Jamieson & Kay's Textbook of Surgical Physiology

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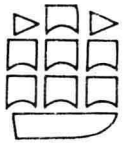
THIRD EDITION



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1. Wound Healing and Fibrosis

The survival of an individual depends on the integrity of his tissues and organs. If continuity is lost following disease or injury, a restorative process is rapidly initiated. In superficial abrasions and certain visceral injuries this is predominantly a regenerative process but elsewhere the end result is simple fibrous union by scar. This non-specific connective tissue is most easily recognised in a healing incision but is found wherever tissues are damaged. The same general process can be observed in organising thrombus, granulating wounds and the reactive tissue round a slowly growing neoplasm. Usually scar formation is uneventful but sometimes it is excessive. The resulting fibrosis impairs function and may threaten life.

THE ORGAN OF REPAIR

Connective tissue is produced by granulation tissue. This delicate matrix of cells and capillaries heals the wound and should be accorded the status, albeit temporary, of the organ of repair (Fig. 1.1). Good healing is dependent on its healthy growth and development and when repair is over it disappears. The fibroblast is a key cell, synthesising collagen and ground substance. Its normal function is critically dependent on a readily available supply of diffusible oxygen and the limiting level of 10 to 15 mmHg is found 50 to 80 μm from the nearest normally perfused capillary (Fig. 1.2) (Hunt *et al.*, 1969; Silver, 1969). For this reason the fibroblasts and capillaries develop together as a unit, and anything interfering with the delivery of oxygen to the wound has adverse effects on the repair process.

THE REPAIR PROCESS

Mechanical aspects

The rate of gain of strength is of particular importance in many wounds and has proved to be one of the most useful indications of the progress of repair. The general form of recovery is the biological growth curve with three distinct phases. In the first few days there is no recordable tensile strength but enzyme and cellular activity is marked. This is the *phase of preparation* during which the foundations of repair are laid. After the fourth or fifth day collagen and ground substance appear in the wound in increasing amounts and strength rises rapidly. This is the *phase of proliferation* in which the fibroblast-capillary system is most active. After a month or so the wound activities moderate. Strength recovers more slowly and there is a progressive diminution of cell population and vascularity. This *phase of maturation* continues for many months.

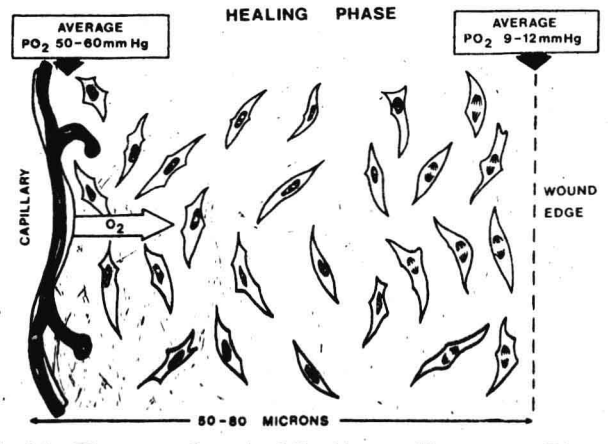

Fig. 1.1 The organ of repair of fibroblast-capillary system. Diagram showing Po_2 gradients in healing granulation tissue. The activity of fibroblasts is limited at Po_2 10 mmHg and they must therefore keep within 50 to 80 μm of the nearest functioning capillary. Healing cannot progress until new capillaries develop. (Reproduced by permission from Hunt, T. K. *et al.*, 1969.)

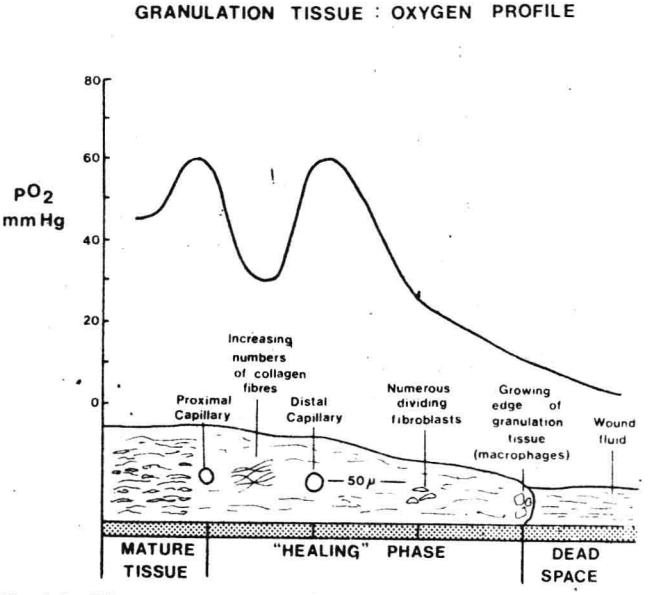

Fig. 1.2 Direct measurements of Po_2 in granulation tissue growing into a wound chamber. There is a steady fall from the normal mature tissue level of around 54 mmHg to anoxic levels in the centre of the wound. Macrophages have a lower oxygen requirement than fibroblasts and are found at the free edge of the growing granulation tissue. (After Silver, I. A., 1969.)

Over 75 per cent of the strength of the intact abdominal wall resides in its aponeurotic layers. Wounds in this tissue recover remarkably slowly. There is a rapid gain in strength during the first few weeks but after that progress is less obvious and by the end of a year there is only 70 per cent recovery (Fig. 1.3) (Douglas, 1952). More recently the same strength changes have been recorded in healing skin wounds, but this is of less moment since skin scar is protected from direct physical forces by its elastic surrounds.

Connective tissues are complex visco-elastic materials with time dependent properties. Their true ability to resist rupture is therefore incompletely assessed by simple breaking strength studies. A good scar has to be both strong and pliable. This is

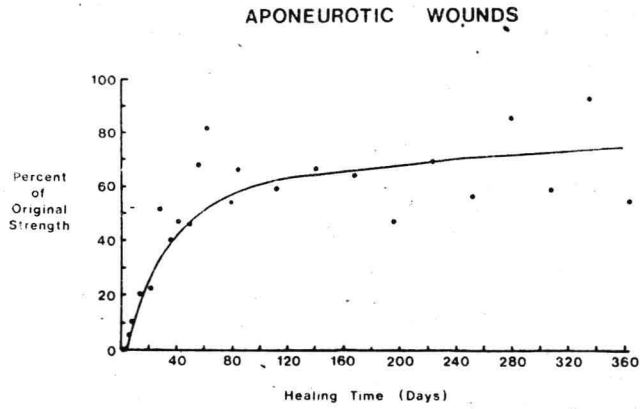

Fig. 1.3 Breaking strength of healing aponeurotic wounds. Strength increases rapidly for several weeks but then slows. There is only 70 per cent recovery by the end of a year. (After Douglas, D. M., 1952.)

exemplified using bioengineering techniques to analyse healing skin wounds (Forrester *et al.*, 1970). Scar tissue is not only weaker but more brittle than normal. After five months it has only half the ability of normal tissues to resist rupture (Fig. 1.4).

Histological aspects

Light microscopic studies show a characteristic sequence of events (Fig. 1.5). The fresh wound is rapidly united by a fibrin coagulum containing trapped red cells, debris and devitalised tissue. Neutrophils can be seen in increasing numbers after 8 hours and monocytes towards the end of the first day. Fibroblasts can be recognised after 24 hours but are not numerous till active microcirculation is established a few days later. At the end of a week the fibroblast-capillary system is actively synthesising collagen and ground substance. The neutrophils play an important role in dealing with contaminating bacteria but apart from this are not directly involved in the process of wound healing. When an animal is treated with anti-neutrophil serum, they disappear from the wound but

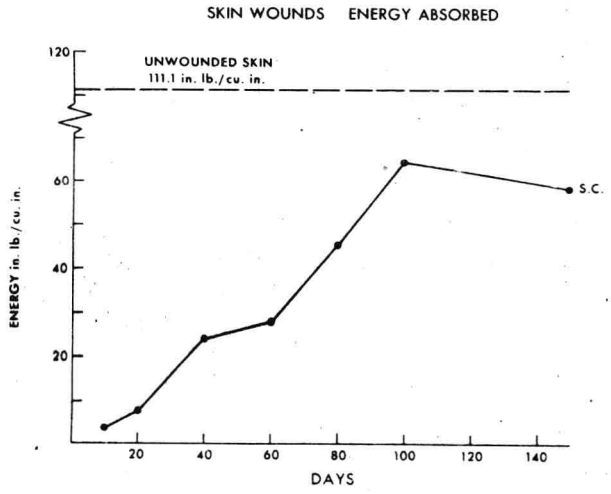

Fig. 1.4 The ability of a wound to resist rupture expressed as its energy absorption. There is only a 50 per cent recovery by 150 days. (Reproduced by permission from Forrester, J. C. *et al.*, 1969, *Journal of Surgical Research*, **9**, 207-212.)

