A Textbook of
Surgical Pathology

Sir Charles Illingworth
Bruce M. Dick

TWELFTH EDITION

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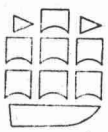

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Preface to the Twelfth Edition

Since the first edition of this book appeared in 1932 the surgical scene has undergone many changes, and some diseases have ceased to be of surgical interest while others have taken their place. Moreover, our whole approach to the scientific study of disease has altered, and being no longer encompassed by the autopsy room and the microscope we now draw information from a host of newer laboratory investigations.

In keeping with these developments I have interpreted the title 'Surgical Pathology' as embracing the whole science of surgical diseases. Therefore in addition to the traditional features of morbid anatomy and histology, I have included the relevant aspects of physiology, biochemistry, immunology, nuclear medicine and other laboratory disciplines.

The book is designed for senior students and registrars, and for the equivalent grades of surgical residents in America. It covers the scientific aspects of the whole range of general surgery and the related specialist subjects. I have endeavoured to provide a balanced and reasonably comprehensive account of present day knowledge in these fields. For readers who wish to go further I have included brief but highly selective lists of references to recent literature, particularly the reviews, symposia and key articles to be found in those journals which are available in any hospital library.

Being aware of the virtue of brevity I have taken care, while retaining everything of significance, to present the information concisely, and by the use of logical sequences and simple prose constructions to make it readable. Among modern medical texts the book is relatively small as judged by the number of words and pages but I believe it to be as comprehensive in scope as many larger compilations.

1979 CHARLES ILLINGWORTH

Preface to the First Edition

This book has been written for graduates and senior students, with the object of providing an account of the pathology of surgical diseases, and especially of those aspects that are outside the scope of textbooks of general pathology.

We have emphasized those features that are of greatest value to the surgeon, and we have laid particular stress upon conditions that are brought to view in the operating theatre and the surgical laboratory; but we have included also such relevant information as can be gained in the pathological department, in the post-mortem room, or in research laboratories.

Presuming a certain knowledge of general pathology on the part of our readers, we have made only passing reference to such fundamental processes as inflammation, suppuration, ulceration, and repair. Their omission has given us room to expand certain subjects in directions which, we hope, will increase the readers' interest. For example: in the chapter on Tumours we have referred at some length to experimental researches, and to modern views on the precancerous state and on the nature of tumour-formation; in the chapter on Diseases of Bones we have discussed various theories of the growth, modelling, and repair of bone; and in the chapter on Diseases of the Thorax we have included much that is usually dealt with only in special works.

The labour of preparation has been lightened by the encouragement which our many colleagues have combined with their advice and assistance. Our especial gratitude is due to Mr. D. M. Greig, Conservator of the Royal College of Surgeons of Edinburgh, who has offered many stimulating suggestions and helpful criticisms, and has corrected the greater part of the script. Our thanks are due also to Professor D. P. D. Wilkie and to Mr. J. M. Graham, who have given much helpful encouragement; to Dr. E. B. Jamieson, who has read a considerable portion of the book, and criticised it constructively; and to Mr. J. J. M. Shaw and Dr. Douglas Miller, who have given valuable advice in regard to the chapters on Tumours, and Diseases of the Female Generative Organs, respectively.

In the matters of illustrations our colleagues have been equally helpful. Mr. Greig has permitted us to use many specimens from the College museum, and has lent many photographs from his own collection. Professor Wilkie has allowed us the full use of the University Department of Surgery, and Professor J. I aser and Professor R. W. Johnstone have provided similar facilities in the Departments of Clinical Surgery and Diseases of Women, respectively. We are grateful to Mr. J. W. Struthers for the loan of several valuable specimens from his collection. These illustrations and those lent to us by other friends are acknowledged individually in the text.

Almost all the photomicrographs are from the cabinet gallery of the Royal College of Physicians of Edinburgh, and are the work of Colonel W. F. Harvey, I.M.S., and Mr. T. D. Hamilton. To them, and to the laboratory committee, we would express our great indebtedness.

We are indebted to Miss McLarty for many of the drawings, to the technical staff of the University Department of Surgery for some of the photographs, and to Miss M. Robertson for her care in preparing much of the typescript. Lastly, we have to thank Mrs. C. F. W. Illingworth, who has typewritten a large part of the manuscript, and whose constant encouragement has done much to lighten the task of preparation.

Edinburgh
December 1931

C. F. W. Illingworth
B. M. Dick

Contents

1. The Response to Injury

The response to injury is a fundamental reaction of living organisms in defence of the integrity of their tissues. In its broadest sense it includes a number of different mechanisms, ranging from the 'fight or flight' response at the moment when danger is first threatened, to the final stage of repair when the wound is brought to complete healing. It includes the reaction of the body to blood loss, the clotting mechanism, the arrest of haemorrhage, the restoration of blood volume, the marrow response; it includes the metabolic and biochemical consequences of injury; it includes the tissue reaction at the site of wounding and the mobilisation of reserves manifest in the leucocyte response; it includes the defence against bacterial invasion and the immunity reaction; and in a still broader sense it should even include the psychological response of the individual and the effect of the injury on the mind and memory.

Traditionally, however, we turn our attention first to the local response occurring in the living tissues at the site of damage, the changes which begin with inflammation and proceed, either uninterruptedly or after an interval occupied by infective complications, to healing and repair. In essence the local response is the same whether the injury takes the form of a clean open wound or a septic pinprick, a superficial burn or a rupture of the bowel; but there are obvious differences of degree and emphasis depending upon the site and extent of the lesion, and especially upon the presence or absence of bacterial contamination.

