Underwood: Chapter 4: Responses to Cellular Injury

Cellular Injury

- Numerous causes: physical and chemical agents including products of micro-organisms

- Various mechanisms: disruption, membrane failure, metabolic interference (respiration, protein synthesis, DNA), free radicals

- May be reversible, or end in cell death

Causative Agents

- trauma

- thermal injury

- poisons

- drugs

- infectious organisms

- ionising radiation

Failure of Membrane Integrity

Cell membrane damage is an important mode of cellular injury for which there are several possible mechanisms:

- complement-mediated cytolysis

- perforin-mediated cytolysis

- specific blockage of ion channels

- failure of membrane ion pumps

- alteration of membrane lipids

- cross-linking of membrane proteins

Cell membrane damage is the one of the consequences of complement activation; some of the end products of the complement cascade (C5b, 8 and 9) have cytolytic activity. Another recently discovered effector of cytolysis is perforin, a mediator of lymphocyte cytotoxicity, that causes damage to the cell membrane of the target cells such as those infected by viruses.

Verapamil is a calcium channel blocker used in the treatment of hypertension and ischaemic heart disease.

Membrane pumps are dependent on an adequate supply of ATP. Any chemical agents that deplete ATP, either by interfering with mitochondrial oxidative phosphorylation or by consuming ATP in their metabolism, will compromise the integrity of the membrane pumps and expose the cell to the risk of lysis. The Na/K ATPase in cell membranes can be directly inhibited by ouabain.

Just as disastrous for the cell is biochemical alteration of the lipoprotein bilayer forming the cell membrane. This can result from reactions with either the phospholipid or protein moieties. Membrane phospholipids may be altered through peroxidation by activated oxygen species, such as free radicals, and by phospholipases. Membrane proteins may be altered by cross-linking induced by free radicals.

Blockage of Metabolic Pathways

Cellular Respiration

Prevention of oxygen utilisation results in the death of many cells due to loss of their principal energy source. Cyanide acts in this way by binding to cytochrome oxidase and thus interrupting oxygen utilisation. Cells with higher metabolic requirements for oxygen (i.e., cardiac myocytes) will be most vulnerable.

Protein Synthesis

The potent toxin, ricin, derived from the castor oil plant, acts in this manner at the ribosomal level. Many antibiotics, such as streptomycin, chloramphenicol and tetracycline, act by interfering with protein synthesis, although toxic effects by this mechanism are fortunately rare.

DNA Damage or Loss

Damage to DNA may not be immediately evident unless it involves a region of the genome that is being actively transcribed. Cell populations that are constantly dividing (i.e., labile cells such as intestinal epithelium and haemopoietic cells) are immediately affected by a dose of radiation sufficient to alter their DNA.

Normal erythrocytes are particularly sensitive to injury because they lack a nucleus and, therefore, the DNA template essential for repair.

Deficiency of Essential Metabolites

As vitamin E has an antioxidant effect, this may be protective in any situation characterised by the release of free oxygen radicals.

Oxygen Deprivation

The pathological process resulting from lack of oxygen due to impaired blood supply is *ischaemia.* The specific process of necrosis resulting from lack of blood supply is *infarction.*

Under some conditions it is possible for the onset of coagulative necrosis to be delayed until blood flow has been restored. This paradoxical phenomenon is known as *reperfusion injury* and may be due to the generation of reactive oxygen species and to the requirement for calcium ions, in the perfusing blood, in the ultimate stages of the development of necrosis.

Glucose Deprivation

Hormone Deficiency

Free Radicals

Free radicals are atoms or groups if atoms with an unpaired electron; as such, they may enter into chemical bond formation. They are highly reactive, chemically unstable, generally present only at low concentrations, and tend to participate in, or initiate, chain reactions.

Free radicals can be generated by two principal mechanisms:

- Deposition of energy, i.e., ionisation of water by radiation. An electron is displaced, resulting in free radicals.

- Interaction between oxygen, or other substances, and a free electron in relation to oxidation-reduction reactions. In this instance the superoxide radical could be generated.

The consequence of free radical formation include the following:

- A chain reaction may be initiated in which other free radicals are also formed. A common final event is damage to polyunsaturated fatty acids, which are an essential component of cell membranes.