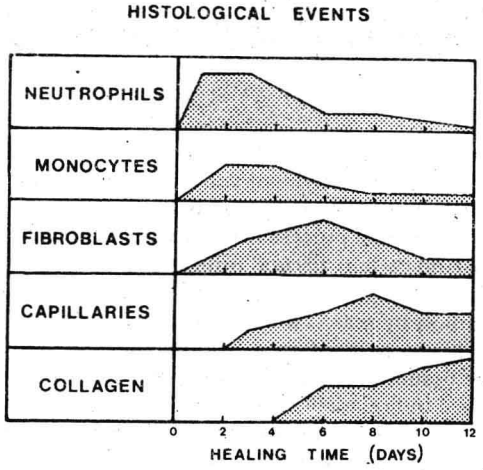

Fig. 1.5 The characteristic sequence of events in the first few days of wound healing. Neutrophils and monocytes appear first. Collagen appears following development of a functioning fibroblast-capillary system.

healing is undisturbed (Simpson and Ross, 1972). The monocyte is the precursor of the macrophage but not the fibroblast. Macrophages have low oxygen requirements and are found at the free edge of the wound (see Fig. 1.2) (Silver, 1969). In addition to their scavenging activities they stimulate fibroplasia. When antimacrophage serum is used along with steroids to induce monocytopenia collagen formation is delayed. A platelet factor is also known to be important in stimulating fibroblasts to synthesise collagen.

The fibroblast is the surgeon's cell arriving on the scene to synthesise the collagen and ground substance of wound repair. When its work is done it disappears. Studies in parabiotic rats show it is of local origin from the perivascular areolar tissue (Ross *et al.*, 1970). This is an important argument for avoiding unnecessary local trauma or tissue undermining during surgery.

Healing wounds have two striking physical abnormalities. First, the collagen bundles in the scar are distinctly narrower than those found in the mature tissue on either side. Secondly, normal collagen is markedly birefringent whereas wound collagen is not. This indicates a failure of organisation at the molecular or small fibril level (Douglas *et al.*, 1969).

Scanning electron microscopy is particularly useful for demonstrating physical factors such as fibre shape and weave (Forrester *et al.*, 1969). It provides a high magnification, three-dimensional image of large volumes of tissue and resolution is particularly good since it is determined by electron optical considerations. Normal skin has a well organised network of large collagen fibres (Fig. 1.6). Each large fibre is made up of a bundle of fine cross-banded fibrils. Wound collagen is quite different. At 10 days the collagen fibrils lie relatively haphazardly (Fig. 1.7). As time goes by the fibrils coalesce to form large irregular masses. However there is no evidence of fibril sub-structure and remodelling is minimal. It seems likely that normal collagen fibre patterns are not restored (Fig. 1.8).

Biochemical aspects

Scar tissue is a matrix of cells and fibres embedded in a ground substance. There is little doubt that the physical

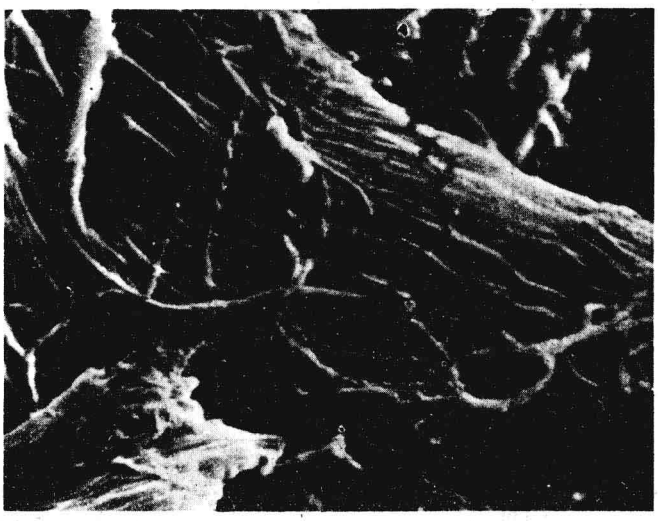

Fig. 1.6 Scanning electron micrograph of part of a normal collagen fibre showing that it is made up of bundles of cross-banded fibrils (× 9750). (Reproduced by permission from Forrester, J. C. *et al.*, 1969.)

properties of the wound are determined by their interaction as well as the quantity and quality of each. In practice, collagen is the main element contributing to wound strength and the permanent soundness of repair. Apart from being prominent in healing wounds it is the general support tissue of the body, forming some 30 per cent of the total protein content of most animals. A knowledge of its formation and resorption mechanisms is fundamental to understanding normal growth and development and a variety of connective tissue disorders.

Collagen is formed in the endoplasmic reticulum of the fibroblast and excreted into the extracellular space in monomeric form (tropocollagen) (Grant and Prockop, 1972). When synthesis is upset as in scurvy, precursor material

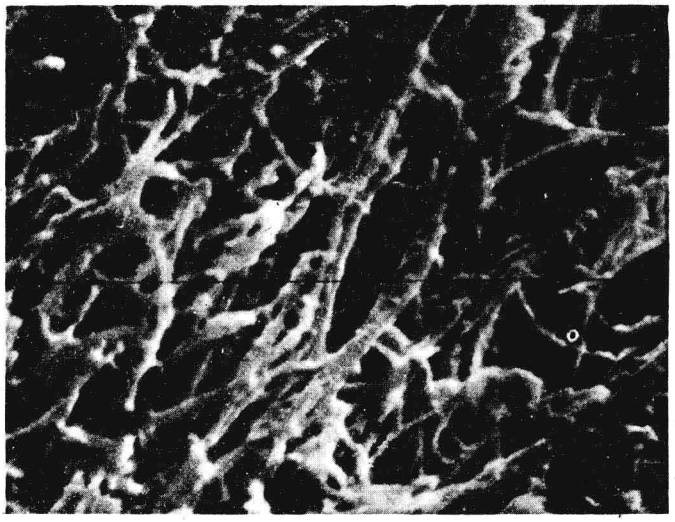

Fig. 1.7 Scanning electron micrograph of a 10-day sutured wound showing the randomly orientated collagen fibrils. They show little tendency to aggregate. Cross-banding is not apparent (× 9750). Compare with the normal skin shown in Figure 1.6 at the same magnification. (Reproduced by permission from Forrester, J. C. *et al.*, 1969.)

Fig. 1.8 Scanning electron micrograph of a representative portion of a 100-day wound. The collagen fibrils have aggregated to form large collagen masses but the network architecture of the normal has not been restored. Compare with the unwounded skin in Figure 1.6.

collects and distorts the cell (Figs. 1.9 and 1.10) (Ross and Benditt, 1964). The collagen molecule is a rigid rod 300 nm long and 1·5 nm wide. Each is composed of three polypeptide chains (α-chains) wound in a left-hand helix. The molecule itself is twisted the opposite way in a right-hand super-helix. There are five genetically distinct α-chains and these are grouped into four types of collagen molecule. Type I predominates in mature skin, tendon and bone, Type II is found in cartilage, Type III features in cardiovascular structures and infant skin while Type IV is confined to basement membranes (Miller and Matukas, 1974).

Each α-chain contains more than 1000 amino acids but

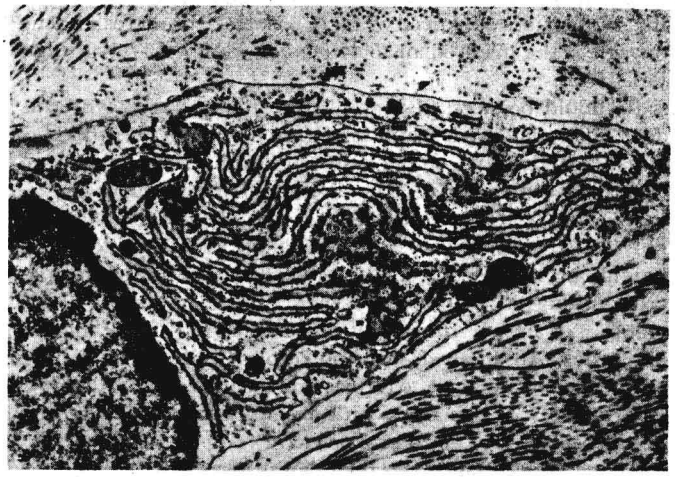

Fig. 1.9 Electron micrograph of part of a normal fibroblast. Note the characteristic well developed endoplasmic reticulum. The lining ribosomes, which are responsible for its 'rough' appearance, are the active site of collagen synthesis. New collagen fibrils are rapidly excreted and are seen here surrounding the cell. Electron micrograph (× 9000). (Courtesy of Professor Russell Ross, Seattle.)

glycine, proline and hydroxyproline together account for over half the molecule. The individual amino acids are assembled in the endoplasmic reticulum of the fibroblast beginning at the amino terminal end and proceeding towards the carboxy terminal end. Hydroxyproline and hydroxylysine are not incorporated directly into the collagen molecules. A proline and lysine rich collagen precursor molecule, protocollagen, is formed and then hydroxylation is carried out under the influence of protocollagen hydroxylase. This enzyme has the specific requirements of molecular oxygen, alpha-ketoglutarate, ferrous iron and ascorbic acid and is one reason why collagen synthesis is delayed in scurvy (Hutton *et al.*, 1967). Iron deficiency has no practical importance but hypovolaemia and poor delivery of oxygen can markedly retard

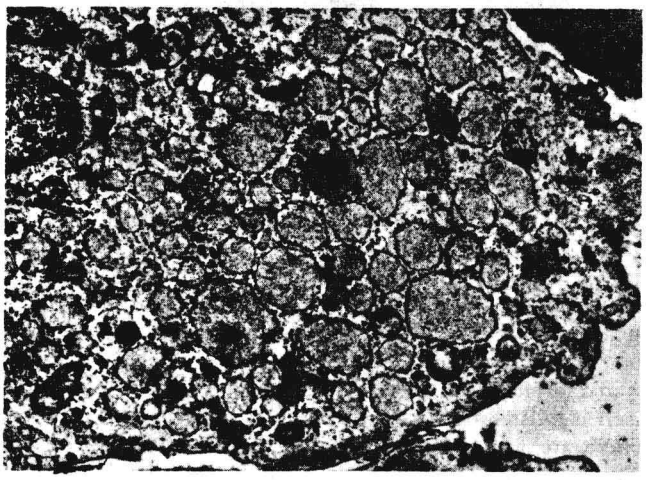

Fig. 1.10 Electron micrograph of part of a scorbutic fibroblast. Note the typical distended endoplasmic reticulum. There is no sign of collagen but it will appear within 24 hours of providing ascorbic acid. Electron micrograph (× 9000). (Courtesy of Professor Russell Ross, Seattle.)

collagen synthesis (Heughan *et al.*, 1974). Recent studies show that synthesis is enhanced when PO_2 is raised by increasing the oxygen in the inspired air to 45 per cent (Fig. 1.11) (Hunt and Pai, 1972).

