A TEXTBOOK OF SURGICAL PHYSIOLOGY

JAMIESON AND KAY

SECOND EDITION

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BY

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TO

SIR CHARLES ILLINGWORTH

MADE AND PRINTED IN GREAT BRITAIN

PREFACE TO THE SECOND EDITION

THE kind reception given to our first edition has encouraged us to prepare a second.

The whole text has been thoroughly revised. A few chapters have required only minor modification, most have been modified extensively, and one has been written afresh. In the task of revision we have been greatly helped by the criticism and advice of many friends, to whom we tender our thanks.

The new diagrams and line drawings are the work of Mr Robin Callander: their excellence is evident. The source of borrowed diagrams and photographs is acknowledged individually in the text, and we here thank the authors and publishers who have so willingly allowed us to use copyright material.

We are again indebted to our publishers for their invariable courtesy and co-operation.

1964

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PREFACE TO THE FIRST EDITION

ALTHOUGH there are several well-established texts dealing with surgical anatomy and surgical pathology, there is no familiar standard text dealing with surgical physiology. The lack of a suitable text is most sharply felt by the post-graduate student, and it is especially with his needs in mind that we have prepared our manuscript.

In the absence of protocol, our choice of matter for discussion has necessarily been governed by our own experience of surgical practice and surgical teaching. Our aim has been to discuss only those aspects of applied physiology which are fundamental to the practice of general surgery. An occasional excursion into the realm of pathology, and more frequent excursions into the realm of clinical surgery, will, we trust, be readily condoned by the sympathetic reader who is making surgery his career.

For inadvertent omission of matter which should be included we can only apologise, but there are three omissions—two major and one minor—of which we are well aware. We have made no attempt to discuss the central nervous system (which is the province of the specialist neurosurgeon), nor have we discussed the ovary (which, in Britain, is the province of the specialist gynaecological surgeon). Lastly, for a different reason, we have not devoted a chapter to the pituitary: as the surgery of the pituitary is almost restricted to its ablation in the palliative treatment of mammary carcinoma, we have thought it sufficient to devote paragraphs to the pituitary in various chapters throughout the text.

Much of the manuscript was written while we were Lecturers in Surgery at Glasgow University, on the staff of Professor Illingworth. It is to him we are indebted for the idea of writing this book, for much friendly advice, and indeed for encouragement to continue during the periods of depression which afflict all authors. We owe both the inception and the completion of the book to Professor Illingworth, and it is in token of our thanks that we dedicate it to him.

For the sources of our information we are indebted to many—our friends and colleagues who have been at pains to instruct us, visiting surgeons, lecturers at scientific meetings, and the authors of textbooks, monographs and papers. Only a few of these authors are named in the list of references at the end of each chapter, for we have attempted to list only a minimum of readily accessible articles which we have found outstandingly useful.

It is a pleasure to record the readiness with which authors and publishers have given us permission to reprint illustrations. The source of each borrowed illustration is given either by a full reference in the legend to the illustration or by a name and date when the full reference is listed in the bibliography. We believe we have sought and obtained permission for every illustration reprinted: if there is any instance in which we have infringed a copyright we ask that the oversight may be pardoned. For the excellence of the line drawings which appear here for the first time, we are indebted to the skill of Mr Gabriel Donald.

Finally we must record our thanks to our publisher and printer, and especially to Mr Charles Macmillan, for meeting our wishes at all times and for forbearance over the delays inseparable from writing during uncertain periods of leisure.

1959

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CONTENTS

CHAPTER 1

Wound Healing

WOUNDS of soft tissues heal by the formation of connective tissue. This is true of wounds of muscle, fascia, fat, the parenchyma of solid organs, and the central nervous system. An entirely different sequence follows wounds of epithelial surfaces which are repaired by regeneration of epithelium. A third factor which must be considered is the contraction of open wounds during the process of healing.

The properties of collagen and of ground substance merit brief discussion.

The tensile strength of healing wounds does not increase at a uniform rate. There is an initial ' lag period ' of a few days followed by rapid gain in strength. Later there is a further slow gain in strength over a period of several months.

The general metabolic disturbances which may retard healing include protein depletion and deficiency of vitamin C: cortisone in therapeutic doses is no longer regarded as a delaying factor.

