	25	0
Benzathine penicillin	25	0
Dihydrostreptomycin	25	0
Potassium benzyl penicillin	17.9	0
Polymyxin sulphate	25	0
Polymyxin	up to 80	0
Colimycin	up to 80	0
Nystatin	up to 80	0
Mycerin	up to 80	0
Sulphapyridine	25	0
Sulphathiazole	25	0
Streptomycin sulphate	25	3
Dihydrostreptomycin	250	5
Neomycin sulphate	25	4
Sodium benzyl penicillin	250	~3
Benzathine penicillin	250	~3
Phenoxymethyl penicillin	250	~3
Zinc bacitracin	25	7.1
Zinc bacitracin	250	26.7

Loss of potency of solid irradiated pharmaceuticals

Radiation technology in surgery

Experience with tissue transplantation dates back some 2500 years to the Indian surgical empirics, who used a skin flap from the forehead to repair noses damaged in battle. The modern era started with the classical work of the Bologna surgeon Gaspare Tagliacozzi (1549-1599) entitled "The Surgery of Mutilation by Grafting". He described attaching a skin flap from the forearm to the nose, and when the repair had been effected after several weeks, severing the connection. Such a graft from the person to himself is referred to as an *autograft.* Tagliacozzi recognized the problems of transferring a graft from one person to another (termed an *allograft*). He rejected the idea because of "the force and power of the individual". It showed a remarkable prediction of what we now scientifically recognize as immunological rejection.

Surgery has passed through many conflicting phases since Tagliacozzi's time. John Hunter was the first to use the word "transplant", identifying the technique with "grafting" in the plant kingdom. There was a period at the end of the last century when allograft skin and parts of organs were used indiscriminately, and the consensus was that they worked. Reverdin (1842-1929) even reported success using animal graft skin *(xenograft).* In fact, they were confusing true grafting with in-growth of new skin. The period since has been dominated by the newly emerging immunological knowledge, and the conviction grew that only autografts would work. The most influential experiment was when Medawar and Gibson in the Medical Research Council's Burns Unit in Glasgow showed that a second set of skin grafts in a burn patient were rejected quicker than the first set. This seemed the final proof that allografts were of no clinical value.

Not so, however. The judgement was premature. Now more than 500 000 allografts are used surgically every year in the United States alone. The use of ionizing radiation for sterilizing tissue allografts has contributed significantly to this spectacular reversal of fortunes. The IAEA's programme on radiation sterilization of tissues has led to the establishment of multi-tissue banks in 13 countries in the Asia and Pacific region, and other banks now are emerging in Africa and South America.

To further promote progress, especially in developing countries, the IAEA has harnessed the support of major world associations which promote this technology. These include the

American Association of Tissue Banks; European Association of Tissue Banks; and the Asia and Pacific Surgical Tissue Bank Association. International meetings also are frequently convened at which the application of radiation in tissue sterilization and other areas of health care is evaluated.

Origin of the tissues

It is important to recognize that we are dealing here with the transplantation of non-viable (dead) tissues, not live organs. It is, therefore, low technology and extremely inexpensive. The IAEA's programme is concentrated on those tissues which are of maximum benefit to developing countries, and which reduce their dependence on expensive, imported prosthetic devices, artificial skin coverings, and wound dressings. These materials include bone, skin, amniotic membranes, tendons, and cartilage.

Both live and cadaveric human donors contribute to the supply of tissues. Throughout the world, total hip replacement (arthroplasty) surgery is practiced, which requires removal of the head of the femur. This bone from the live donors is retained for processing and future surgical use. When death occurs, donation by consent can provide the tissues within 24 hours after death. There are medical contra-indications which must be strictly observed. Malignancy, infectious diseases, prolonged drug therapy, or poisoning or drowning before death would preclude the use of the tissues.

With live donors, the blood is tested for all transmittable diseases. It further must be quarantined for 6 months, when a second blood test is carried out on the donor. This is because there can be a period of several weeks to 6 months between HIV infection and the appearance of the HIV-antibody.

It must be stressed that extreme sensitivity is maintained in the discussions with relatives to obtain permission for tissue donation. Great dignity is observed with the body and care is taken to reconstitute the limbs after procurement. All removed bones are replaced with identical structures made of wood or plastic so that finally there is no external damage observable on the body.

Processing and sterilization

Processing methodologies have been developed to reduce the level of contamination at each step, and provide the tissue in the form which is safe and useful to the surgeon. For bone in the Clwyd and Oswestry Research Tissue Bank, it has been found that an effective method is as follows:

Initially the bone is pasteurized at 56°C for 3 hours. HIV is inactivated in 20 minutes at this temperature. This treatment also inactivates heat labile enzymes, which might digest components, and kills heat sensitive organisms. At this temperature Bone Morphogenic Protein (BMP), which assists new bone to grow after implantation, is not inactivated. Soft tissues attached to the bone are excised. For femoral heads the cartilage is removed. The bones are then frozen overnight (-20°C) and cut using a motorized band saw. Bone pieces are continuously washed alternately in cold and hot (50°C) jets of water, when marrow and fats are removed. After freezing at -20°C for 4 to 5 days the bone is freeze-dried. The various shapes, sizes, and types of bone are double-packed in radiation resistant polyester/polyethylene film and grid-lacquered medical kraft paper. A third layer of polyethylene is applied at this stage and heat sealed. The package is finally sterilized by gamma radiation. All grafts are labelled, which accesses full details of the donor, and all operations to which the bone has been subjected.