- The free radical may be scavenged by endogenous or exogenous antioxidants, i.e., sulphydryl compounds such as cysteine.

- Superoxide radicals may be inactivated by the copper containing enzyme, superoxide dismutase, which generates hydrogen peroxide, catalase then mops this up to form water.

The clinicopathological events involving free radicals include:

- toxicity of some poisons (i.e., carbon tetrachloride)
- oxygen toxicity
- tissue damage in inflammation
- intracellular killing of bacteria.

Cellular Appearances Following Injury

Hydropic Change

The descriptive term hydropic change is applied to cells when the cytoplasm becomes pale and swollen due to the accumulation of fluid. Minor degrees of intracellular oedema are called cloudy swelling; a further increase in fluid and swelling of organelles results in the cytoplasm appearing vacuolated. Hydropic change is generally the result of disturbances of metabolism such as hypoxia or chemical poisoning. These changes are reversible, although they may herald irreversible damage if the casual injury is persistent.

Fatty Change

Vacuolation of cells is often due to the accumulation of lipid droplets as a result of a disturbance to ribosomal function and uncoupling of lipid from protein metabolism. The liver is commonly affected in this way by several causes, such as hypoxia, alcohol or diabetes. There may be many small vacuoles, or they may coalesce to form one large vacuole filling the cell and displacing the nucleus. Moderate degree of fatty change (steatosis) are reversible, but severe fatty change may not be.

Necrosis

- Death of tissues: causes include ischaemia, metabolic trauma

- Coagulative necrosis in most tissues; colliquative in brain

- Tuberculosis shows caseous necrosis

- Gangrene is necrosis with putrefaction: it follows vascular occlusion or certain infections

- Fibrinoid necrosis: arterioles in malignant hypertension

- Fat necrosis: in pancreatitis, or after trauma.

Death of cells or tissues in a living organism is referred to as necrosis, irrespective of the cause. It is a pathological process following cellular injury, and often involves a solid mass of tissue. Several distinct types of necrosis are recognised:

- coagulative
- colliquative
- caseous
- gangrene
- fibrinoid
- fat necrosis.

Coagulative Necrosis

Coagulative necrosis is the most common form of necrosis and occurs in almost all organs. Following devitalisation, the cells retain their outline as their proteins coagulate and metabolic activity ceases. The gross appearance will depend in part on the cause of cell death, and in particular on any vascular alterations such as dilatation, or cessation of flow. To begin with, the texture of the tissue will be normal or firm, but later it may become soft as a result of digestion by macrophages. This can have disastrous consequences in necrosis of the myocardium following infarction, as there is a risk of rupture of the ventricle.

In the first few hours, there will be no abnormality of staining. Subsequently, there will be progressive loss of nuclear staining until it ceases to be haematoxyphilic; this is accompanied by loss of cytoplasmic detail. The collagenous stroma is much more resistant to dissolution. The tissue retains a faint outline of its structure until such time as the damaged area is removed by phagocytosis (or sloughed off a surface), and is then repaired or regenerated, according to the organ involved. The presence of necrotic tissue usually evokes an inflammatory response.

Colliquative Necrosis

It is seen in the brain because of its lack of any substantial supporting stroma; thus, necrotic neural tissue is liable to total liquefaction. There will be a glial reaction around the periphery, and the site of necrosis will be marked eventually by a cyst.

Caseous Necrosis

Tuberculosis is characterised by caseous necrosis, a pattern of necrosis in which the dead tissue lacks any structure. An amorphous eosinophilic area is stippled by haematoxyphilic nuclear debris.

Gangrene

It is necrosis with putrefaction of the tissues sometimes as a result of the action of certain bacteria, notably clostridia. The affected tissues appear black, because of the deposition of iron sulphide from degraded haemoglobin. Thus, ischaemic necrosis of the distal part of a limb may proceed to gangrene if complicated by an appropriate infection. As clostridia are very common in the bowel, intestinal necrosis is particularly liable to proceed to gangrene; it can be seen as a complication of appendicitis, or incarceration of a hernia if the blood supply is impeded. These are examples of 'wet' gangrene. In contrast, 'dry' gangrene is usually seen in the toes, as a result of gradual arterial or small vessel obstruction in atherosclerosis or diabetes mellitus, respectively. In time, a line of demarcation develops between the gangrenous and adjacent viable tissues.