The use of absorbable or non-absorbable suture material modifies only slightly the healing of surgical incisions.

Repair of peripheral nerves and of bone is discussed elsewhere (Chapters 14 and 15).

FORMATION OF CONNECTIVE TISSUE

The fine anatomy of living healing wounds has been much studied in the transparent tails of tadpoles and in transparent chambers inserted into the ears of rabbits. In general, however, the structure of healing wounds can be studied only histologically.

The earliest events in wound healing are the coagulation of blood in the wound and inflammation of the wound margins. Within a few days the wound begins to be filled in by a vascular granulation tissue containing many fibroblasts. The fibroblasts lay down collagen fibres which mature and form the connective tissue of the definitive repair.

Within a few minutes of wounding blood coagulates in the wound and on its surface.

Next, the wound margins become inflamed. Within a few hours polymorph leucocytes migrate through the walls of the dilated capillaries and pervade the wound margins and the wound itself. At twelve to twenty-four hours the polymorphs are supplemented by macrophages: these have long been thought to originate from the monocytes of the blood and the local histiocytes, but recent studies

suggest that most of the wound macrophages are enlarged and modified lymphocytes (p. 343). The leucocytic infiltration of the wound is accompanied by the formation of a protein-rich exudate derived from the blood plasma. Within a few days the macrophages have ingested and removed much of the debris in the wound, and the inflammation begins to resolve: some macrophages can still be found in the wound after a few weeks and aggregations of them may remain around fragments of suture material for several months.

New blood-vessels begin to grow into the wound by about the third day. They originate from the surviving capillaries of the wound margin as solid buds but soon acquire a lumen. As the new capillaries grow they branch repeatedly and unite with each other, forming a series of anastomotic loops. The 'vascular front' formed in this way advances into the wound at the rate of about 1 mm. a day. The capillaries left in the rear by the advancing front do not remain static. Some of them are transformed into arterioles and venules by acquiring a muscle coat: it is not known whether this muscle coat arises by differentiation of the capillary endothelium or by the migration of muscle cells from the arterioles and venules of the wound margin. Many of the new capillaries later shrink and disappear, and this seems to be the fate of any new capillary which ceases to carry blood for about twenty-four hours. The number of new capillaries which survive is variable, sometimes not more than one in ten, sometimes nearly all (Florey, 1954).

New lymphatic capillaries grow into the wound in the same manner from existing lymphatics of the wound margin. However, the growth of lymphatic capillaries is slower and less profuse than the growth of blood capillaries.

The vascular union of a split-skin graft with its bed exemplifies these processes in miniature. The graft is firmly adherent by about the third day, and by the fifth or sixth day its blood supply is sufficiently developed to allow the graft to show reactive hyperaemia when an arterial tourniquet is released. Dyes which are removed by the lymphatics after their injection into normal skin are not removed at all from skin grafts till about the fifth day, and are not removed at normal speed till about the ninth day.

Fibroblasts have been detected in wounds within twenty-four hours and are easily found by the second or third day. There is no doubt that they migrate into the wound, but their source is still debatable (Russell and Billingham, 1962). The idea that any nearby adult fibrocyte can revert at need to a fibroblast is widely held but probably incorrect. It now appears that most of the fibrocytes of the dermis are incapable of reverting to fibroblasts, and that fibroblasts develop only from fibrocytes lying just below the epidermis, around hair follicles, along blood-vessels, and perhaps in the loose

areolar tissue around fasciae and tendons. These are the only fibrocytes of the wound margin which can be labelled with tritiated thymidine, and it can be presumed that they are the only ones which are incorporating thymidine into the extra DNA which must be synthesised as a preliminary to mitosis. An entirely different source of fibroblasts is the metamorphosis of immigrant leucocytes from the blood, especially monocytes: it has been shown that cells of the lymphocyte-monocyte series can produce connective tissue when grown in tissue culture. The number of fibroblasts in a wound is augmented not only by fresh arrivals but by the mitotic division of the fibroblasts already present. Fibroblasts advance into the wound at the rate of about 0·2 mm. per day. From studies in tissue culture the fibroblasts are known to be actively motile, usually advancing along the grain of the medium, turning aside if they encounter any obstruction, and ceasing to move when they become hemmed in by other fibroblasts.