In former days, when bacterial infection was a regular and predominant feature of open wounds, studies of the healing process were concerned almost exclusively with the phenomena of infection, suppuration and other septic complications. Nowadays, it is more logical to start by considering the process of healing and repair as it takes place in a clean wound, postponing the study of infected wounds until a later page.

Wound Healing

The process of wound healing can be studied in its simplest form in a clean incised wound of the skin. For the first few days there is little change visible to the naked eye—the '*Lag Phase*'—but microscopic and biochemical studies show that the healing process starts almost immediately, provided that the wound margins are well vascularised.

In this initial stage two developments take place: (1) the accumulation of enzymes in the vicinity of the wound and (2) cellular responses in the adjoining healthy tissues.

The enzymes include esterase and adenosine triphosphatase, aminopeptidase and phosphatases. They appear in that order; the first, in favourable circumstances, in little more than an hour after the time of wounding. Their sequence of development has some medico-legal importance as it may serve to establish the time of injury.

The cellular changes are those characteristic of inflammation. They can be observed by direct microscopy of the frog's web or mesentery, or, in warm-blooded animals, through a Clark-Sandison chamber, a plastic box which can be applied over an open wound, most conveniently placed on a rabbit's ear. The cellular changes can be monitored by injecting dyes such as Evans' Blue or Pontamine Blue, which attach themselves to the plasma proteins. The leucocytes can be labelled differentially by colloidal carbon, which is taken up by the cytoplasm of phagocytes. Cells which are about to

divide, and their daughter cells, can be labelled with tritiated thymidine, which is incorporated in the DNA of nuclei in the initial stages of mitosis.

The first change, within minutes of the injury, is that after a transitory period of reflex vasoconstriction the smaller vessels of the part—terminal arterioles, capillaries and small venules—become dilated, probably as the result of the release of histamine or related substances from the damaged cells. The flow of blood through the part is thereby increased. At the same time the endothelium of the smaller vessels becomes more permeable, permitting exudation of plasma-like fluid into the tissue spaces and on to the surface of the wound. This is well seen in the blister fluid of a burn. Very soon thereafter the white cells of the blood—polymorphs and mononuclears—escape into the tissues by diapedesis and contribute to the defence by scavenging dead cells, necrotic tissue and foreign material at the site of injury.

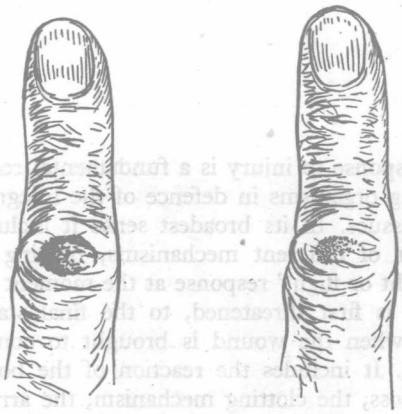
These changes represent the normal biological response to the presence of injured tissue. They are inconspicuous in a clean incised wound but more marked when the tissues have been bruised or crushed or when foreign bodies such as sutures have been introduced.

THE REPAIR PHASE

This phase, which begins in a clean wound within a few days of the time of injury, comprises three elements: (1) the contraction process, which reduces the size of the wound; (2) the process of fibroplasia, which knits together the connective tissues; and (3) the epidermal ingrowth, which covers the surface of the wound.

The Contraction Process

Where the skin is mobile, healing is accelerated by shrinkage of the wound. It is a commonplace observation that the eventual scar is nearly always much smaller than the original wound, even as small as a quarter of the original area (Fig. 1.1). The shrinkage is greatest where the skin and underlying tissues are mobile, for example over the neck or abdomen. It is almost negligible on the chest wall or over the subcutaneous surface of the tibia. The shrinkage is barely perceptible during the 'lag phase', but then it proceeds rapidly for a time and then slows down. Formerly it was attributed to contraction of the newly formed collagen fibres but now it is believed that the fibroblasts themselves are responsible for drawing the wound margins towards the centre, particularly the myofibroblasts. In a large wound the extent to which shrinkage can take place has a material effect on the rate of healing and on the healthiness of the final scar.



(*a*) (*b*)

Fig. 1.1 Wound healing; (*a*) recent wound of knuckle (*b*) contracted healed scar.

This initial shrinkage must be distinguished from contracture or cicatrisation which may occur later if healing is delayed or if the scar is subject to recurring trauma (p. 152).

McMinn, R. M. H. (1978) Cellular aspects of tissue repair. *Ann. roy. Coll. Surg. Eng.*, **60**, 215.

The Process of Fibroplasia

The first microscopic evidence of commencing repair is the appearance of *capillary budding*. From capillary blood vessels in the healthy zone round the wound solid buds of cytoplasm project into the fibrin clot which occupies the cavity of the wound. These solid cords of cells become canalised and form capillary loops which eventually form a scaffolding in the depths of the wound. Fibroblasts follow, between and parallel to the capillaries, and with them phagocytes which scavenge dead material, so that gradually the defect is filled with vascular young connective tissue or *granulation tissue*.