In contrast to the above, primary infection with certain bacteria or combination of bacteria may result in similar putrefactive necrosis. Gas gangrene is the result of infection by *Clostridium perfringens,* while synergistic gangrene follows infection by combination of organisms, such as *Bacteroides* and *Borrelia vincenti.*

Fibrinoid Necrosis

In the context of malignant hypertension, arterioles are under such pressure that there is necrosis of the smooth muscle wall. This allows seepage of plasma into the media with consequent deposition of fibrin. The appearance is termed fibrinoid necrosis. With H-E staining, the vessel wall is a homogenous bright red.

Fat Necrosis

May be due to:

- direct trauma to adipose tissue and extracellular liberation of fat

- enzymatic lysis of fat due to release of lipases.

Following trauma to adipose tissue, the release of intracellular fat elicits a brisk inflammatory response, with polymorphs and macrophages phagocytosing the fat, proceeding eventually to fibrosis. The result may be a palpable mass, particularly at a superficial site such as the breast.

In acute pancreatitis, there is release of pancreatic lipase. As a result, fat cells have their stored fat split into fatty acids, which then combine with calcium to precipitate out as white soaps. In severe cases, hypocalcemia can ensue.

Apoptosis

It is the elimination of individual cells and is a physiological process requiring energy. The process is mediated by endogenous endonucleases. The cell shrinks to a hyperchromatic mass and rapidly fragments into apoptotic bodies. It is the normal means of maintaining the size of an organ in the face of continuing cell turnover, or a reduction in size during atrophy. Lymphocyte proliferation in germinal centres and the thymus is followed by apoptosis of unwanted cells. Pathologically, it is seen in circumstances of individual cell killing, such as in viral hepatitis where the brightly eosinophilic apoptotic cells are known as Councilman bodies.

Healing, Repair and Regeneration

- Cells can be divided into labile, stable or permanent populations; only labile and stable cells can be replaced if lost

- Complex tissue architecture may not be reconstructed

- Healing is restitution with no, or minimal, residual defect, i.e., superficial skin abrasion, incised wound healing by first intention

- Repair is necessary when there is tissue loss: healing by second intention.

Cell Populations

Once adult life is reached cells can be divided into three populations labile, stable and permanent according to their potential for renewal.

Labile Cells

Labile cells have a good capacity to regenerate. Surface epithelial cells are typical of this group; they are constantly being lost from the surface and replaced from deeper layers.

Stable Cells

Stable cell populations divide at a very slow rate under physiological conditions, but still retain their capacity to divide when necessary. Hepatocytes and renal tubular cells are good examples.

Permanent Cells

Nerve cells and striated muscle cells are regarded as permanent because they have no capacity to divide.

Tissue Architecture

Structures such as intestinal villi that depend largely on the epithelium for their shape can be rebuilt. However, complex arrangements such as the renal glomeruli cannot be reconstructed if destroyed.

Complete Restitution

Loss of part of a labile population of cells can be completely restored. For example, consider the result of a minor skin abrasion. The epidermis is lost over a limited area, but at the margins of the lesion there remain cells that can multiply to cover the defect. In addition the base of the lesion probably transects the neck of sweat glands and hair follicles; cells from here can also proliferate and contribute to healing. At first, cells proliferate and spread out as a thin sheet until the defect is covered. When they form a confluent layer, the stimulus to proliferate is switched off; this is referred to as *contact inhibition*, and controls both growth and movement. Once in place, the epidermis is rebuilt from the base upwards until it is indistinguishable from normal. This whole process is called *healing.*

Granulation Tissue

- A repair phenomenon

- Loops of capillaries, supported by myofibroblasts

- Inflammatory cells may be present

- Actively contracts to reduce wound size; this may result in a stricture later.