A fibroblast can assume any shape, but in the tissues is usually compressed by the fibres among which it lies and is therefore usually elongated. A typical fibroblast is about 50 μ in length. It has a central deeply staining nucleus and prominent mitochondria. Its most important property is its ability to generate connective tissue fibres. How it does so is only imperfectly understood, and is discussed further on page 9.

Fibres begin to appear among the fibroblasts at the third or fourth day, and are then laid down rapidly. The earliest fibres are extremely delicate and have the property of staining black on treatment with salts of silver. Although these fibres consist essentially of collagen they are termed 'reticulin' to distinguish them from mature collagen, which is not argentophil. As the collagen develops and matures, the strength of the wound steadily increases, and at the same time the cellularity and vascularity of the granulation tissue diminish.

The rate at which healing progresses varies with the nature of the wound.

In an accurately coapted wound such as a surgical incision the wound edges are very firmly bound together by tough collagen by the end of two or three weeks. Nevertheless the scar is not yet fully mature. Slowly over the course of the next few months it contracts, its collagen thickens, its cellularity diminishes even further, and it becomes almost avascular. Even at this time the few remaining fragments of catgut may be surrounded by collections of inflammatory cells, or, if non-absorbable sutures have been used, they may permanently retain a narrow mantle of round cells and foreign-body giant cells.

Healing in an open wound, or in a wound with loss of tissue,

follows the same course but at a slower pace. The presence of blood clot and foreign bodies, and the inevitable occurrence of infection, prolong the initial inflammatory phase. Even so, the margins of the wound are lined within three or four days by vascular granulation tissue which forms an efficient barrier protecting the normal tissues from invasion by the bacteria growing in the wound. If the wound is freely open to the surface the granulation tissue proliferates rapidly, but its development is arrested round deep-lying pockets of pus and around foreign bodies. So long as the wound remains open, only a little collagen is laid down in deeper layers, and the granulations tend to proliferate rather than mature. But proliferation stops when the surface becomes covered with epithelium. In small open wounds the epithelium may be restored within a few days, and the whole process of healing may be almost as rapid as in a sutured incised wound. In larger wounds the healing process is correspondingly prolonged, and the bulk of the scar is greater.

The modern practice of early skin-grafting of extensive wounds, particularly burns, is aimed at minimising the quantity of fibrous scar, relying on the principle that granulation tissue ceases to proliferate when it acquires a covering of epithelium.

Healing under a scab is very similar to healing of an open wound, but tends to be faster. The scab immobilises the wound, and protects it from trauma and from bacterial contamination.

REGENERATION OF EPITHELIUM

Epithelium grows centripetally over the wound surface from the surviving epithelium at the margin. The first evidence of this growth can be found within a few hours, and a narrow peripheral ring of new epithelium is formed as early as the end of the first day. Extension of epithelium over the wound takes place surprisingly rapidly, but not necessarily at a steady pace. The advance is liable to temporary periods of arrest, especially when epithelialisation is almost complete, but also at other stages. The sheet of new epithelium is thin, delicate, and easily torn off by the clumsy removal of adherent dressings. Histological examination shows that the new epithelium lacks the pigmented and cornified layers of normal skin. A feature of particular interest is the complete absence of mitotic activity from the newly formed epithelium. Mitotic activity is increased at and beyond the wound margin, but appears over the wound itself only at a late stage when the new epithelium begins to thicken. The absence of mitotic activity combined with the formation of a sheet of epithelium indicates that its component cells have migrated inwards from the margin and have not been formed by cell division over the wound. In their migration they do not carry with them specialised