The fibroblasts secrete collagen and discharge

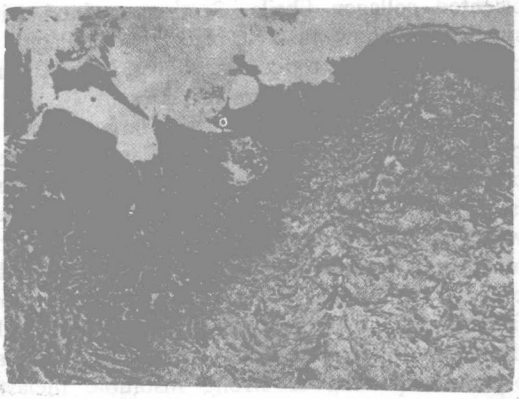


Fig. 1.2 Wound of integuments, twenty-four hours old. The cavity of the wound (on left) is filled with clot. Early inflammatory changes are seen at the margin.

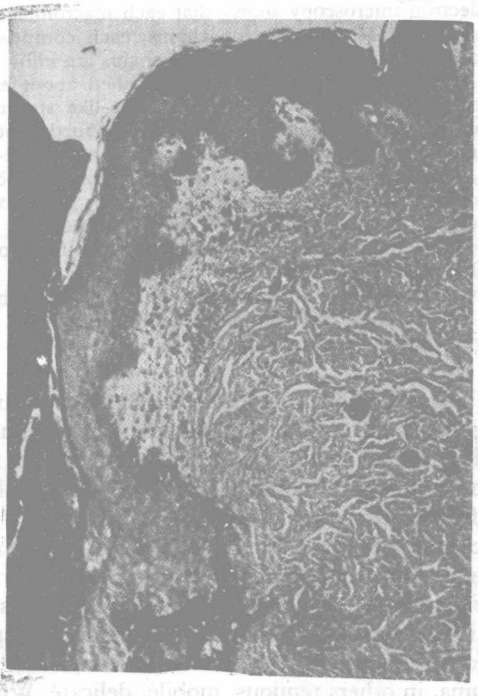


Fig. 1.3 Wound of the integuments, three days old. The cavity of the wound (left) is filled with clot. There is a vigorous downgrowth of epidermis over the edge of the wound.

it into the extracellular spaces. They also secrete muco-polysaccharides which form the ground substance of the developing connective tissue. As

Fig. 1.4 Wound of the integuments, ten days old. The wound is filled with young connective tissue and covered by epithelium. Some islands of epithelial cells are included in the scar.

Fig. 1.5 Wound of integuments, thirteen days old. High-power view showing character of the young fibrous tissue occupying the wound. The epidermis is beginning to become keratinised.

the wound matures the collagen becomes increasingly tough (p. 4), the fibroblasts arrange themselves in the lines of stress, and the intercellular fibrils lend strength to the tissue. Later the fibroblasts diminish in size and functional activity and form the fibrocytes of the residual scar. The capillaries also diminish in size and some become obliterated, so the scar becomes relatively avascular.

The process of epidermal ingrowth

Synchronising with these early developments in the connective tissue, healing proceeds in the epidermis. In a clean wound, within a few hours of the injury healthy epidermal cells at the margins of the wound begin to spread down the side of the defect (Fig. 1.3) and across the surface of young fibroblastic tissue now beginning to occupy the floor of the crater (Figs. 1.4 and 1.5).

Two factors are concerned in the spread of epithelium to cover the defect. In the first place, there is active migration of sheets of cells from the epidermis at the wound edge, first down the side of the defect, then through the fibrin clot or across its surface towards the centre of the wound. Secondly, there is active mitosis in the basal layer of the epidermis at some little distance back from the edge of the wound.

The cause of the migration of epithelial cells over the wound surface has been studied in tissue culture experiments. When cells are grown on a surface such as a glass cover slip the cells lying at the free edge tend to spread centrifugally as a continuous sheet, but if they come into contact with other islands of cells this movement is arrested by a process known as 'contact inhibition'. In a wound, this only happens when the raw area has become completely covered.

In *large open wounds*, such as third-degree burns, healing is delayed by the simple difficulty of filling the defect. The epidermis grows in for a centimetre or so and then slows down and comes to a halt, and unless the process is expedited by skin grafting, a raw area will persist indefinitely, forming a shallow pale indolent ulcer with a dense fibrous base and circumference.

In any type of wound the young epithelium never attains the character of normal epidermis. It remains thinner than normal, it does not keratinise so completely, and it possesses no sebaceous or sweat glands and no hair follicles.

The *tensile strength* of wounds depends upon the micro-architecture of the collagen network, which confers certain physical and mechanical properties of great importance in the final stages of wound healing.

If the dermis is examined microscopically under polarised light it is seen to consist mainly of a fabric of interlacing bundles of doubly-refractile material set in a ground substance containing fibrocytes, reticulum cells and small blood vessels. The interlacing fabric is made up principally of course bundles (up to 100 μ in diameter) of oriented collagen fibrils. Sections stained with silver salts show that in places the collagen is condensed into reticulum fibres, while fine branching elastic fibres are also present.

Collagen is a polypeptide with a large content of proline and hydroxyproline. Collagen synthesis takes place within the fibroblast, where the proline is converted into hydroxyproline and combined with glycine before being extruded in soluble form into the intercellular matrix. At this stage the collagen is soft and friable, its fibres lie in random fashion and it possesses little tensile strength. In the course of maturation it is converted into an organised pattern of strong insoluble inelastic fibres giving a high degree of mechanical strength. This change is brought about by the formation of macromolecules of tropocollagen.