When specialised tissue is destroyed, it cannot be reconstructed; a stereotyped response then follows, a process known as *repair*. Capillary endothelial cells proliferate and grow into the area to be repaired; initially they are solid buds but soon they open into vascular channels. The vessels are arranged as a series of loops arching into the damaged area. At the same time, fibroblasts are stimulated to divide and to secrete collagen; they also acquire bundles of muscle filaments and attachments to adjacent cells and stroma. These modified cells are called myofibroblasts, and display features and functions of both fibroblasts and smooth muscle cells. As well as secreting a collagen framework, they play a fundamental role in wound contraction. This combination of capillary loops and myofibroblasts is known as granulation tissue. The name derives from the appearance of the base of a skin ulcer; when the repair process is observed, the capillary loops are just visible and impart a granular texture. Such a name is less appropriate for an internal repair, but is used despite this. Granulation tissue must not be confused with a granuloma (an aggregated of epithelioid histiocytes).

Organisation

- The repair of specialised tissues by the formation of a fibrous scar

- Occurs by the production of granulation tissue and removal of dead tissue by phagocytosis.

Organisation is the name given to the process whereby specialised tissues are repaired by the formation of mature fibrovascular connective tissue. Granulation tissue is formed in the early stages, often on the basis of fibrin, and any dead tissue is removed by phagocytic cells such as neutrophil polymorphs and macrophages. The granulation tissue contracts and gradually accumulates collagen to form a scar.

Organisation is a common consequence of pneumonia, inflammation of the alveoli of the lung in which inflammatory exudate fills the alveoli. The exudate subsequently becomes organised. Organisation also occurs when a volume of tissue dies as a result of cessation of its blood supply (an infarct). In all instances, the organised area is firmer than normal, and shrunken or puckered.

Wound Contraction and Scarring

Wound contraction plays a considerable role in reducing the volume of tissue for repair; the tissue defect may be reduced by 80%. It is the result of the contraction of myofibroblasts in the granulation tissue. These are attached to each other and to the adjacent ground substance, so that granulation tissue as a whole contracts and draws together the surrounding tissues. Collagen is secreted at the same time and forms a local scar in place of the specialised tissues lost.

Although wound contraction serves a very useful function, it can also lead to problems. If the tissue damage is circumferentially around the lumen of the gut, subsequent contraction may progress until it causes obstruction. Similarly, burns to the skin can be followed by considerable contraction, with resulting cosmetic damage and, often, impaired mobility.

Outcome of Injuries in Different Tissues

Skin

The process of healing of a skin wound depends on the size of the defect.

Incised Wound: Healing by First Intention

An incision such as that made by a surgical scalpel causes very little damage to tissues on either side of the cut. If the two sides of the wound can be brought together accurately, then healing can proceed with the minimum of delay or difficulty. It is obvious that at least some small blood vessels will have been cut, but these will be occluded by thrombosis, and close apposition of wound edges will help. Fibrin precipitated locally will then link across the two sides. Coagulated blood on the surface forms the scab, and helps to keep the wound clean. This join is very weak, but is formed rapidly and is a framework for the next stage. It is important that it is not disrupted, and sutures, sticking plaster or other means of mechanical support are invaluable aids. Over the next few days, capillaries proliferate sufficiently to bridge the tiny gap, and fibroblasts secrete collagen as they migrate into the fibrin network. If the sides of the wound are very close, then such migration is minimal, as would be the amount of collagen and vascular proliferation required. By about ten days, the strength of the repair is as good as the adjacent normal tissues. The only residual defect will be the failure to reconstruct the elastic network in the dermis.

The basal epidermal cells proliferate to spread over any gap. If the edges of the wound are gaping, then the epidermal cells will creep down the sides. Eventually, when the wound is healed, these cells will usually stop growing and be resorbed, but occasionally they will remain and grow to form a keratin-filled cyst (implantation dermoid).

Tissue Loss: Healing by Second Intention

When there is tissue loss or some other reason why the wound margins are not apposed, then another mechanism is necessary for repair. For example, if there is haemorrhage locally, then this will keep the sides apart and prevent healing by first intention; infection will have a similar effect in addition to its own particular consequences. A local loss of an epithelial covering is referred to as an *ulcer*. This is a purely descriptive term and does not imply any particular cause, such as trauma, inflammation or neoplasia. The response will be characterised by:

- phagocytosis to remove any debris
- granulation tissue to fill in defects and repair specialised tissues lost
- epithelial regeneration to cover the surface.