It should be stressed at this point that collagen synthesis does not equate with wound healing. Although many factors enhance individual components of the healing process no factor has as yet gained general clinical significance.

As soon as tropocollagen leaves the fibroblast it starts to polymerise and forms strong covalent crosslinkages with neighbouring molecules. Intramolecular and intermolecular crosslinking is initiated by oxidative deamination (lysyl oxidase) of amino groups of lysine and hydroxylysine to form aldehydes. An aldehyde can undergo an aldol condensation with a second aldehyde to form a strong covalent bond directly. Alternatively, it can react with an amino group and form a Schiff base (Grant and Prockop, 1972).

At one time collagen was regarded as metabolically inert. In scar tissue this is far from the case (Madden and Peacock, 1968). Although the total amount of collagen in a wound may reach normal levels after 60 to 80 days qualitative changes continue for a good deal longer (Fig. 1.12). These play a major role in determining the ultimate strength of wounds in fascia

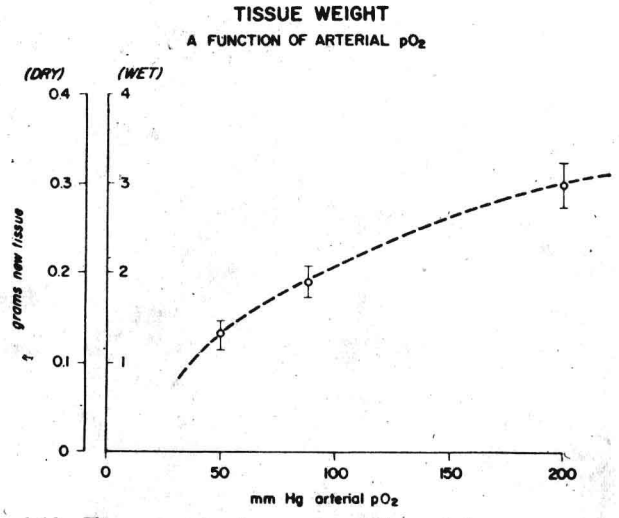

Fig. 1.11 The amount of new tissue formed in a wound is considerably greater when arterial PO_2 is increased by changing the ambient oxygen from 14 to 20 to 45 per cent for 25 days. (Reproduced by permission from Hunt, T. K., 1970, *J. Trauma*, **10**, 1001-1009.)

and skin. Specific studies of wound collagen turnover using tritiated proline show how these qualitative changes may be brought about. Collagen synthesis and lysis continue to run at high rates long after the total amount of collagen in the wound has returned to normal (Fig. 1.13). The loss of collagen substance is not confined to the wound and is particularly marked in the mature collagen on either side (Fig. 1.14). As a result it temporarily becomes weaker and may hold sutures less well. The continued collagen turnover means that wound scar is less stable than normal. For example, in scurvy collagen

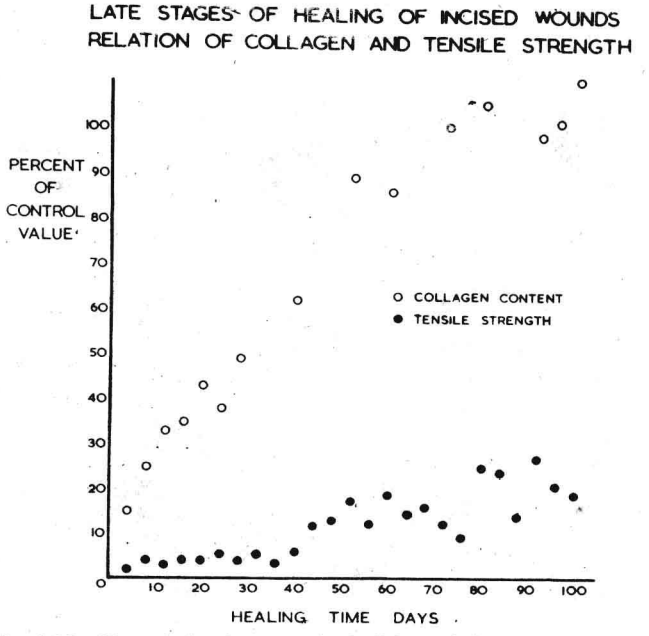

Fig. 1.12 The relation between the build-up of fibre collagen and tensile strength in healing guinea-pig skin wounds. The collagen has reached its control value by 80 days when the wounds are still only 25 per cent as strong as unwounded skin. (Reproduced by permission from Douglas, D. M. *et al.*, 1969.)

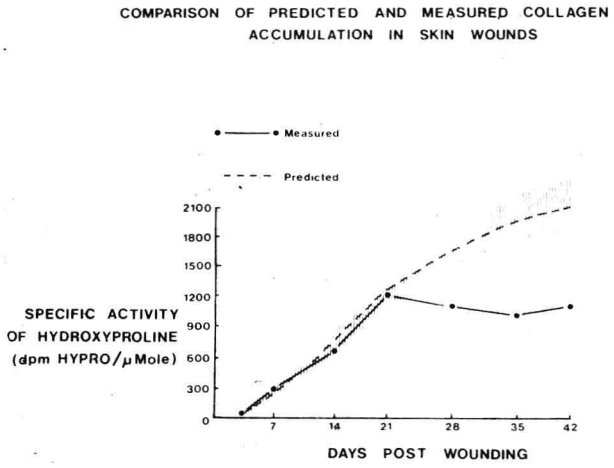

Fig. 1.13 Comparison of scar collagen accumulation predicted from its rate of synthesis with that actually measured. Total collagen does not increase after 3 weeks even though it continues to be synthesised and deposited at a rapid rate. Collagen is now being removed as quickly as it is formed (collagenolysis). The difference between the curves represents scar collagen turnover. (Reproduced by permission from Madden, J. W. and Peacock, E. E. Jr., 1971, *Annals of Surgery*, **174**, 511-520.)

synthesis fails and if lysis continues the wound will weaken and possibly break. If lysis is less prominent than synthesis then a hypertrophic or keloidal scar may result (Craig *et al.*, 1975). Enzymes other than collagenase are also active in the early phases of wound healing (Fig. 1.15) (Raekallio, 1972). Adenosine tri-phosphatase can be found within an hour of injury. Aminopeptidase is present after about 2 hours and the phosphatases appear at 4 and 8 hours. This sequence can be detected histochemically and used together with the degree of leucocytic infiltration to determine the age of a wound. It also proves to be a useful way of assessing wound treatments and dressings and suture absorption mechanisms (Salthouse and Williams, 1969).

The ground substance

All connective tissues contain fibres and cells embedded in a variable quantity of ground substance. The chemistry of the ground substance is complex and incompletely understood (Bentley, 1967). In general, there are a number of related structural polysaccharides, of which chondroitin-4-sulphate is one of the better known. In wounds these are usually found as large protein-polysaccharide complexes called proteoglycans (mucopolysaccharides) (Jackson, 1975). The basic structure is a central protein core bordered by repeating disaccharide units. The ground substance appears to play a role in the organised precipitation of collagen as well as helping determine the physical properties of the scar. The mechanical behaviour of a fibre-gel-fluid system depends as much on its amorphous element as its fibrous component, and there is evidence that the interaction between collagen and ground substance in scar is different from that occurring in normal tissue.

Superficial wounds

Although epithelial and mesenchymal interactions are prominent in embryonic life there is less indication of their relationship after birth. It is therefore not inappropriate to consider the healing of superficial or open wounds separately from the general process of connective tissue formation.

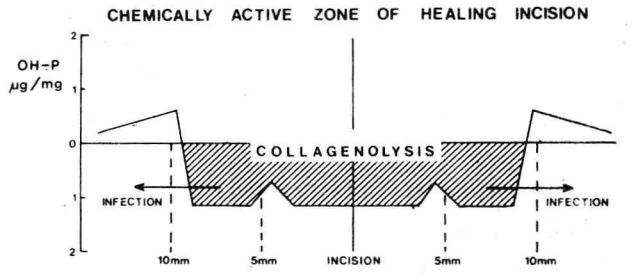

Fig. 1.14 The chemically active zone of an incised wound extends for at least 5 mm on either side of it. Collagenolysis is prominent in the first week and is even more marked when infection is present. (After Adamsons, R. J. *et al.*, 1966, *Surgery, Gynecology and Obstetrics*, **123**, 515-521.)

Superficial or open wounds heal by a combination of epithelialisation (Van Winkle, 1968) and contraction. The stimulus for epithelial repair is not clear but the loss of contact of one cell with another is of prime importance (Abercrombie and Heaysman, 1954). There is also evidence that intact epithelium produces an inhibitory local hormone or chalone (Bullough and Laurence, 1960). When epithelium is removed chalone levels fall. Either way repair is accomplished by a combination of cell migration and multiplication which does not cease until edge to edge apposition of cells has been re-established. Epithelialisation is delayed by drying and scab formation, and proceeds most readily in moist areas, provided they can be kept free from infection. It now appears that in many apparently normal situations the oxygen supply is less than optimal, for epithelialisation has been accelerated using oxygen permeable wound covers and intermittent hyperbaric oxygenation (Winter, 1972).