Electron microscopy shows that each macromolecule consists of three polypeptide chains, each comprising about a thousand amino acids. The chains are individually coiled in left-hand helixes and coiled about each other in a right-hand direction—a rope-like structure which combines strength with flexibility. Furthermore, the macromolecules are polarised so that they lie end-to-end, with adjacent molecules overlapping lengthwise by a quarter of their length, and bound to their neighbours by cross linkages. Finally, the fibrils formed by the linked macromolecules are arranged in the form of a meshwork resembling a knitted fabric, so that while the individual fibrils are non-extensible the tissue as a whole can be stretched and moulded in conformity with the movements of the body (Fig. 1.6).

The rate at which the tensile strength of a wound is restored after operation is remarkably quick under optimal conditions. It is always a matter for wonder that an abdominal incision, held together by fragile stitches of absorbable catgut, so rarely gives way under the strains imposed by vomiting, coughing and ambulation (see also p. 254).

Elasticity of the skin. The skin provides a flexible covering, in some places thick, tough, fixed to underlying structures and resistant to trauma, in others tenuous, mobile, delicate. When an isolated piece of skin is stretched it exhibits two forms of response, an elastic recoil and a non-elastic plastic flow. Thus, if the stretch is applied quickly and then released the skin returns to its original length, but if the stretch is applied slowly the skin when released remains elongated for a measurable period of time. The elasticity is due

to the fibres of elastin embedded in the dermis; the plastic flow occurs because fluid is squeezed out and takes some time to return.

When skin is incised it gapes, owing to the pull of its elastic fibres, but the extent to which it gapes depends upon the direction of the incision. This is because in different parts of the body the collagen bundles and elastic fibres are disposed according to the stresses to which the skin is subject. In general, they lie parallel to the skin creases or the wrinkles which can be produced by displacing the

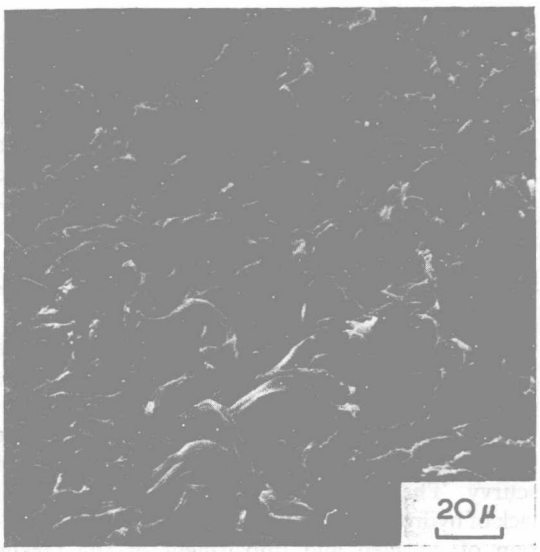


Fig. 1.6 Electron micrograph of collagen.

skin. Consequently, at operation it is important to incise the skin in the same direction, so far as that is possible, and to avoid incisions across the crease lines where tension will subsequently cause the wound to gape and to heal with a broad scar. Similarly, an incision should never be made longitudinally on the flexor aspect of a joint, for the scar will bow-string and become liable to recurring trauma whenever the joint is extended.

Annotation (1977) Burst abdomen. *Lancet*, **1**, 28.
Douglas, D. M. et al. (1969) Physical aspects of collagen. *Brit. J. Surg.*, **56**, 219.
Gibson, T. & Kenedi, R. (1965) Micro-architecture of collagen. *Brit. J. Surg.*, **52**, 764.
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Grant, M. E. & Prockop, D. J. (1972) Biosynthesis of collagen. *New Eng. J. Med.* **286**, 194, 242, 291.
Ordman, L. J. & Gillman, T. (1966) Healing of cutaneous wounds. *Arch. Surg.*, **93**, 857, 883.
Peacock, E. E. & Winkle, W. V., (1970) *Surgery and Biology of Wound Repair*. London & Philadelphia: Saunders.

Estimation of the hydroxyproline content, which is an index of collagen synthesis, shows that the total amount of collagen in the wound stabilises within two or three weeks but synthesis and simultaneous lysis may continue, in lessening degree, for months or even years. This is the explanation of the old observation that scurvy (which impairs the maturation of developing collagen) sometimes led to the breakdown of wounds and even fractures which had been healed for years.

LOCAL FACTORS IN WOUND HEALING

The following factors are important for sound healing:

(1) *Vascularity*. Wounds of the face heal with great rapidity (despite constant movement and some bacterial contamination), and so do wounds of the scalp, whereas wounds of less vascular skin over the trunk and limbs heal much more slowly. If the blood supply to a part is seriously diminished as a result, for example, of local scarring or obliterative vascular disease, healing may be greatly delayed. This is seen in its most serious form when an operation is undertaken in a part previously subjected to radiotherapy.

(2) *Necrosis* at the wound margin, whether due to impaired vascularity or to infection, has the same effect. Here healing is delayed until the dead tissue has been loosened by enzyme action and cast off as a slough.

(3) *Lymph drainage*. Impairment of lymph drainage slows the process of repair, as is seen clearly in oedema. The beneficial effect of elevation of a wounded limb is due to the improved lymph drainage.

(4) *Movement*. Movement of the wounded part is well known to delay healing and indeed immobilisation is a cardinal principle of treatment. It not only prevents damage to the young granulation tissue and its epithelial covering but also diminishes

the flow of lymph. Apart from delaying the healing process, movement also causes stretching of the scar and predisposes to the formation of a keloid.

(5) *Anchorage to subjacent structures* impairs shrinkage of the wound and thereby delays healing, e.g. in deep wounds involving a bone, in varicose ulcers and in the chronic sinuses of osteomyelitis.