The time scale will depend upon the volume of the defect, since this determines the amount of granulation tissue to be generated and the area to cover with epithelium. Quite large expanses of tissues can be removed if necessary, and the defect left to heal by second intention. The final cosmetic result will depend upon how much tissue loss there has been, as this will affect the amount of scarring.

Keloid Nodules

Dermal injury is sometimes followed by excessive fibroblast proliferation and collagen production. This phenomenon is genetically determined, and is particularly prevalent among Negroes. A mass several centimetres across may follow surgery or injury, particularly burn.

Gastrointestinal Tract

The fate of an intestinal injury depends upon its depth.

Mucosal Erosions

An erosion is defined as loss of part of the thickness of the mucosa. Viable epithelial cells are immediately adjacent to the defect, and rapidly proliferate to regenerate the mucosa. Such an erosion can be covered in a matter of hours, provided that the cause has been removed. Notwhitstanding this remarkable speed of recovery, it is possible for a patient to lose much blood from multiple gastric erosions before they heal. In such a patient, if endoscopy to identify the cause of haematemesis is delayed, the erosions may no longer be present, and thus escape detection.

Mucosal Ulceration

Ulceration is loss of the full thickness of the mucosa, and often the defect goes much deeper to penetrate the muscularis propria. Destroyed muscle cannot be regenerated, and the mucosa must be replaced from the margins. Damaged blood vessels will have bled and, in time, the surface will be covered by a layer of fibrin. Macrophages then migrate in to remove any dead tissue by phagocytosis. Meanwhile, granulation tissue is produced in the ulcer base, as capillaries and myofibroblasts proliferate. Also, the mucosa will begin to regenerate at the margins and spread out on to the floor of the ulcer.

If the cause persists, the ulcer becomes chronic and there is a continuing oscillation between further ulceration and repair. This may result in considerable destruction of the gastric wall. If healing ever proceeds far enough, the fibrous scar tissue that has replaced muscle will contract, with distortion of the stomach and possible obstruction. There may be a zone of inflammation around the ulceration, and if this abuts the vessel it results in a reactive proliferation of the vascular intima. This feature is referred to as *endarteritis obliterans* on account of the obliteration of the lumen; it has nothing specifically to do with end arteries.

Bone

- Haematoma organised and dead bone removed
- Callus formed, then replaced by trabecular bone
- Finally remodelled
- Fracture healing delayed if bone ends are mobile, infected, very badly misaligned or avascular.

Fracture Healing

Immediately after the fracture, there will be haemorrhage within the bone from ruptured vessels in the marrow cavity, and also around the bone in relation to the periosteum. Clinical management must take account of the volume of blood lost since this may be substantial if several large bones are broken (i.e., femur, tibia and pelvis in a severe road traffic accident); although occult, such haemorrhage may result in shock. A haematoma at the fracture site facilitates repair by providing a foundation for the growth of cells. There will also be devitalised fragments of bone, and probable soft tissue damage nearby. The opening phases of repair will thus be removal of necrotic tissue and organisation of the haematoma. The latter takes a special form, as the capillaries will be accompanied by fibroblasts and osteoblasts. These lay down bone in an irregularly woven pattern. The mass of new bone, sometimes with islands of cartilage, is called *callus;* that which lies within the medullary cavity is internal callus, while that in relation to the periosteum is external callus. The latter is helpful as a splint, although it will need to be resorbed eventually. Woven bone is subsequently replaced by more orderly, lamellar bone; this in turn is gradually remodelled according to the direction of mechanical stress.

Problems With Fracture Healing

Several factors can delay, or even arrest, the repair of a fracture:

- movement

- interposed soft tissues

- gross misalignment

- infection

- pre-existing bone disease.

Movement between the two ends, apart from causing pain, also results in excessive callus and prevents or slows down tissue union. If continued, movement will prevent bone formation and collagen is laid down instead to give fibrous union; the result is the formation of a false joint at the fracture site. Movement of a lesser degree gives rise to excessive callus which takes a long time to be resorbed and may impinge on adjacent structures.

Gross misalignment also slows the rate of healing and will prevent a good functional result, leading to increased risk of accelerated degenerative disease (osteoarthrosis) in adjacent joints.