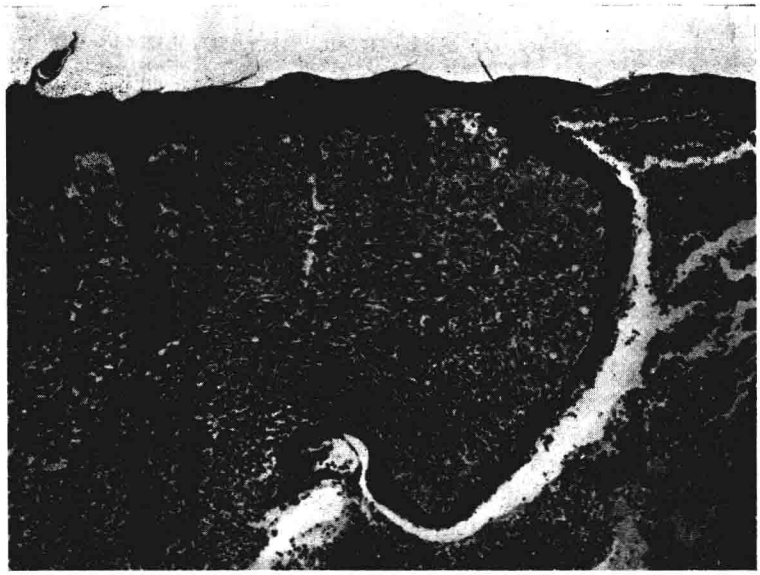

FIG. 1A

Healing of wound with loss of tissue, at sixth day. New epithelium, growing from surviving skin, covers the wound margin.

FIG. 1B

Higher magnification of same wound, showing extreme thinness of advancing edge of epithelium. (*Courtesy of Dr H. E. Hitchison, Department of Pathology, Western Infirmary, Glasgow.*)

organs such as hair follicles and sweat glands, and these structures are permanently lacking from the scar.

The rate of healing of skin wounds lends itself to measurement, and a number of formulae have been worked out which provide estimates of the average rate of healing. Workers who are familiar with this field of experiment have been careful to point out that individual wounds vary widely in their behaviour and that the advance of epithelialisation is prone to temporary periods of arrest without obvious cause. Unfortunately this essential variability has often been overlooked, and extravagant claims have been made for the value of various ' healing agents ' on the basis of study of very small series of cases. Moreover, in accidental wounds it is rarely possible to compare the rate of healing under the influence of a ' healing agent ' with the healing of a control wound elsewhere, and comparison with a hypothetical average rate of healing is unsatisfactory. At the present time no agent has been convincingly shown to accelerate normal healing. Although it is not possible to accelerate normal healing, it is conceded that the delaying influence of various harmful factors can be minimised by such measures as controlling local sepsis, by preventing chemical and physical trauma to the healing wound, and (in patients with arterial disease) by improving the local blood supply by sympathectomy.

WOUND CONTRACTION

While open wounds are healing they shrink owing to the centripetal movement of the margins over the wound bed. Most surgeons and many biologists call this normal process of early shrinkage ' contraction,' reserving the term ' contracture ' for the late and often disabling shortening of a scar.

A good method of studying changes in wound size is to excise a disc of skin within a ring of tattoo marks which serve to identify the original wound margin permanently. As normal skin is under tension it retracts when the wound is made, and the fresh wound is therefore larger than the disc of skin excised. The wound margins become adherent to the deep fascia at about the second day. They begin to advance over the wound bed between the third and fifth days, and contraction of the wound then continues until the central zone has healed by epithelial regeneration. In this way much of the wound becomes covered not by new skin but by old. In rabbits, contraction can provide 80 per cent of the skin cover in large wounds and about 40 per cent in small wounds (Abercrombie *et al.*, 1961). Even after a wound has healed its size does not remain static. In laboratory animals the scar ceases to shrink and actually expands slightly after about the twenty-fifth day.

In experimental wounds which remove only the skin and superficial fascia the contracting wound margins slide over the deep fascia without distorting it. Thus if the exposed deep fascia has been marked with metal clips, the clips do not come closer together as healing proceeds.

The mechanism of wound contraction is by no means fully understood. It is agreed that the wound margin is not thrust forward over the wound by interstitial growth of the skin farther out, for the margin does not retract if a ring of skin is excised just outside the wound perimeter. Nor can there be any sphincter-like contraction of the margin itself, for triangular or rectangular wounds retain their sharp angles. Another possibility (Grillo, Watts and Gross, 1958; Watts, Grillo and Gross, 1958) is that a narrow rim of the margin (termed by these authors the 'picture-frame') migrates over the deep fascia by means of some inherent locomotive force, but this speculation is not now widely accepted. Most workers believe that the wound margin is neither pushed forward nor actively migrates but is pulled forward by contraction of the tissues in the wound itself. In favour of this view Abercrombie *et al.* (1961) point out that if a circular incision is made just within the wound margin the central island of granulation tissue contracts, indicating that it has been exerting traction on the margin. Again, if wound contraction is prevented for several days by gluing Perspex splints to the wound margin, the removal of the splints is followed by rapid contraction of the wound, and excision of the central granulation tissue leads to the margin again retracting.