The other mechanism by which an open wound closes is contraction (Van Winkle, 1967). This form of tissue migration involves the entire thickness of skin and subcutaneous tissues. The prime movers are specialised myofibroblasts in the wound margin (Ryan *et al.*, 1974). It therefore proceeds independently of collagen formation but is readily disturbed by irradiation and cortisone. Although less important in man than many

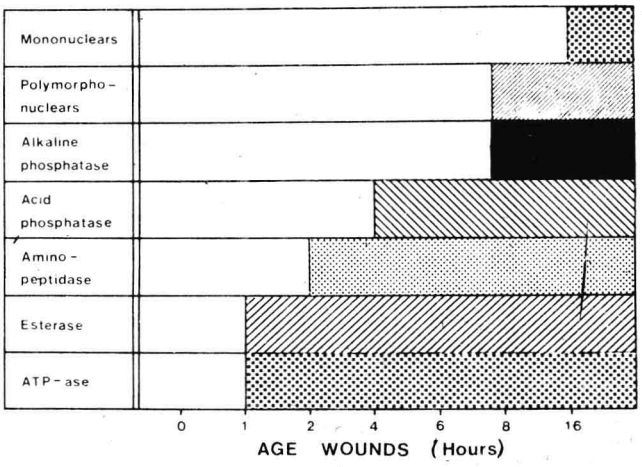

Fig. 1.15 Schematic diagram showing the histochemical estimation of the age of ante-mortem skin wounds. (Reproduced by permission from Raekallio, J., 1972.)

animals it contributes significantly to wound closure where skin is slack, as on the abdomen and back of the neck. Elsewhere it is less effective. It is important to differentiate this physiological process from pathological fibrosis and wound contracture.

FACTORS AFFECTING HEALING

Although many factors affect healing few have attained general clinical significance. Studies of the metabolic response to trauma show that the wound has a compelling biological priority and usually heals satisfactorily even in ill patients. Many of the principles have been established in animal studies and may have less significance for man. For instance, guinea pigs die relatively quickly when ascorbic acid is withheld and rats do not tolerate starvation for more than a week or two. In both situations man can survive for months.

Age

Healing is at its most vigorous in the young and hyperplastic scars and keloids are more common then.

Protein

Experimental studies showed that protein starvation retarded repair unless sulphur-containing amino acids such as methionine were supplied. Recent work confirms the adverse effects of protein deprivation but does not support the claims made for methionine. In patients the situation is less clear. Uneventful healing is usually the rule and hypoproteinaemia is not always correlated with wound dehiscence (Keill *et al.*, 1973). It seems that protein deficiency has to be associated with a body weight loss of about 20 per cent before the chance of wound failure becomes significant.

Vitamin C

Although ascorbic acid is required for synthesis and maintenance of collagen there is little evidence that it matters much in practice. However, following trauma and general bodily stress there is an enormous metabolic demand for it and daily supplements of up to one gram are fully utilised (Fig. 1.16).

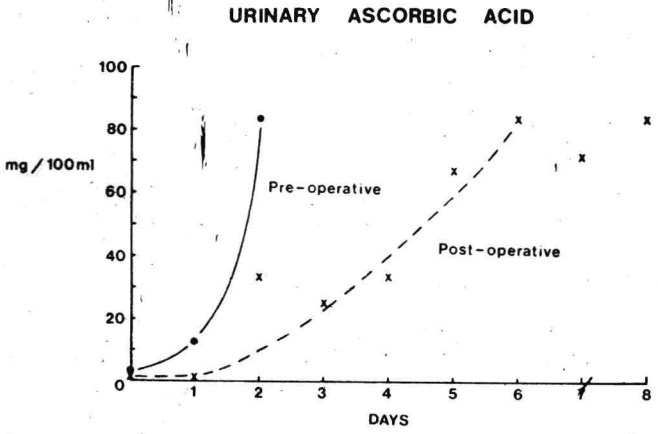

Fig. 1.16 The effect of trauma on the urinary excretion of a daily oral supplement of one gram of ascorbic acid. Normally, tissue saturation is effected within 48 hours and urinary levels are high. Following operation the body's requirement for ascorbic acid appears to be considerably increased, and tissue saturation is not achieved for 5 to 6 days.

Therefore, when sub-clinical scorbutic states are suspected it would seem wise to supplement it (Booth and Todd, 1970).

Oxygen

Good healing is dependent on a readily available supply of oxygen. Although fibroblasts, neutrophils and macrophages do not necessarily die in low oxygen concentrations they are unable to perform their more specialised synthetic and bactericidal functions. The fibroblast requires an ambient PO_2 of around 10 mmHg if it is to synthesise collagen and ground substance properly. Prior to the establishment of a functioning microcirculation wound PO_2 is well below this (Hunt *et al.*, 1969). When wound perfusion is normal satisfactory PO_2 levels are found up to 70 μm from the nearest capillary (Silver, 1969). The delivery of oxygen depends on the natural vascularity of the tissue as well as the quality of blood flow. Wounds in highly vascular tissues such as the face heal more rapidly than those in relatively ischaemic areas. The single most important factor is maintenance of blood volume but blood viscosity, vasomotor activity and pulmonary and cardiac function can seriously impair oxygen supply and delivery. Experimental studies confirm the essential rate limiting role of oxygen in healing reactions. Collagen synthesis is increased by raising the concentration of inspired oxygen to between 35 and 70 per cent (Niinikoski, 1969; Hunt and Pai, 1972).

Trauma

The wound that heals best is the sharp clean cut. Any further local injury delays healing by impairing the vitality of the

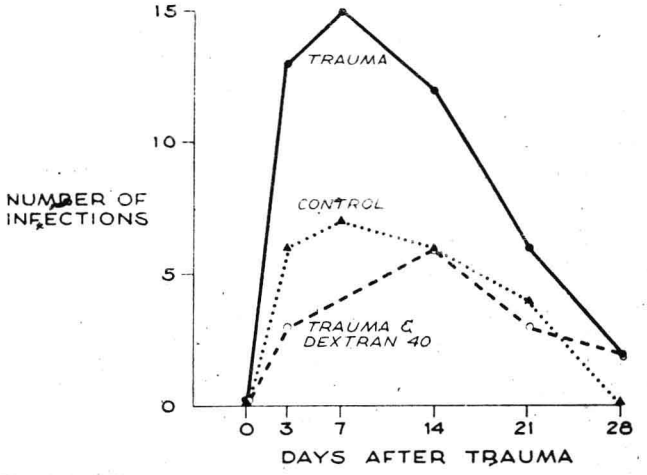

Fig. 1.17 There is a marked increase in infections when wound perfusion is impaired following injury to another part of the body. Restoration of blood flow by administration of low molecular weight dextran reduces the infection rate to normal. (Reproduced by permission from Connolly *et al.*, 1969, *Surgery, Gynecology and Obstetrics*, **128**, 713-718.)

tissues. This in turn encourages the development of infection which further interferes with healing. A severe injury elsewhere in the body may also upset healing and enhance infection by causing a generally impaired capillary flow and wound hypoxia. An infusion of low molecular weight Dextran or simple restoration of blood volume reverses these effects (Fig. 1.17) (Zederfeldt and Hunt, 1968).

Metabolic diseases

Diabetes, jaundice and uraemia are associated with impaired healing of an unpredictable degree (McDermott *et al.*, 1968; Lee, 1972). In diabetes the main problem is believed to be due to the upset carbohydrate metabolism in the wound. The poor tissue perfusion and increased susceptibility to infection simply make matters worse. In jaundice there is evidence of impaired fibroblast function and delay in angiogenesis. Uraemia retards connective tissue formation and slows epithelial repair.

Corticosteroids

Cortisone impairs collagen synthesis and enhances collagen lysis (Berliner *et al.*, 1967). A minimal inflammatory response is required for satisfactory wound healing and because of this anti-inflammatory drugs such as cortisone markedly impair healing when administered at the time of wounding. After three days, when healing is established, the effect is much reduced. In open wounds cortisone retards contraction at any time but healing has been restored to normal on several occasions by systemic or local applications of vitamin A (Ehrlich *et al.*, 1973).

Radiation and cytotoxic drugs

Since healing is primarily a cellular activity agents causing cell damage should have a marked effect on it. Ionising irradiation destroys cells and irreversibly damages capillaries and small blood vessels. The effects are cumulative and progressive and fully irradiated tissue finishes up as a somewhat ischaemic material with little potential for repair. Scars in irradiated areas are unstable and may break down or become neoplastic.

Although cytotoxic drugs interfere with cell proliferation they do not have a marked effect on wound healing. Topical nitrogen mustard impairs healing but intra-arterial injection has no effect (Newcombe, 1966) provided it is given before cell proliferation is prominent. Other studies are less easily interpreted since the picture is confused by general systemic effects such as weight loss and bone marrow depression. As a general rule systemic administration of cytotoxic drugs in therapeutic doses causes less problems than their local application.

Temperature and cartilage powder

Vital processes involve chemical reactions. In cold blooded animals a very marked increase in healing rate results when the temperature is raised from 20°C to 30°C. Likewise, the increased blood flow and warmth following sympathectomy has a markedly beneficial effect on healing in peripheral vascular disease. Recent studies show that both open wounds and incisions heal best when a thermo-neutral state is maintained at environmental temperature of 30°C (Cuthbertson, 1970). Attempts to accelerate healing in other ways have met with little success. For example, addition of a mucopolysaccharide preparation of cartilage results in a 20 per cent increase in wound strength at 7 days but the effect is not maintained (Prudden *et al.*, 1957). In terms of ultimate wound strength it is of no practical significance.