(6) *Foreign bodies* and irritant applications. Apart from inert materials such as stainless steel and certain plastics, nearly all foreign bodies induce a reaction, varying from minimal inflammation to suppuration which will persist until the foreign substance has been absorbed or extruded. Even the most inert material carries a small risk of promoting bacterial infection. Antiseptics similarly may delay wound healing because of the tissue damage to which they give rise.

(7) *Sutures.* The material of which the suture is made may act as an irritant. Catgut is the worst offender. Derived as it is from the submucous coat of the sheep's intestines, it acts as a collagen heterograft, stimulating a foreign-body reaction which persists until the whole suture has been broken down by phagocytosis and absorbed or extruded. Its only virtue is that it is ultimately got rid of. Chromic catgut is less irritant than plain catgut, for the processing binds the collagen fibres so that they cause a less severe reaction.

Other foreign fibres such as silk or cotton also cause a foreign-body reaction but of mild degree. Their main disadvantage is that their fibrous structure provides a nidus for bacterial growth. If this is avoided, the suture becomes enclosed in a delicate fibrous covering and remains permanently innocuous.

Sutures may also delay wound healing by reason of the way in which they are applied, and particularly if they are drawn so tight as to constrict the tissues and produce pressure necrosis. The cross scars traversing many operation wounds which have been stitched under tension, or where tension under the sutures has been created by inflammatory oedema, bear witness to this action.

The ideal suture should be strong but slender, flexible to apply and conformable so that it knots readily and does not come loose. It should be completely non-reactive, and smooth on the surface so that it offers no cavities for bacterial growth. At the present time the material with greatest promise is a synthetic polymerised polyglycolide, which is non-antigenic and absorbs slowly by hydrolysis without phagocytosis.

(8) *Infection.* Of all the local factors which influence wound healing, infection is undoubtedly of the greatest importance. Much depends upon the nature of the infecting organism. Of the common ones the haemolytic streptococcus and the coagulase-positive staphylococcus are the most harmful. The physical state of the wound is a factor of importance in minimising the risk of infection, particularly its vascularity and freedom from foreign material.

CONSTITUTIONAL FACTORS IN WOUND HEALING

The following factors are of importance:

(1) *Protein.* A high level of protein is required to subserve the demands of cell proliferation in the healing wound, and to make good the catabolic loss of protein in the urine. Impaired wound healing is seen in emaciated subjects and in any condition in which the blood protein level is depleted. It is seen in its most extreme form in patients with long-continued intestinal malabsorption.

Sulphur-containing amino acids such as methionine are especially important since they are essential for the synthesis of new protein.

The histological changes in healing wounds where protein is lacking are similar to those of scurvy. The fibroblasts do not mature and the lack of hydroxyproline leads to delay in the maturation of collagen and impairment of the tensile strength of the wound.

(2) *Vitamin C.* Failure in wound healing has been recognised as an important manifestation of scurvy since the eighteenth century. Under modern conditions gross avitaminosis is rare, but minor deficiencies of vitamin C still occur, especially in elderly solitary people and in patients with gastro-intestinal symptoms who have been put on inadequate or unsuitable diets. It is seen most often in peptic ulcer cases and in patients with intestinal malabsorption. Such patients present an increased risk of postoperative wound disruption.

Microscopic examination of early wounds in vitamin-deficient cases shows that the epithelial proliferation is unimpaired; the defect is concerned only with the connective tissues. The essential defect is a failure in the maturation of collagen. Fibroblasts are present in normal numbers but the capillaries are few and ill-formed.

The fundamental feature is a defect in the conversion of proline into hydroxyproline so that the macromolecules of collagen are scanty and make a poor contribution to the tensile strength of the wound.

(3) *Cortisone.* Experimental observations on the healing of wounds of the cornea in rabbits show that cortisone retards the proliferation of fibroblasts and young capillaries. There is a dearth of fibroblasts and collagen-formation is deficient. Fortunately the clinical effects in patients under treatment with cortisone are minimal even after heavy doses unless continued for a long time.

(4) *Zinc.* This element is an essential constituent of many enzymes and a co-factor in the enzyme systems involved in protein synthesis. It is thus important for wound healing, and in experimental studies depletion of zinc has been shown to impair the normal gain in tensile strength. However, it has not yet been established that depletion of zinc sufficient to have this effect can occur in the human subject.

(5) *Blood dyscrasias.* In rare cases breakdown in the normal healing process occurs in certain blood dyscrasias, such as the 'giant polymorph disease' of genetic origin. In this disease and others in this category the epithelial growth is particularly disturbed, so that incisions break down and fistulas form. Remarkably enough, in some such cases the administration of cortisone corrects the abnormality.

Douglas, D. M. (1968) Repairs of incised wounds. *J. roy. Coll. Surg., Edin.*, **13**, 92.

Ehrlich, H. P. & Hunt, T. K. (1968) Effect of cortisone on wound healing. *Ann. Surg.*, **167**, 324.

Fluids and Electrolytes

The delicate mechanisms for controlling the internal environment and maintaining homoeostasis are readily upset in many surgical diseases, so it is important that the surgeon should comprehend the underlying physiological processes and the principles governing treatment.

These mechanisms control the overall balance of water and electrolytes, the internal adjustment between the volume of fluids in the various compartments, the relative proportions of the different electrolytes in each compartment, and the acid–base balance.

THE FLUID SPACES

It is customary to describe the body fluids as occupying three spaces or compartments, the blood vessels, the tissue spaces and the cells. Alternatively they may be divided into the extracellular compartment (which includes the blood vessels and tissue spaces) and the intracellular compartment. But to make the picture complete we must add the *transcellular spaces*, namely the serous and synovial cavities, the duct systems of glands, the intestinal tract and the renal tubular system.