Although wound contraction can thus be attributed to the margin being pulled inwards by tension developed in the granulation tissue, the factor responsible for the tension is not known. The idea that contraction of the wound can be equated with contraction of collagen must be rejected, for wound contraction proceeds normally in scorbutic guinea-pigs even though little or no collagen is laid down. It is known that the total mass of granulation tissue in a wound is reduced by more than half as wound contraction proceeds, but how this is brought about remains unexplained.

WOUND HEALING IN VARIOUS TISSUES

Discussion up to this point has centred on the healing of wounds of the skin. The healing of the dermis by connective tissue is representative of the healing of fascial and supporting tissues in general. The healing of the epidermis by regeneration is similar to the healing of other epithelia, but there are some differences in points of detail. Only a brief discussion of healing in other tissues is attempted here: a fuller discussion can be found in Russell and Billingham (1962) and Douglas (1961, 1963).

Intestine.—Wounds of the outer coats of the intestine heal by the formation of connective tissue, and the mucosa by regeneration. In the stomach and small intestine the new mucosa not only covers the defect but reproduces the specialised secretory glands. In the colon and rectum the mucosa appears capable merely of restoring epithelial continuity without further specialisation.

Respiratory Tract.—Epithelial migration over a defect is rapid. A stratified epithelium is formed in the first instance, but in a few weeks this reverts to normal thickness and again becomes ciliated.

Gallbladder and Urinary Bladder.—Migration of epithelium is rapid. In other organs mitotic activity is not seen in migrating epithelial cells, and begins only when the restored epithelium begins to thicken. In the gallbladder and urinary bladder mitotic activity is present from the start. The very great recuperative power of the transitional epithelium of the urinary bladder is well known, and the whole bladder can soon be relined from a few remaining fragments.

The *uterus* after menstruation becomes relined very rapidly by epithelium which has regenerated from the remnants of the endometrial glands.

Liver and Kidney.—Incised wounds of the liver and kidney heal by the formation of connective tissue, and there is very little restoration of functioning epithelium. This is not to deny that both organs have great powers of epithelial growth. If much of the liver is excised or destroyed by toxins the surviving tissue shows very striking new growth of bile ducts and parenchyma. If the renal epithelium is extensively destroyed, as in acute tubular necrosis, it soon regenerates from the few surviving cells. However, after incised wounds epithelial growth is slight and abortive.

Muscle has powers of regeneration similar to nerve. If muscle is crushed without division of the endomyseal tubes the dead part of the muscle fibre is removed by phagocytes and the surviving part later grows and re-occupies the tube. If the muscle has been transected the regenerating fibres throw out several sprouts when they reach the open ends of the endomyseal tubes, and some of the sprouts find their way across the gap into endomyseal tubes beyond. However, if the cut ends of the muscle have been allowed to retract there is no repair by bridging, and the gap becomes filled with scar tissue.

Aponeuroses.—A detailed study of healing in the powerful and relatively avascular lumbo-dorsal fascia of the rabbit has been reported by Douglas (1961). He found that the tensile strength of the wound increased steadily for about 100 days and then very slowly up to a year, but never acquired the strength of intact fascia.

The healing of *nerve* and *bone* is described in Chapters 14 and 15.

COLLAGEN AND GROUND SUBSTANCE

The strength of healing wounds depends wholly on the development of collagen fibres. They are laid down in the ground substance of the granulation tissue but whether their formation is influenced by the ground substance is uncertain.

Collagen.—The structure and composition of collagen is believed to be the same in all animals from marine sponges to man. Mature collagen is the most stable protein known, but young collagen is soluble in several solutions from which the typical fibres can easily be re-formed *in vitro*. Although all animals can make and re-model collagen there are no known collagenases of animal origin: collagenases are, however, present in some bacteria, notably *Cl. welchii*.