Zinc

Small amounts of zinc are essential to life, and quite large oral supplements appeared to accelerate healing of pilonidal wounds and indolent leg ulcers (Pories *et al.*, 1967). This role is still not clarified because the subject is exceedingly complex and a number of good studies have produced conflicting results. Recently there has been renewed interest. In areas of the world where zinc is naturally deficient it limits growth and the onset of puberty in man. There is also evidence that it plays an important role in stabilising macromolecules and biological membranes as well as in the biosynthesis of collagen. In silicotic lung disease, zinc appears to stabilise lysosomes and therefore reduces tissue necrosis and the resulting fibrosis. It also directly protects the macrophage from damage by silica (Chvapil, 1974).

FAILURE OF HEALING

When healing is progressing normally it gives little trouble but when it is defective life may be endangered. Although healing is a unified response to injury, failures usually present in the apparently distinct categories of infection, dehiscence and fibrosis. In practical terms it is of inestimable value to be able to predict these problems before they arise and so avoid or minimise their effects.

Infection

Wound sepsis is the most important cause of defective healing. It retards collagen synthesis and enhances breakdown of pre-existing collagen. Although bacterial contamination is a prerequisite several other factors help determine whether or not a wound suppurates.

The susceptible individual is often debilitated or suffering from a generalised disorder such as diabetes or leukaemia. Alternatively his lowered resistance may be a side effect of immuno-suppressive regimens, long-term corticosteroids or cancer chemotherapy. In cardio-pulmonary disease wound perfusion is often poor and local oedema makes matters worse.

Bacterial contamination may be exogenous or endogenous. The relative importance of each depends on the particular circumstances under consideration. Usually, endogenous organisms outnumber exogenous and the latter only become important when there is little or no endogenous component, as in the clean wound types associated with specialised orthopaedic, cardiac and neurosurgical procedures.

Exogenous contamination is minimised by strict attention to the established aseptic and antiseptic regimens. The importance of protective coverings for patient and staff is unquestioned although the enhanced bacterial transfer when these become wet is sometimes overlooked. Glove technique is important even when skin preparation is faultless. Examination of gloves shows that almost one-third become punctured or torn during surgery and up to one thousand staphylococci can pass through a single needle hole within a minute. Plenum ventilation with 12 to 18 changes of filtered air per hour suits most theatre requirements.

Ultraviolet irradiation reduces airborn contaminants by half and sterile laminar flow systems discourage mixing with air that may already be contaminated (Charnley, 1973). These measures can be important in ultra-clean surgery but have little

relevance when endogenous organisms predominate. A simple and effective way to cut down aerial contamination is to keep physical activity to a minimum, avoid unnecessary conversation and adopt hand signals where possible. Staphylococcal carriage is only important in those who 'shed' the organism. Fortunately shedding is usually from a single site and can be eliminated effectively if not permanently by prompt local treatment with appropriate topical antibiotics.

In general surgery, endogenous organisms are the principal contaminants (Shaw *et al.*, 1973) and less than 5 per cent of wound infection results from airborne bacteria. In the absence of active inflammatory disease the potential contaminants are to be found on the body surfaces so, when the skin is prepared effectively, the wound is not exposed to bacteria unless an internal epithelial surface is breached. Wounds for operations such as lumbar sympathectomy and thyroidectomy, in which

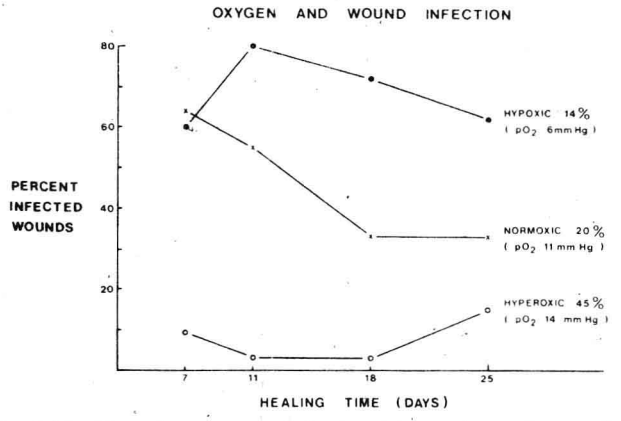

Fig. 1.18 Hypoxia enhances infection in experimental wounds. Increasing the oxygen in the inspired air has the reverse effect. (Reproduced by permission from Hunt, T. K. *et al.*, 1972, *Surgical Forum*, **23**, 47-49.)

there is no internal epithelial incision, are classified as 'clean' and should not become infected in more than 1 or 2 per cent of cases. Elective gastric and biliary operations include internal epithelial incision and are classified as 'clean-contaminated' wounds. Their infection rate may be as high as 5 or 6 per cent. When infection rates rise above these levels the likely causes are breaks in asepsis or poor surgical technique. When the operation site is acutely inflamed or purulent the wound is 'severely contaminated' and may have an infection rate as high as 40 per cent.

Sometimes pathogens reach the wound following transient bacteraemia associated with bowel manipulations or the gentle rocking of an infected tooth in its socket. On other occasions there is an obvious septic focus elsewhere in the body. Recent studies have identified the particular hazard of contaminated intravenous catheters. This is most troublesome in long-term use but can be found to some degree at almost any time. In-line bacterial filters and local antibiotics deal with this problem very effectively (Wilmore and Dudrick, 1968).

Although infection rates can be predicted from these assessments of bacterial load the fact remains that few contaminated wounds ever get infected. The healing wound is remarkably resistant to infection and factors that impair this resistance are almost as important as bacterial ones in determining whether or not sepsis occurs.

The susceptible wound is one in which tissue viability has been impaired by local trauma. Poor surgical technique is the prime example since the tissues may be subject to the repeated assaults of retraction and haemostatic manoeuvres with diathermy and ligature. Tight sutures compound the problem by impairing wound perfusion. Susceptibility is also enhanced when remote trauma is associated with hypovolaemia (see Fig. 1.17). Here too the defect is impaired perfusion of the wound with its attendant hypoxia (Fig. 1.18). Macrophages require oxygen to activate their peroxidase system and enable them to kill ingested bacteria. Hypoxia allows the bacteria to multiply and kill the cells.

The presence of extraneous material in a wound increases the likelihood of infection developing. A single piece of sterile silk has enhanced the infectivity of staphylococci several thousand times. When a ligature is tied the resulting local

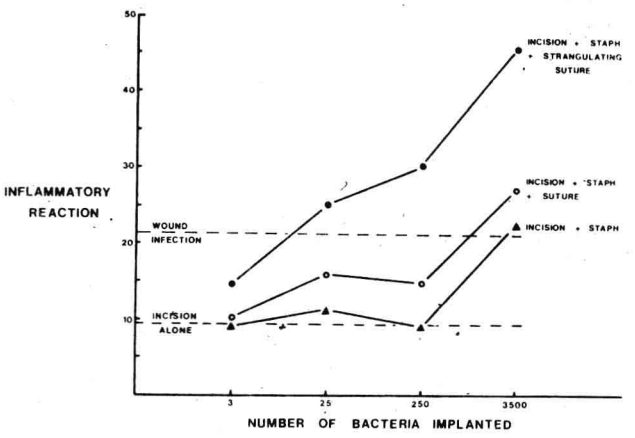

Fig. 1.19 The presence of extraneous material in a wound enhances the likelihood of infection developing. The presence of one tied silk suture doubles the chance of a contaminated wound becoming infected. (After Howe, C. 1966, *Surgery, Gynecology and Obstetrics*, **123**, 507-514.)

necrosis makes matters worse (Fig. 1.19). For these reasons it would seem wise to avoid sutures in contaminated wounds and this is borne out in practice. Further benefits accrue when the skin wound is left unclosed; the wound surface may become infected but invasive infection is very rare (Edlich *et al.*, 1969). If, after 5 days or so, healthy granulation tissue is developing the wound may safely be closed with little loss of total healing time. This technique (delayed primary closure) is very effective but the 'fail-safe' way to preventing invasive infection in a heavily contaminated wound is to leave it open and let it heal by itself.

Although the majority of wound infections are due to organisms implanted before the wound is closed, it can be infected afterwards (Fig. 1.20). A primarily closed wound has no resistance to bacteria swabbed on its surface during the first 6 hours. Thereafter it becomes increasingly difficult to infect it. By 5 days it is as resistant as the surrounding skin. In practice the wound is not challenged so severely and may be left without dressings after 24 to 48 hours provided it is dry and not exposed to an obvious local source of contamination.

The use of antibiotics is controversial. The overall incidence of surgical infections has not changed since their introduction; only the types of infection have altered

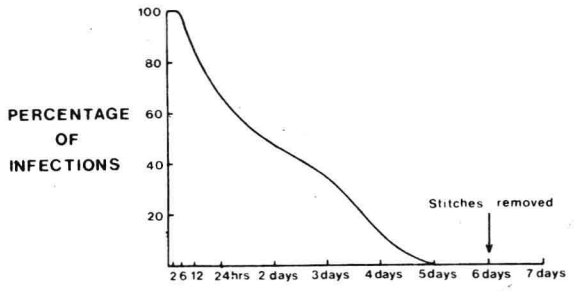

Fig. 1.20 The vulnerability of a healing incised wound to surface contamination with microorganisms. During the first 6 hours it has no resistance. Thereafter it becomes increasingly resistant to invasion, and by 5 days it is as resistant as normal skin. (After Du Mortier, J.J., 1933, *Surgery, Gynecology and Obstetrics*, **56**, 762-766.)