If the bone broken was not normal, the break is called a *pathological fracture.*

Liver

Hepatocytes have excellent regenerative capacity, although they are a stable population and replicate only slowly. The hepatic architecture, however, cannot be satisfactorily

reconstructed if severely damaged. Consequently, conditions that simply result in hepatocyte loss may be followed by complete restitution, whereas damage destroying both the hepatocytes and architecture may not. In the latter situation, the imbalance between hepatocyte regeneration and failure to reconstruct the architecture may proceed to cirrhosis.

Kidney

The kidney is similar to the liver. Loss of tubular epithelium following an ischaemic episode or exposure to toxins may result in clinical renal failure, but in general there is sufficient surviving epithelium to repopulate the tubules and enable normal renal function to return. Inflammatory or other damage resulting in destruction of the glomerulus is likely to be permanent or result in glomerular scarring, with loss of filtration capacity. Similarly, interstitial inflammation is liable to proceed to fibrosis and, thus, impaired reabsorption from tubules into the circulation.

Muscle

Voluntary and cardiac muscle fibres and smooth muscle cells are a permanent population; vascular smooth muscle may be different, in that new vessels can be formed. This means that damaged muscle is replaced by scar tissue. However, if the contractile proteins only are lost, then it is possible to synthesise new ones within the old endomysium.

Neural Tissue

- CNS does not repair effectively

- Peripheral nerves show Wallerian degeneration distal to trauma; variable recovery depending on alignment and continuity

- May produce amputation neuroma.

There is no effective regeneration of neurones in the CNS. Glial cells, however, may proliferate in response to injury, a process referred to as *gliosis.*

Peripheral nerve damage affects axons and their supporting structures, such as Schwann cells. If there is transection of the nerve, axons degenerate proximally for a distance of about one or two nodes; distally, there is Wallerian degeneration followed by proliferation of Schwann cells in anticipation of axonal regrowth. If there is good realignment of the cut ends, the axons may regrow down their previous channels (now occupied by proliferated Schwann cells); however, full functional recovery is unusual. When there is poor realignment or amputation of the nerve, the cut ends of the axons still proliferate, but in a disordered manner, to produce a tangled mass of axons and stroma called an *amputation neuroma.* Sometimes, these gives rise to painful sensations and have to be removed.

Modifying Influences

- Damage to fetus or infant may affect subsequent development

- In general, children heal rapidly

- In old age, reserve capacity is reduced and there may be coexistent disease, such as ischaemia

- Vitamin C deficiency impairs collagen synthesis

- Malnutrition impairs healing and resistance to disease

- Excess steroids, advanced malignancy, and local ischaemia impair healing

- Denervation increases tissue vulnerability.

Various factors can impair healing and repair:

- age, both very young and elderly

- disorders of nutrition

- neoplastic disorders

- Cushing's syndrome and steroid therapy

- diabetes mellitus and immunosuppression

- vascular disturbance

- denervation.

Age

Early in life, cellular injury is likely to impair or prevent the normal growth and development of an organ. Organogenesis is at risk if there is impaired function, differentiation or migration of the precursor cells.

The distal pulmonary airways may be permanently damaged by severe infection or mechanical stress, as in whooping cough.

Disorders of Nutrition

Wound healing is profoundly influenced by the ability to synthesise protein and collagen. The latter is dependent on vitamin C for the hydroxylation of proline as a step in collagen synthesis. Scurvy (vitamin C deficiency) leads to wound healing of greatly reduced strength; capillaries are also fragile and thus haemorrhages occur.

Protein malnutrition, whether due to dietary deficiency or the consequence of protein loss, also impairs wound healing. In addition, severe malnutrition reduces the ability to respond to infection; tissue damage may then proceed unimpeded with a fatal outcome. For example, measles is generally a transient problem in well-nourished children, but is frequently fatal in the malnourished.

Neoplastic Disorders

In advanced malignant neoplastic disease with widely disseminated tumours, or gastrointestinal symptoms such as dysphagia, the patient is malnourished. However, a catabolic state with profound weight loss may be an early feature of some cancers. Such patients show evidence of impaired healing, and this may compromise the recovery from attempted surgical removal of the lesion.