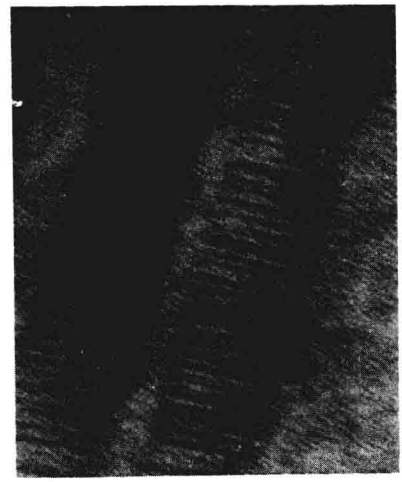

FIG. 2

Electron micrograph of collagen fibrils showing regular cross-banding. The structure of collagen is believed identical in all species: this preparation is from a rat sarcoma.

(*Courtesy of Dr F. N. Ghadially, University Department of Pathology, Sheffield.*)

Collagen, like other proteins, contains many amino-acids such as glycine, glutamic acid, proline and lysine, and it characteristically contains also much hydroxyproline and a little hydroxylysine. These two amino-acids are virtually lacking from other proteins and their amount in a tissue is therefore an index of the amount of collagen. Collagen contains no tryptophane and only small amounts of other aromatic amino-acids, and it contains no cystine: for this reason gelatin (which is denatured collagen) is a relatively poor source of food protein.

Most authorities believe that molecules of collagen are formed within the fibroblasts but polymerise to form fibrils only after being extruded. The finest fibrils detectable by electron microscopy lie just outside the cell membrane. The collagen molecule is shaped like a needle, 3,000 Å in length and 14 Å in diameter, and its molecular weight is about 340,000. These molecules aggregate to form fibrils which are not smoothly cylindrical but regularly banded at intervals of 640 Å (Fig. 2).

Reticulin and collagen are essentially the same in structure and composition: reticulin, however, stains black with silver salts, probably because polysaccharides adhere to its surface. Reticulin

and young collagen are soluble in various solutions including dilute solutions of sodium chloride, dilute alkalis, and acid-citrate buffers: more mature collagen is only partly soluble: old collagen can be dissolved only slowly in strong organic acids. Typical fibrils of collagen can easily be formed *in vitro* from these solutions by removing the salt or by neutralisation. The increasing stability of collagen as it ages is attributed to a slow increase of hydrogen cross-bonding between adjacent chains of collagen polymer, the hydroxyproline and hydroxylysine providing the points of attachment of the bonds. The formation of collagen fibres is either defective or wholly lacking in scurvy (p. 16), but in what manner vitamin C is required in fibre formation is unknown.

Ground Substance.—This term is an inaccurate translation of the German ' Grundsubstanz ' which means fundamental substance. It refers to the matrix in which lie the formed elements of any tissue. It consists primarily of the tissue fluid and comprises chiefly water and various solutes. It characteristically contains also mucopolysaccharides which are responsible for altering its physical state from a liquid to a gel. The consistence of this gel is usually thin, but in cartilage it is solid and elastic, and in inflamed tissues it is watery owing to the polysaccharides becoming depolymerised. The use of hyaluronidase as a spreading agent similarly depends on depolymerisation.

There are at least seven different mucopolysaccharides. They are enormous chains built up from paired units. One unit of each pair is glucuronic acid which differs from glucose only in possessing a –COOH group. The other unit is either glucosamine or galactosamine which differs from the corresponding sugar in possessing a $-NH_2$ group: the hexosamine carries an acetyl radical attached to the $-NH_2$ and often a sulphate radical attached elsewhere. Examples of the mucopolysaccharides are hyaluronic acid and chondroitin (which are not sulphated) and the three chondroitin sulphates designated A, B, and C.

These substances stain metachromatically in that they change the colour of toluidine blue to pink. The dye is believed to attach itself only to terminal molecules, and intense staining is therefore held to indicate the presence of relatively short polymer chains. The ground substance of normal tissues stains only a faint pink, but in healing wounds or growing cartilage it stains deeply. Formerly this intense staining was wrongly attributed to an increased total concentration of mucopolysaccharides.

A few years ago the synthesis of mucopolysaccharides was thought to be increased in healing wounds. This belief was based partly on the increased intensity of metachromatic staining mentioned above, and partly on the demonstrable increase of hexosamine in