(Altemeier *et al.*, 1973). In the past staphylococci accounted for almost two-thirds of the invasive infections. Now it is the Gram-negative ones which predominate. Recent work has clarified the position. Antibiotics are highly effective when used properly. The importance of matching the drug to the organism is obvious but the critical nature of the timing of the first dose is still not widely appreciated (Burke, 1964). As a result there has been unnecessary controversy over the value of antibiotic prophylaxis of wound infection and delay in adopting this effective routine. Prophylactic antibiotics are of most value when they reach the wound at the same time as the contaminating organisms. They are not effective if started 2 to 3 hours later (Fig. 1.21). The routine administration of penicillin and tetracycline within 45 minutes of injury has reduced the infection rate in traumatic abdominal wounds from 30 per cent to 7 per cent. In other clinical studies, cephaloridine has more than halved infection rate (Polk and Lopez-Mayor, 1969; Evans and Pollock, 1973). Antibiotics used in this true prophylactic fashion are not continued beyond the first or second day. As a result, resistant strains are not encouraged and possible side effects of treatment are minimised.

In clean wounds, there is little justification for using antibiotics. The infection rate is already minimal and any risk of side effects may well be unacceptable. In heavily contaminated wounds antibiotics do not influence the outcome greatly. A better routine is to leave the wound open (Edlich *et al.*, 1969). So far as the route of administration is concerned, it appears that topical antibiotics are almost as effective as intravenous (Belzer *et al.*, 1973). However, they can only be used while the wound is open and do not have the same opportunity to saturate the tissues. A major criticism of using prophylactic antibiotics is that they cannot be selected with absolute certainty of matching the bacterial sensitivities. Antiseptic routines are not open to this objection and iodine coupled with polyvinylpyrrollidone has proved its worth in several studies of contaminated wound management. The reduced infection rate is comparable to that obtained with antibiotics (Gilmore and Sanderson, 1975; Pollock and Evans, 1975).

Therapeutic antibiotics are rarely required in surgery since the more direct measures of incision and drainage are usually sufficient. Sometimes a therapeutic and prophylactic problem present together. A patient being operated upon for a ruptured appendix has two problems, a therapeutic one in the abdomen (peritonitis) and a prophylactic one in the wound (sepsis). In this case the antibiotic regimen starts off as a combined therapeutic and prophylactic one and continues after 48 hours as a therapeutic one.

Wound drainage is required when infection is established but may become a hazard if it has to be prolonged. The exit point is colonised by pathogens and a fresh invasive infection may develop. Ideally drains should be placed well to the side of incisions to minimise contamination. When the wound is the problem it should be left open rather than drained. A drain in the wound itself completely negates the beneficial effect of topical ampicillin following appendicectomy.

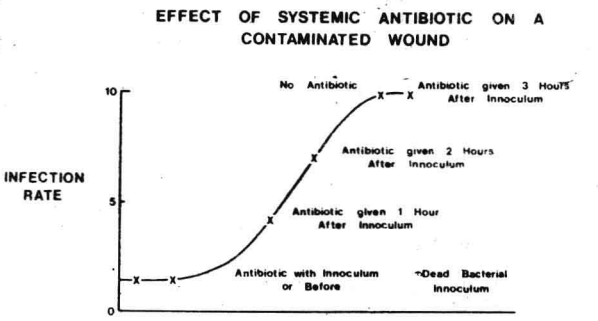

Fig. 1.21 Prophylactic antibiotics are really only effective if given immediately. When they are administered more than 3 hours after bacterial inoculation they do not influence the incidence of infection. (After Burke, J. F., 1961, *Surgery*, **50**, 161-168.)

A good dressing protects the wound from post-operative contamination but if it becomes wet it does more harm than good. Local moisture and abrasion enhance infectivity. Biological dressings, like skin grafts, behave differently. They enhance local defence mechanisms and help sterilise the surface of infected open wounds.

Dehiscence

If a superficial wound breaks open it can safely be left to heal by itself. In most other sites secondary healing is unacceptable and immediate repair must be undertaken. Abdominal wound dehiscence serves to illustrate the problem but it is relatively unimportant compared with breakdown of colonic or vascular anastomoses.

A fresh wound has no strength of its own and requires artificial support with sutures (Forrester, 1972). If the support system fails before functional integrity is regained then the wound edges break apart Reitamo and Möller, 1972; Keill *et al.*, 1973). Although suture failure plays an obvious role the main problem is upset connective tissue formation in the scar. Local sepsis is the single most important factor delaying collagen synthesis and increasing collagen lysis. Softening of the wound edge is even more marked when local trauma has been excessive.

Although sutures are required for security they may contribute to dehiscence by enhancing the infectivity of wound pathogens. The determinants are the mass of implanted suture material and its natural irritating propensity. It is therefore important to ensure that unnecessarily heavy gauges are avoided and bland materials are used whenever possible. The synthetic sutures fit these requirements best and in monofilament form are particularly non-reactive. Absorbable sutures

lose strength before they are absorbed and by the end of a month are behaving as a foreign body without helping support the wound. So far as 'cutting out' is concerned, this is minimised by ensuring that the sutures are placed through fascia and other condensed collagen layers. They are the only tissues with significant holding power for sutures.

Wound dehiscence often reflects an error of judgement on the part of the surgeon. That is, a failure to assess the risk of breakdown and adopt the appropriate wound closure technique to prevent it. In assessing risk, all factors that delay collagen formation and enhance its lysis are important. Prominent among these are starvation with loss of body weight, long-term corticosteroid treatment, sepsis and antimetabolites. The single most important factor is poor surgical technique and in particular tying the sutures too tight and compromising wound perfusion. Continuous sutures provide the most uniform

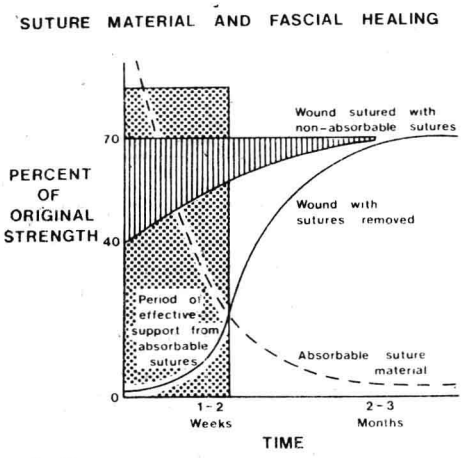

Fig. 1.22 Strength is recovered slowly in fascial wounds and suture support is required for about 3 months. The moment a wound is sutured it has between 40 and 70 per cent of its original strength. This is maintained when non-absorbable sutures are used. Absorbable sutures lose their strength before the wound has fully recovered and dehiscence is more likely

support but interrupted sutures are more secure. Since there is initially quite marked softening of the wound edges security is further ensured by placing the stitches well back (5 to 7 mm) from the wound edge (see Fig. 1.14).

Wounds in the abdominal wall require strength and since this develops slowly the continued support of non-absorbable sutures is necessary (Douglas, 1952) (Fig. 1.22). The moment a wound is sutured it has 40 to 70 per cent of the strength of unwounded tissue. If non-absorbable sutures have been used strength is maintained indefinitely and by 3 months the strength of the scar is sufficiently great that suture support can safely be removed. Absorbable material, on the other hand, loses strength rapidly and after 2 weeks is contributing very little to wound strength. If healing is delayed, say by infection, absorbable sutures cannot be relied upon to provide adequate support and the wound may break open.

Wound dehiscence with evisceration is rare. Immediate resuture is usually followed by rapid uneventful healing and if the true healing time is not taken into account it appears to be more rapid than normal (Fig. 1.23). The disruption is simply a mechanical event and no biochemical disturbances have been detected. Since the fibroblast-capillary system is active the

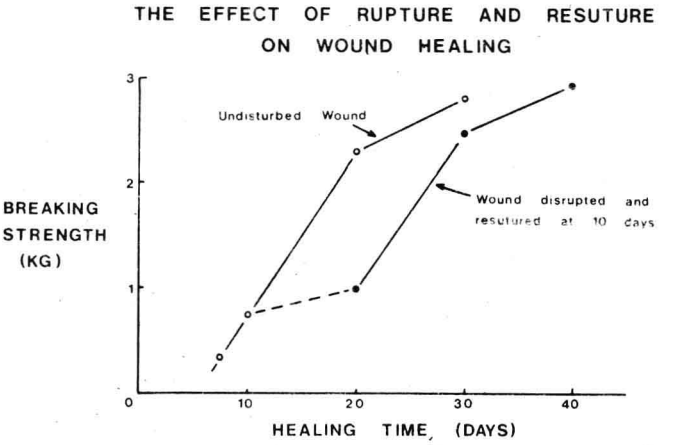

Fig. 1.23 If a healing wound is broken open and resutured it picks up strength rapidly. Ten days later it is stronger than a fresh 10-day wound, but still a good deal weaker than if it has been left undisturbed.

resutured wound has a head-start and the preparatory phase of healing is not repeated. These active local changes persist throughout the period of fibroplasia and a similar rapid recovery of strength should be anticipated if a further operation has to be performed through the same scar. After several months when the scar has matured and devascularised this is no longer the case.