Moreover we must recognise that these various fluids are far from static. During every hour of life the heart propels 300 litres of blood through the vessels, the glomeruli excrete 7 litres of filtrate into the renal tubules (of which 99 per cent is reabsorbed), the alimentary glands secrete half a litre of fluid into the intestinal lumen (of which also 99 per cent is reabsorbed). In health there is a constant and wonderfully vigorous flow of water and electrolytes between the blood stream, the tissue spaces and the cells. In surgical diseases these movements may be greatly altered, leading to profound effects on the fluid distribution and the acid–base balance, with consequent harm to tissue perfusion and cell oxygenation.

Measurement of the Body Spaces

Under stable conditions nearly all the body spaces can be measured by the dilution technique, in which a suitable substance is injected and, after an interval to allow mixing, a sample of blood is withdrawn so that the degree of dilution of the marker substance can be estimated. Unfortunately, accurate results cannot be obtained from these methods of measurement in conditions of instability, for example when there is acute fluid loss after haemorrhage or in abdominal emergencies.

The *plasma volume* can be measured readily under stable conditions and with fair accuracy by the dye Evans' Blue or by radio-active iodine. Either of these agents attaches itself to the plasma proteins and therefore remains in the intravascular compartment for an appreciable time, so that the degree of dilution gives an index of the plasma volume.

The radio-iodine method is preferable. It has

the advantage that, if ^{132}I with a short half-life is used, successive estimations can be made at intervals of a few hours, so that changes in the plasma volume can be noted and corrected. The method is to add 5 milligrams of stable iodine, containing a trace of the isotope, to 50 millilitres of the patient's plasma. It is then injected intravenously, and samples withdrawn at intervals are compared with the injected dose in a scintillation counter. Allowance must be made for the fact that some iodine escapes through the capillary walls (10 per cent or more in the first hour). Normally the plasma volume is about 7 per cent of the total body water or roughly 4 per cent of the total body weight—about 3 litres in the average adult man.

The *red cell volume* can be measured indirectly from the plasma volume on the basis of the haematocrit reading, or by the direct method, in which a known volume of red cells, tagged with radioactive chromium, is injected intravenously, with subsequent sampling. In the average male adult the red cell volume amounts to a little over 2 litres.

Table 1.1 Approximate fluid volumes (70 kilo man)

Red cells		2 litres
Extracellular fluid		
Plasma	3 litres	15 litres
Interstitial fluid	12 litres	
Intracellular fluid		30–35 litres
Total body water		approximately 50 litres

The *extracellular fluid* can be measured by the dilution technique, and if the plasma volume is known the volume of the interstitial fluid can be obtained by subtraction. Unfortunately different agents give different estimates of the extracellular fluid. The one most widely used is sodium thiosulphate, which in an average adult man gives a reading of about 15 litres for the extracellular fluid, made up of about 3 litres of plasma and 12 litres of interstitial fluid. Unfortunately the test needs several hours for complete mixing and diffusion.

The *total body water* is measured by the dilution method, using either deuterium oxide (heavy water; D_2O) or tritium oxide (T_3O). The total body water measures from 45 per cent to 60 per cent of the body weight. Since there is practically no free water in neutral fat, the proportion in obese subjects falls to 25 per cent, whereas in emaciated subjects it rises to 70 per cent. In oedema it may rise to as much as 80 per cent.

The *intracellular fluid* is not readily measured. This is unfortunate, for it is much less subject to variations than the fluid in the other compartments, and the range of variation compatible with life is probably not great. The only direct method is by muscle biopsy and even here an allowance must be made for the extracellular water contained between the muscle bundles. The intracellular fluid can be estimated indirectly by subtracting the extracellular fluid from the total body water, but the measurement is subject to great error. In general terms, the intracellular fluid of the soft tissues amounts to about 26 litres, the fluid in bone to about 4 litres.

THE MICROCIRCULATION

The propulsive force of the heart, which depends upon the integrity of the myocardium and the venous inflow to the right atrium, raises the mean blood pressure within the aorta to 100–150 mmHg. As the main arteries divide and subdivide, the overall cross-section increases, and correspondingly the pressure falls, so that in the smaller arterioles it is reduced to approximately 40 mmHg.

The microcirculation extends from the terminal arterioles to the smallest venules. The terminal arterioles are vessels of less than 50 μ diameter and have a wall lined by endothelium based on a single layer of plain muscle cells. They lead into the precapillary sphincters, which possess a well-defined circular muscle coat innervated by sympathetic axons. Similar sphincters exist on the venous side.

These precapillary and postcapillary sphincters are subject to control by the sympathicomimetic drugs. In general terms, adrenalin and noradrenalin cause arteriolar vasoconstriction whereas isoprenalin (isoproterenol) decreases the total peripheral resistance and improves tissue perfusion. These sphincters are also, and to a far greater extent, subject to local conditions such as the oxygen tension and the concentration of metabolic waste products.

In the veins the pressure is approximately 7

mmHg, which suffices, along with the negative intrathoracic pressure, to return the blood to the right atrium. The veins serve both as conduits and as low-pressure reservoirs (venous capacitance vessels). Their muscle coat is scanty so small increments of internal pressure can cause large alterations in capacity while conversely a moderate increase of muscle tone can transfer large volumes of blood towards the right side of the heart.