There may also be evidence of impaired healing localised to the vicinity of the tumour. Skin stretched over a superficial tumour will often break down and ulcerate, and it is necessary to treat the tumour to promote healing of the ulcer. A pathological fracture of bone through a metastatic deposit of tumour may not heal unless the tumour is dealt with first; in practice, the management often includes irradiation to the tumour and internal fixation of long bones.

Cushing's Syndrome and Steroid Therapy

Excessive circulating corticosteroids, whether they result from tumour or from therapeutic administration, have two effects on tissue injury:

- Due to their immunosuppressive actions, the consequences of injury of infection may be more severe.

- Steroids impair healing by interfering with the formation of granulation tissue and, thus, wound contraction.

Diabetes Mellitus and Immunosuppression

They increase susceptibility to infection by low-virulence organisms, and put the patient at risk of tissue damage. The normal healing responses are possible, although they may be impaired by continuing infection. Diabetes may affect polymorph function, and may also result in occlusion of small blood vessels and cause neuropathy.

Vascular Disturbance

An adequate vascular supply is essential for normal cellular function. An impaired supply can result in ischaemia or infarction. What is an adequate supply for resting tissue may prove inadequate if the demand increases.

Healing is impaired. This occurs because hypoxia and reduced local nutrition result in poorer tissue regrowth or repair.

Denervation

An intact nerve supply supports the structural and functional integrity of many tissues. In addition, nerves have a role in mediating the inflammatory response which is part of the host mechanism for limiting the effects of injury. Denervated tissues may become severely damaged, probably through a combination of unresponsiveness to repeated minor trauma, and lack of awareness of intercurrent infection or inflammation. Thus, patients with conditions such as peripheral neuropathy or leprosy may develop ulceration of the foot (neuropathic ulcers); with intervention and care to prevent further injury, healing is possible. A neuropathic joint (Charcot's joint) may be damaged unwittingly and progressively beyond repair.

Ionising Radiation

- Electromagnetic and particulate: background, accidental, occupational and medical exposure

- Indirect effect of oxygen radicals and hydroxyl ions on DNA

- Rapidly dividing cell populations show early susceptibility

- Chronic effects: fibrosis and increased tumour risk

- Tumour induction roughly proportional to dose received.

Definition and Sources

The formation of ions on interaction with matter (ionising radiation). The exception is UV light.

Ionising radiation includes:

- electromagnetic: X-rays and gamma-rays

- particulate: alpha, beta (electrons), neutrons.

Electromagnetic Radiation

Only part of the electromagnetic spectrum produces ionising events. The production of ions requires a photon of high energy and thus of short wavelength, in practice shorter than that of ultraviolet light.

Particulate Radiation

The distinction between beta particles and electrons is the same as that between gamma-rays and X-rays; beta particles are produced through the process of radioactive decay, whereas electrons are a structural component of atoms.

Units of Dose

The current unit of absorbed dose is the gray (Gy). It is equivalent to 100 rads, the previous unit, and is the usual measure of therapeutic irradiation when a uniform type of irradiation is administered to a specific tissue.

Alpha particles are about 20 times more damaging than beta particles or X-rays. For comparative purposes it is useful to make mathematical corrections, and express the result as the effective dose equivalent, measured in sieverts (Sv): this is the equivalent to 100 rem, the previous unit.

Another relevant unit is a measure of the rate of disintegration of unstable atoms. One becquerel (Bq) is one emission per second; it replaces the curie (Ci); one Ci equals 3.7×10^{10} Bq. The becquerel is not itself a measure of dose, because it expresses only a rate of disintegration irrespective of the nature or energy of the products of disintegration. However, for any particular atom the latter is known, so the dose can be calculated.

Background Radiation

In the UK the average annual dose is 2. mSv, which comes from:

- natural sources (87%)

- artificial sources (13%).

Over 90% of the artificial component is from medical usage. The natural component is made up from cosmic, terrestrial, airborne and food sources. The most locally variable among these is the airborne radiation, which derives mainly from radon and radon daughters; these diffuse out of the ground and are commoner in certain types of rock, such as granite.