The colon does not have great natural strength. Following anastomosis healing is rapid and full strength is recovered in 3 weeks. Despite this rapid healing wound breakdown with anastomotic leakage is not all that uncommon (Irvin and Hunt, 1974). The unusually high turnover rate of collagen is responsible (Figs. 1.24 and 1.25). During the first 4 to 6 days up to 40 per cent of the old collagen in the wound is lost as a result of marked collagenase activity (Cronin *et al.*, 1968a; Cronin *et al.*, 1968b). Normally strength is maintained by rapid synthesis of new collagen. However, with such high rates of turnover the balance is easily upset. Local factors such as trauma, foreign material and bacterial contamination have adverse effects and the mechanical effects of faecal abrasion compound the problem. When an anastomotic leakage is believed to be likely

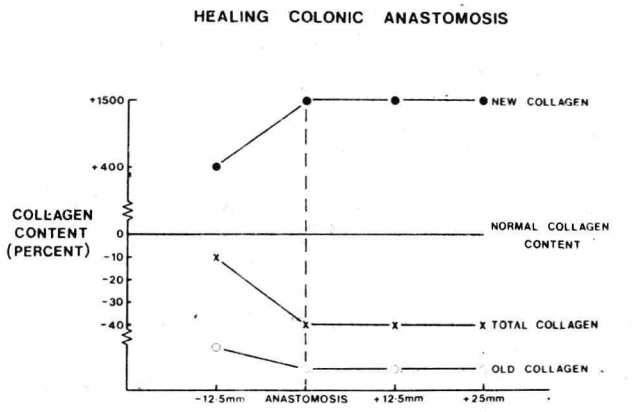

Fig. 1.24 Collagen is synthesised rapidly in colonic wounds but during the first 4 days there is extensive destruction of pre-existing sub-mucosal collagen and net losses of up to 40 per cent are found on either side. (After Cronin, K. *et al.*, 1968.)

the continued support of fine non-irritant non-absorbable sutures is recommended. In addition tension-relieving hitch stitches to adjacent structures may be beneficial.

The connective tissue response in the cardiovascular system is limited and the continued support of non-absorbable material is essential if wound breakdown is to be prevented (Berger *et al.*, 1972). In prosthetic grafts a pseudo-intima rapidly develops but longitudinal in-growth of fibrous tissue is limited to a few centimetres at either end. The graft proper is well supported by circumferential collagen. Surgical mobilisation activates collagenase and may be responsible for rapid enlargement of aortic aneurysms following laparotomy.

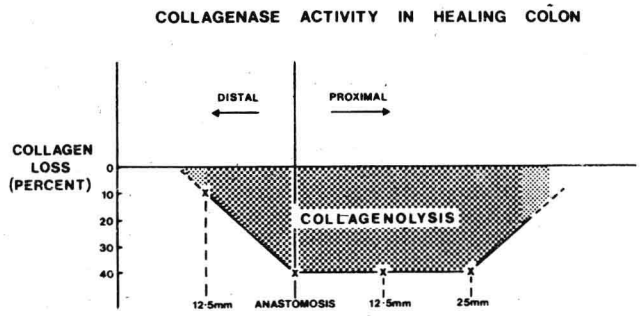

Fig. 1.25 During the first few days of healing there is marked collagenolytic activity above and below the site of anastomosis. As a result sutures may become insecure. (After Cronin, K. *et al.*, 1968.)

Fibrosis

Healing is usually uneventful and may even proceed relatively normally when genetic disorders such as dermatosparaxis and Ehlers-Danlos syndrome are present. Physical integrity is best restored by the smallest amount of scar and attempts to improve repair by encouraging excessive scar formation are unsuccessful because it is an inherently weak material. When scar tissue is naturally over-produced it causes fibrosis. This abnormally contracting material is often a late sequela of injury or inflammatory disease and features a whole range of chronic fibrotic processes, from simple adhesions in peritoneum and tendon sheath to interstitial pulmonary fibrosis. Other troublesome examples are benign oesophageal strictures, mitral stenosis, hepatic cirrhosis and the post-traumatic cerebral scar. Attempts are now being made to control fibrosis by specific anti-fibrotic treatment of the scar and non-specific methods aimed at diminishing the inflammatory process that precedes fibroblast activation (Chvapil, 1974).

Drugs which affect collagen metabolism have specific effects in scar because of its high rate of turnover. Collagen synthesis can be prevented by interfering with hydroxylation of protocollagen within the fibroblast. This is accomplished by removing cofactors such as iron and ascorbic acid or disturbing the configuration of the unhydroxylated molecule with proline analogues. These techniques work *in vitro* but are disappointing in practice.

The most effective approach is to delay the maturation of the wound by preventing polymerisation of tropocollagen. Simple accumulation of un-crosslinked collagen does not interfere with function. It is the development of rigid crosslinked collagen masses that causes fibrosis and deforming contractures. The abnormal physical behaviour appears to be associated with failure of soft tissue remodelling following irretrievable fixation of the random collagen fibril patterns by rapid intermolecular crosslinking. When physical forces are applied to the wound before polymerisation is complete the fibrils are aligned and mechanical properties enhanced (Forrester *et al.*, 1970). More useful effects follow if polymerisation is arrested using B-amino-propionitrile (Peacock and Madden, 1972). This drug works by blocking aldehyde formation and crosslinking. Penicillamine has similar effects. It chelates newly formed aldehydes before they bond. Uncrosslinked collagen is free to organise in more physiological patterns and these are maintained when crosslinking is allowed to proceed. Since these new molecular patterns are reflected in the shape and weave of the collagen fibres themselves the physical properties of the scar should be nearer normal (Fig. 1.26) (Forrester, 1975).

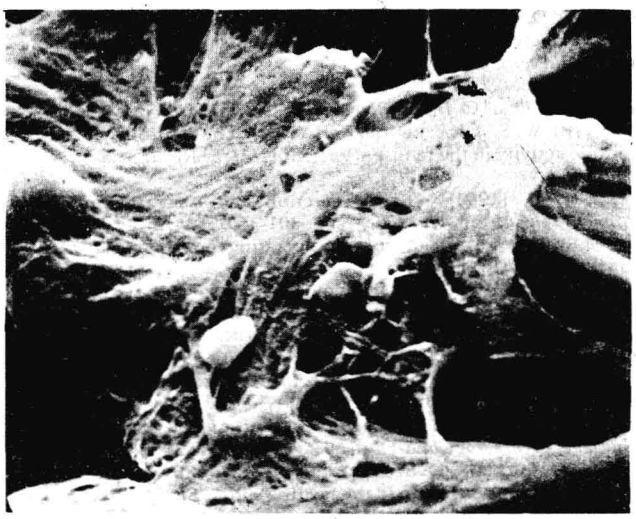

Fig. 1.26 Scanning electron micrograph of a 60-day penicillamine-treated wound (×3250). The collagen fibre patterns are better organised than in the untreated wound (see Fig. 1.8). Large fibril bundles are well demarcated and a network structure is developing.

Non-specific methods are aimed at controlling fibrosis by limiting the inflammatory process that precedes fibroblast activation. Anti-inflammatory drugs of steroid and non-steroid type prove useful here but more precise effects appear likely when the tissue mediators and activators of fibroblasts are properly identified. Following tissue injury lipid peroxidases are activated and lysosomes break open. The lysosomal enzymes damage the macrophages and the damaged macrophages stimulate the fibroblasts to increase collagen production. In this way trauma creates necrosis, and fibrosis results. If necrosis is reduced fibrosis is less. Studies in silicotic lung disease suggest that zinc may be useful here. It stabilises lysosomes and protects macrophages from damage by silica. There is a considerable reduction in necrosis and fibrosis (Chvapil, 1974).

The present methods of managing fibrosis are imprecise, relying on surgical excision and judicious use of corticosteroids. The need for effective anti-fibrotic therapy is obvious. Until it is available the serious health hazard of excessive scar formation remains.

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2. *Biological Effects of Radiation*

INTRODUCTION

This chapter describes the unique effects of the class of radiation used medically in treatment of cancer and in diagnosis. Radiation of this kind is referred to as 'ionising', the process by which energy is transferred. The effects are not simply those of burning or freezing, like, for example, diathermy, laser beams and cryosurgery; they are those of selective 'cell killing' for neoplastic and normal tissues, as well as other important short- and long-term effects, genetic and somatic. The special advantage of 'ionising' radiation in treating many kinds of neoplastic tissue is that it may be possible to give a suitable dose schedule of radiation so that all tumour cells are killed while the normal tissue bed receives no more than temporary, repairable, damage (the 'radiation reaction'). The main advantage of using ionising radiation to treat cancer — radiotherapy — is that the treatment is selective, to a chosen volume of tissue; this compares with the general effect of hormones or of chemotherapy to the whole body, and in addition there is no need for any removal of tissue, the obvious main disadvantage of surgery.

IONISING RADIATION

History and physics

The main kinds of radiation used medically consisted until the 1940's of X-rays and of the rays emitted by radium. Both of thes were discovered at the end of the nineteenth century.

Roentgen discovered and named X-rays in 1895. He found that when cathode rays (beams of negatively charged electrons) struck the anode (or positive electrode) in an evacuated glass tube, rays were emitted which could fog photographic plates and could penetrate opaque materials. It was found at once that these X-rays would penetrate soft tissue more easily than dense tissue such as bone; radiographs could be taken of the body to show normal and pathological organs as well as foreign bodies.