A total quality system which encompasses good manufacturing practice governs all management and operations of the tissue bank. The processing reduces the antigenic properties and improves graft incorporation after transplantation. The cleaning and freeze-drying, followed by gamma radiation, applies equally to the processing of other tissues.

Programmes under the IAEA's Regional Co-operative Agreement for Asia and the Pacific now centre on introducing total quality systems and associated training. This is to ensure that all tissue banks have access to the best practices and full information about the most effective processing procedures. Open learning methods also are being introduced. When uniform systems are in operation, it is anticipated that individual tissue banks can be validated and sterile tissue allografts exchanged throughout the region.

For bone, sterilization by radiation is undoubtedly now the method of choice if only for its complete penetration of the most massive bone allograft. Additionally, toxic effects of freeze-dried bone allografts sterilized by ethylene oxide have recently been reported. In the irradiation process, the freeze-drying step reduces the water content to less than 5%, which reduces secondary effects from water-derived free radicals. The tissues most stable to radiation are those containing the highest proportion of collagen. The glycosaminoglycan is the most radiation-labile component of connective tissue. Excessive irradiation doses can, therefore, in-

fluence the mechanical behaviour of the tissue. Dose selection, therefore, is important. (A full account of this subject is available in the IAEA's 1986 Technical Document-454, *Technical and Economic Comparisons of Irradiation and Conventional Methods.)* The Agency's Co-ordinated Research Programme has enabled the optimum conditions to be established for minimal damage to the tissues on irradiation.

Surgical utilization

When bone is lost by disease or trauma, it must be replaced if the limb is to function. Prosthetic devices have been ingeniously produced from metal and synthetic polymers to support the body's mechanical structures. Once implanted, these must remain in the body throughout the person's lifetime. On the other hand when radiation sterilized allograft bone is used to replace the missing bone, it acts as a biocompatible scaffold. If the necessary criteria are followed, the patient's own bone, often in a matter of weeks, will grow into and incorporate the allograft. The structure is, therefore, all the patient's own bone. The dead bone has been transformed into new living bone. Hence, the motto of the USA's Bethesda Tissue Bank, *Et Mortua Vita* (The Dead Lives). Now, knowledge about the role of BMP, addition of the patient's own autologous marrow during transplantation, and good surgical fixation can greatly assist the growth of new bone by osteoconduction and osteoinduction.

Smaller allografts. The IAEA programme has not yet addressed the production and use of massive allografts for replacing sections of complete limbs when amputation may be the only other option. In general orthopaedics, the smaller allografts have a wider range of successful uses. Examples are:

- filling a cavity after removal of a cyst or benign tumours. The packed bone rapidly incorporates, promoting healing and re-modelling.
- acting as a buttress for skeletal structures. Here it is an osteoconductive scaffold for fractures involving articular surfaces.
- augmenting the amount of autograft which is necessary for promoting union ("biological weld") as in spinal fusion for scoliosis.
- in revision hip arthroplasty resulting from bone loss due to wear caused by the implanted prosthetic, resulting in loose hip and knee metal implants. This use will dramatically increase particularly for the younger, higher demand patient.
- in a wide range of oral surgery to fill cavities, repair trauma bone loss, and tumours of the mandible.

Allografts have many advantages over autografts. They can be stockpiled, and are available in quantity and in various sizes and shapes. In developing countries, they also help surgeons avoid taking the autograft from the patient, a process which extends surgical theatre time, consumes expert manpower, anaesthetics, and blood, for example, and is a potential new site of infection.

Membraneous tissues

Open wounds caused by either burn or ulcerations are the site of infection and fluid loss. The resulting metabolic dearrangements can prove fatal. In such circumstances, therefore, it is necessary to convert an open, potentially contaminated wound into a closed, clean wound as soon as possible. Radiation-sterilized, freeze-dried allograft skin or amnion can serve as a lifesaving bandage. With amnion, the angiogenic factors remaining in the processed membrane which sustained the baby in the womb also can assist when it is used as a bandage to promote granulation of the tissue and the development of new skin.

The IAEA programme has placed great emphasis on production of radiation-sterilized freeze-dried amnion dressings since many Moslem countries cannot readily obtain cadaver tissue. Treatment of burns in this way considerably lessens the pain and is extremely cost-effective when compared with the commercial alternatives. In Pakistan, for example, amnion is being produced at a fraction of a rupee per square inch, compared with 80 rupees for commercial skin/dressing.

The surgeon's approach to the use of allografts has, therefore, gone full circle. First misplaced confidence, then disenchantment, and now a realistic appraisal of the value. Radiation-sterilized allografts are now a part of the armoury of all up-to-date orthopaedic surgeons. Burn treatment can be greatly assisted by the use of allograft skin and amnion, which in developing countries can reduce the dependence on costly commercial synthetic alternatives.

Compared with the Creator, the chemist is still a novice in fabricating tissues. ❐