The capillaries, which measure nearly a millimetre in length, have a wall consisting of a single layer of elongated endothelial cells, which lie either unsupported or invested by a tenuous connective tissue sheath. They have no muscle coat and dilate or collapse passively according to the local pressure relationships. Under conditions which have not been clearly defined, the blood may be shunted past the capillary field through arteriovenous anastomoses. In health a large proportion of the capillaries are collapsed and empty.

Normally of the total blood volume about 20 per cent is contained within the heart and arteries, 75 per cent within the veins and less than 5 per cent within the capillaries. But in some pathological states, and particularly in shock, the capillaries become dilated so that the volume of the capillary bed is enormously increased.

It has been estimated that each day there is an interchange of over 1000 litres through the semipermeable capillary walls between the blood and the tissue spaces, according to the following physical factors:

(1) The hydrostatic pressure within the capillaries is greatest at the arterial end and lowest at the venous end. It varies in different capillaries at different times and also depends upon the level of the capillary relative to the heart, but in general it is of the order of 30 mmHg at the arterial end, falling to about 20 mmHg at the venous end. Its effect is to force fluid out of the capillaries.

(2) The osmotic pressure exerted by the plasma proteins exceeds the osmotic pressure exerted by the colloids of the tissue fluids by about 22 mmHg. Its effect is to draw fluid into the capillaries.

(3) The tissue pressure, which depends upon such factors as the filtration rate, the rate of lymph flow and the elasticity of the tissues, amounts to from 1 to 3 mmHg. Its effect is to force fluid from the tissue spaces into the capillaries.

Thus it will be seen that at the arterial end of the capillary the hydrostatic pressure exceeds the sum of the osmotic and tissue pressures, so fluid will leave the vessel; whereas at the venous end the position is reversed and some of the fluid is reabsorbed (the remainder draining into lymphatic channels).

This delicate mechanism is readily upset in disease or injury. For example, in diseases where the plasma proteins are lowered the osmotic pressure is reduced, so oedema and ascites may result. After haemorrhage the fall in hydrostatic pressure permits an increased flow of fluid from the tissues into the vessels. In prolonged hypotension, in adrenal failure and in severe intoxications, the permeability of the capillary membrane is upset and fluid leaks from the blood stream into the tissues. This is a development of great importance in septic shock (p. 17).

RENAL FLUID INTERCHANGE

Each day about 170 litres of fluid are filtered through the renal glomeruli but only a small proportion (in health 0·5 to 2·5 litres) appears as urine. The rest is absorbed through the renal tubules. This circulation is of fundamental importance in maintaining the balance of fluids and electrolytes, of acids and bases.

About 85 per cent of the glomerular filtrate is reabsorbed isosmotically in the proximal convoluted tubules; that is to say, the water is absorbed along with sodium and other electrolytes in the proportions present in the filtrate. In the distal tubules there is a differential absorption of water and electrolytes under hormonal control.

The *antidiuretic hormone* of the posterior lobe of the pituitary gland determines the reabsorption of water (independent of sodium) and is the principal mechanism for varying the volume of urine in relation to the water intake. Secretion of ADH is provoked by nervous stimuli originating in the supra-optic nuclei in response to impulses from osmoreceptors sensitive to changes in the water content of the blood.

The *aldosterone mechanism* determines reabsorption of sodium (and therefore also of water) and the excretion of potassium and hydrogen ions at the distal convoluted tubule. The aldosterone mechanism is considered in greater detail on p. 83.

WATER AND ELECTROLYTE DEPLETION

Dehydration, in the strict sense, means depletion of water, but the term is commonly used to include mixed depletion of water and electrolytes.

Simple water depletion occurs as a result of reduced intake of water. It is common experience that unless the depletion is severe and prolonged it has little harmful effect. Unlike depletion of electrolytes it has little influence on blood volume —doubtless because there is time enough for osmotic withdrawal of water from the tissue spaces and the cells—so usually there are no serious circulatory effects. However, in ill patients simple water depletion due to obstruction to the gullet, or to mere inability to lift the cup, may aggravate other forms of depletion.

Sodium

Sodium is the predominant cation of the extracellular fluid. It has no specific biological action and its function is to conserve the isotonic balance and thus maintain the volume of fluid in the interstitial space. It has been aptly described as 'osmotic stuffing'. Sodium is also present in high concentration in the bone cells. About 50 per cent of this component is exchangeable, that is to say, it is readily mobilised and so forms a reserve against depletion.

Table 1.2 Plasma electrolyte levels

Na	135–145 mmol/l (mEq/l)
K	3·5–4·5 mmol/l (mEq/l)
Cl	95–110 mmol/l (mEq/l)
HCO_3	25–30 mmol/l (mEq/l).

Normally there is an efficient mechanism for conserving sodium, by tubular reabsorption under aldosterone control. The mechanism is so efficient that in severe depletion the sodium content of the urine may be reduced to zero.

Sodium depletion is rarely due to low intake but commonly due to excessive loss. (1) The loss may be due to excessive sweating, especially in the tropics. If the thirst is relieved by drinking water without electrolytes the resulting acute sodium hypotonicity may lead to cramps. In fibrocystic disease of the pancreas where the sweat contains much sodium an acute sodium loss may occur with little visible perspiration. (2) Excessive loss may result from failure of sodium reabsorption in the distal tubules in aldosterone deficiency due to Addison's disease, or after adrenalectomy. (3) In surgical practice excessive gastro-intestinal loss is the common cause. The gastric juice contains from 20 to 200 mmol/l (mEq/l) of sodium (varying inversely with the free acid level) while intestinal secretions may contain as much as 300 mmol/l (mEq/l). Consequently severe degrees of sodium depletion are seen most often as a result of vomiting, diarrhoea, intestinal obstruction, paralytic ileus and fistulous discharge. In these diseases the clinical effects of the depletion will be exaggerated if intravenous fluids lacking sodium are administered.