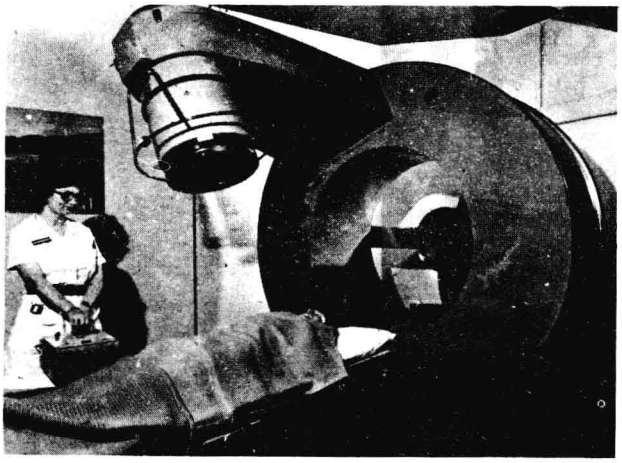

Fig. 2.1 Superficial X-ray therapy unit.

Modern X-ray tubes have been made more reliable and powerful and the potential difference or voltage applied across the electrodes is still often used to describe the kind of unit in use. Diagnostic X-ray tubes usually operate at up to 140 kV (kilovolts). Therapy tubes will not only have a high output quantitatively but will also use higher voltages, producing more penetrating X-rays. Superficial X-ray therapy units (Fig. 2.1), suitable for treating skin conditions will operate at 50 to 150 kV. The common 'deep' X-ray therapy tube (Fig. 2.2), or 'orthovoltage' will produce 200 to 500 kV (usually 250 to 300 kV) X-rays of medium penetration; these tubes which used to

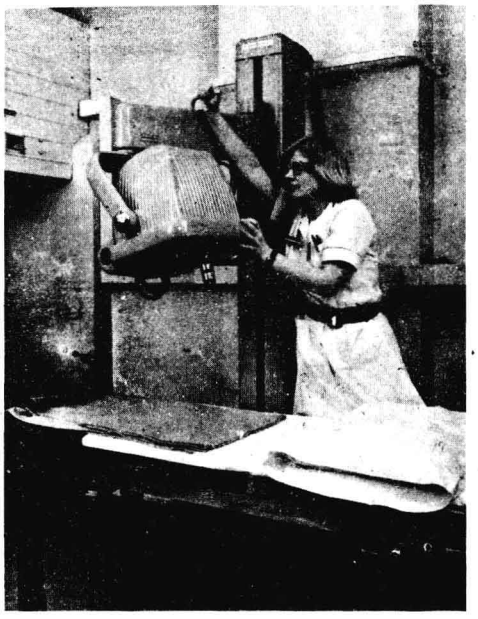

Fig. 2.2 Deep X-ray therapy unit.

be the mainstay of radiotherapy departments are now considerably superseded by linear accelerators (Fig. 2.3). These use high frequency radio waves which are fed into a wave guide (an evacuated metal tube) and accelerated to nearly the speed of light. A beam of electrons is also fed in and in effect 'surf-ride' on the crests of the radio waves to a very high energy. The electrons then strike a metal target and are converted into megavoltage (million volt) X-rays, with a very high output, so that individual treatment times are only a few minutes and large numbers of patients can be treated.

Radium was isolated by the Curies in 1902 and was found to emit three kinds of ionising radiation, alpha rays, charged helium atoms; beta rays, electrons; and gamma rays which are high energy X-rays under another name. Radium is the main natural radioactive isotope, the gas radon being another. Many artificial radioactive isotopes (usually but incorrectly called only 'isotopes') are now available from nuclear reactors and from cyclotrons. All will disintegrate, giving off radioactivity, or 'decay', with a constant exponential half-life. The radiation

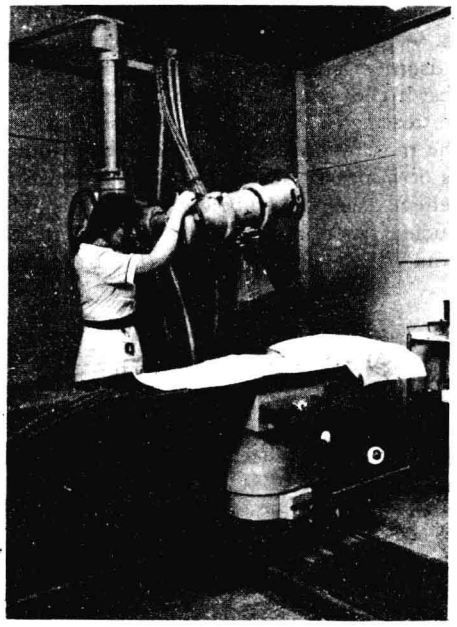

Fig. 2.3 Linear accelerator.

emitted is occasionally α-rays but more commonly β- and γ-rays of constant energy, expressed in a 'decay-scheme'. Many are used in medicine for diagnosis and therapy.

Table 2.1 Isotopes used commonly in radiotherapy

Isotope	Half-life	Radiation (MeV energy)		
		α	β	γ
Caesium-137	27 yr	—	0·52, 1·2	0·67
Cobalt-60	5·2 yr	—	0·32	1·2, 1·3
Gold-198	2·7 days	—	0·96	0·41
Iodine-131	8 days	—	0·25-0·81	0·08-0·72
Iridium-192	74 days	—	0·66	0·14-0·65
Phosphorus-32	14 days	—	1·7	—
Radium-226 decays to	1620 yr	4·6, 4·8	—	0·19
Radon-222 decays to	3·8 days	5·5	—	—
Radium-C-214	19·7 min	5·5	1·6, 3·1	0·4-2·4
Strontium-90 decays to	28 yr		0·54	—
Yttrium-90	64 h	—	2·2	—
Tantalum-182	111 days	—	0·52	0·07-1·2

'Interstitial' treatment by implants of needles or wires remains of value when localised irradiation is required, for example to intra-oral tumours (Fig. 2.4) and small carcinomas of the bladder. Radium, radon seeds (now obsolete), and grains or wires of gold-198, iridium-192 or tantalum-182 can be used.

Intracavitary radium treatment is mainly used for gynaecological cancer, especially of the cervix (Fig. 2.5) and body of the uterus. Radium tubes are now commonly replaced by caesium-137 tubes.

Very high intensity remote loading machines such as the 'cathetron' which use cobalt-60 sources can also be used, avoiding all radiation exposure to doctors and nurses. The most important unit however is the telecobalt unit (Fig. 2.6), using a small high specific activity source of cobalt-60 — 1000

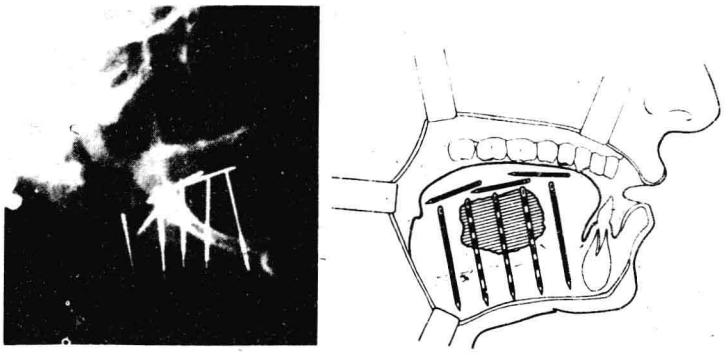

Fig. 2.4 A radioisotope needle implant for carcinoma of tongue.

curies or more — in a shielded head with a shutter and collimator system; this gives a beam similar to that from a linear accelerator.

All external beam units, whether X-ray or γ-ray, are constructed with a collimation system of interchangeable applicators or a continuously variable diaphragm so as to give square or rectangular beams ranging from about 4 × 4 to 30 × 30 cm (superficial units giving even smaller fields, often circular and down to 1 cm diameter circles). The depth dose in the body (Figs. 2.7 and 2.8) will depend firstly upon the f.s.d. or s.s.d. (focus- or source-skin-distance) — the dose falling inversely as the square of the distance. A long f.s.d. of 100 cm is therefore desirable. Secondly the penetration will vary according to the energy of the radiation used.

X- and γ-rays are not the only rays used in modern radiotherapy. Several charged particles can be used, such as the small sub-atomic particle called a π-meson, and the common uncharged particle, the neutron, that is a major component of the atomic nucleus.

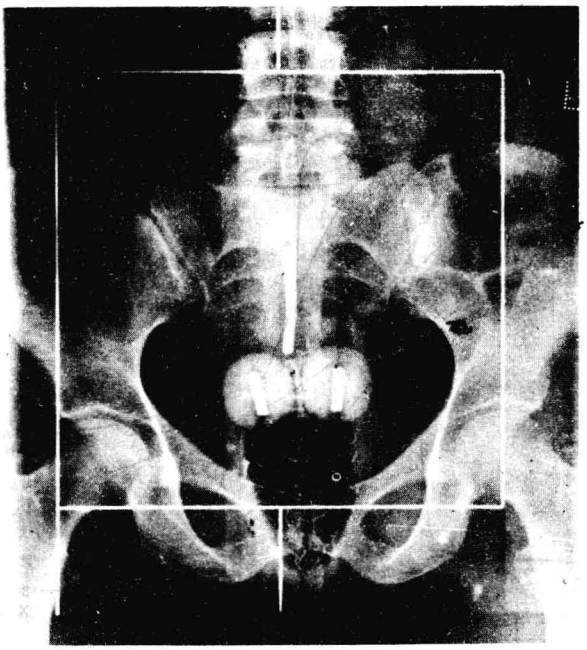

Fig. 2.5 Treatment of carcinoma of the uterine cervix by insertion of radioisotope tubes into the cervical canal and the lateral fornices of the vagina, as shown on a verification X-ray film.