Mode of Action

When radiation passes through tissue, any collisions within it will be randomly distributed amongst its components. However, it seems that direct damage as a result of ionisation of proteins or membranes does not make a major contribution to the biological end result. Water is the most prevalent molecule, and following ionisation several types of short-lived but highly reactive radicals are formed such as H+ and hydroxyl radical OH-. In a well-oxygenated cell, oxygen radical will also be formed, i.e., hydroperoxyl radical, HO_2- and superoxide radical O_2-.

These radical then interact with macromolecules, of which the most significant is DNA.

DNA Damage

The types of radiation-induced DNA damage include:

- strand breaks

- base alterations

- cross-linking.

Breakage of the DNA strand is a common result of irradiation. When only one strand is broken, repair can generally be accomplished accurately; however, double-strand breaks may prove impossible to repair because there is no template.

Base alterations are also frequent, such that the DNA strand no longer transcribes correctly.

DNA strand cross-linking occurs when irradiation fuses the complementary strands, resulting in an inability to separate and thus to make a new copy. DNA replication is therefore blocked. This effect is also the mechanism of action of alkylating agents, hence their description as 'radiomimetic drugs'.

Mammalian cells given about 1.5 Gy of X-rays will show extensive base damage and about 1000 strand breaks, some 50 of which will be double-strand; two-thirds of the cells will die. However, there are repair enzyme systems to cope with ionising radiation and similar damage from UV light. If these are deficient, as in the condition xeroderma pigmentosum, the patient will show increased radiosensitivity.

Effects on Tissues

DNA damage may have three possible consequences:

- cell death, either immediately or at the next attempted mitosis

- repair and no further consequence

- a permanent change in genotype.

Acute Effects

They are generally the result of cell killing and the interruption of successful mitotic activity. Hierarchical cell organisations, such as the bone marrow or gut epithelium, which have a dividing stem cell population and daughter cells of finite life expectancy, will show the most pronounced effects. In essence, the supply of functioning differentiated cells is cut off or suspended. In addition, there is vascular endothelial damage, resulting in fluid and protein leakage rather like that of the inflammatory response.

Chronic Effects

Vascular endothelial cell loss will result in exposure of the underlying collagen. This will prompt platelet adherence and thrombosis, which is subsequently incorporated into the vessel wall and is associated with the intimal proliferation of endarteritis obliterans. A possible result of this is long-term vascular insufficiency with consequent atrophy and fibrosis.

However, the observed atrophy may simply be a function of continuing cell loss over a long period of time, reflecting an inherently slow rate of proliferation of cells in the tissue concerned. If this is the case, the vascular alterations are part of the chronic radiation process, but not the cause of the atrophy.

The cellular alterations induced by irradiation are permanent. The limits of tissue tolerance cannot be exceeded even if many years have elapsed.

Bone Marrow

Ultraviolet Light

It has a range of wavelengths:

- UVA 320-400 nm

- UVB 290-320 nm.

UVB is associated with sunburn and can also cause skin tumours; although not ionising, it damages DNA by inducing pyrimidine dimers and thus strand linkage. UVA probably induces non-dimer damage, and also inhibits DNA repair processes. The tumours produced are basal cell and squamous cell carcinomas, and malignant melanomas.

Far-UV (210-290 nm) is very toxic and is used in germicide lamps. However, the solar radiation in this range is filtered out by the ozone layer.

Therapeutic Irradiation: Radiotherapy

- Fractionation enables higher doses to be given

- Typical tumours treated: basal cell carcinoma of skin, squamous cell carcinoma of larynx, malignant lymphoma, seminoma of testis

- Effects and complications are delineated by the fields given.

Localised malignant lymphoma is often irradiated, whereas generalised lymphoma is treated by chemotherapy. Metastatic seminoma of testis in para-aortic lymph nodes is usually irradiated.

Palliative radiotherapy is often given to treat metastatic tumour deposits, such as painful bone secondaries.

Response Modifiers

The most common reason for reduced sensitivity in a tumour is a low oxygen tension.

Radiosensitisers are drugs that diffuse into tissues, including avascular areas, and, by mimicking the effect of oxygen, enhance the response. The nearest equivalent is the use of psoralens to enhance the efficacy of UV light in the management of psoriasis.

Complications of Radiotherapy

Nausea and vomiting are more likely to occur when large volumes of tissue are treated.

Permanent atrophy of major and minor salivary glands.