The main deleterious effect of sodium depletion (which is always combined with water loss) is that the volume of fluid in the extracellular space is reduced. Both the plasma volume and the interstitial fluid volume share in the depletion. This leads to the clinical state commonly described as dehydration, with peripheral vasoconstriction, dryness of the tissues, sunken eyeballs, oliguria, rising pulse rate, falling blood pressure.

Sodium retention (with a rise in the plasma sodium level) occurs: (1) as a normal physiological response to trauma (p. 14); (2) in heart failure, due to impaired renal perfusion; (3) as a result of certain types of kidney disease (nephrosis); (4) in conditions of adrenocortical overactivity such as Cushing's disease and aldosteronoma; (5) following overzealous cortisone treatment. By leading to retention of water it causes plethora of the extracellular and vascular compartments and thus to oedema and arterial hypertension.

Thomas, T. H. et al. (1978) Severe hyponatraemia. *Lancet*, **1**, 621.

Potassium

Potassium is the predominant intracellular cation. Over 95 per cent of the total body potassium is contained within the cells so changes in potassium level usually represent intracellular events. Potassium is only present in small amount in the extracellular fluids (3·5–4·5 mmol/l (mEq/l) as compared with about 140 mmol/l (mEq/l) of sodium) so it plays little part in maintaining osmotic equilibrium.

In health the urinary output of potassium almost equals that of sodium, but since the total extracellular potassium is small the balance is more precarious. Moreover, there is no adequate mechanism for conserving potassium, so there is a continued loss in the urine even though intake is stopped and even in the presence of severe extrarenal loss. Consequently acute potassium depletion is a common and dangerous feature of many types of fluid loss.

Potassium depletion is apt to occur in vomiting, diarrhoea, intestinal obstruction, paralytic ileus and fistula. The depletion is a disproportionate one, for the concentration of potassium in the gastro-intestinal secretions may be twice that of the plasma. Potassium depletion may also occur in cases of potassium-secreting papilloma of the colon (p. 281), and where there is excessive urinary loss due to nephrosis or resulting from an aldosteronoma (p. 86).

The most dangerous situation is that in which potassium deficiency is combined with alkalosis (hypokalaemic alkalosis). This is seen surgically in cases of pyloric stenosis, where there is a state of metabolic alkalosis due to excessive loss of hydrogen ions. Under such conditions, and especially if the relative deficiency is aggravated by infusions of water, glucose solution or sodium chloride solution, severe symptoms will result (p. 243).

The major effect of potassium deficiency is upon muscle action. The heart muscle weakens, leading to extrasystoles and dilatation. Smooth muscle becomes atonic, hence paralytic ileus. Weakness of voluntary muscle is seen in its most marked form in periodic paralysis. Severe deficiency is indicated by a fall in the plasma potassium level below 3·5 mmol/l (mEq/l), or by the electrocardiograph tracing, which shows inversion of the T wave, depression of the ST segment and prolongation of the QT interval.

Potassium retention, with elevation of the plasma potassium level, is equally dangerous. It is seen most often in surgical practice in cases of renal failure, due to tubular necrosis following renal shut-down. A plasma potassium level of 7mmol/l (7 mEq/l) indicates an urgent need for dialysis.

Symposium on Potassium Metabolism (1974) *Scot. med. J.*, **19**, 135.

Calcium

The level of calcium in the extracellular fluid is not great (about 5 mmol/l (mEq/l) so like potassium it plays little part in maintaining osmotic equilibrium but it has important specific effects, of which the most vital are that it enhances the contractility of heart muscle and the conductivity of nerves.

Owing to the immense reserve of calcium in the skeleton, its level in the extracellular fluid is not usually disturbed in the depletions seen in surgical diseases, except in diseases of the parathyroid glands and the kidneys, and in widespread skeletal lesions. Thus, a rise in the blood calcium level is seen in any conditions where decalcification is proceeding rapidly, e.g. in malignant bone metastases. A fall in the blood calcium level is seen after removal of a parathyroid adenoma and in renal failure. (See also pp. 71, 171.)

Magnesium

The level of magnesium in the extracellular fluid is low (1·7–2 mmol/l (mEq/l)), so it plays little part in osmotic regulation, but it has certain specific effects, especially in maintaining the contractility of muscle and the excitability of nerves.

Magnesium deficiency rarely occurs in isolation and is usually found in association with severe grades of potassium depletion with alkalosis. It is most common after abdominal operations, especially when complicated by the development of intestinal fistula. Patients with Crohn's disease and ulcerative colitis are particularly at risk since they may have a partial magnesium depletion preoperatively. The depletion gives rise to fibrillary twitchings, gross muscle tremors and choreiform movements which may respond to the administration of magnesium sulphate intravenously.

Paymaster, N. J. (1976) Magnesium Metabolism *Ann. roy. Coll. Surg. Eng.*, **58**, 309.

ACID–BASE BALANCE

Disturbances of acid–base balance play a major part in many of the pathological processes encountered in surgical practice, so a clear understanding of the subject is of importance to the surgeon-pathologist. Fortunately the modern concept of these mechanisms is becoming increasingly clear.

Essentially, the acidity of a solution depends upon the degree to which its hydrogen ions are