PATHOLOGIC BASIS OF DISEASE

Tissue Repair

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the peripheral axon is injured, regeneration of a new process may proceed from the cell body or from the remaining proximal axonal segment. In such injury, the distal segment degenerates entirely, and the proximal segment degenerates only to the nearest node of Ranvier. If the proximal segment, growing at a rate of 3 to 4 mm. per day, recontacts the channel of the original nerve fiber, the integrity of the neural innervation may be reestablished. In some injuries, however, the regenerating axonal process is isolated from the distal segment because tissues, coagulated blood (hematoma) or masses of fibrous scarring are interposed. The extending axonal process then gives rise to a tangled mass of fibers, sometimes termed an *amputation or traumatic neuroma.*

REPAIR BY CONNECTIVE TISSUE

Fibroblastic proliferation and scarring are the most ubiquitous features of repair, and are seen in all but the very few injuries in which only stable or labile cells are damaged and the connective tissue stroma remains intact. Since a connective tissue scar is a more primitive, simpler form of tissue than the specialized types that it replaces, scarring which is irreversible produces permanent loss of specialized function. Thus, fibrous replacement of kidney structure following an abscess or an infarct depletes renal function. Connective tissue repair is best presented in the context of wound healing. This will be divided into the events of primary union by which an incised wound such as a surgical incision closes, and those of secondary union by which an open tissue defect such as an ulcer of the skin heals.

PRIMARY UNION

The least complicated example of connective tissue repair is the healing of a clean surgical incision. The tissues are approximated by surgical sutures or tapes, and healing occurs without significant bacterial contamination and with a minimal loss of tissue. Such healing is referred to surgically as *"primary healing" or "union by first intention."* The incision causes the death of a limited number of epithelial cells as well as dermal adnexa and connective tissue cells; the incisional space is narrow and immediately fills with a scant amount of clotted blood. Dehydration of the surface clot forms the well known scab which covers the wound and seals it almost at once from the environment. The precise chronologic order of the subsequent events is still a subject of contention. Specifically at issue are the following questions: How soon does epithelial closure occur? How soon does subepitheial fibroblastic bridging take place? How rapidly does the incision achieve the full tensile strength of unwounded skin? What cells or extracellular products impart such strength? A reasonable consensus follows.

Within 24 hours, the characteristic changes of the acute inflammatory response appear in the subepithelial connective tissue in the margins of the incision. The gathering leukocytes are mainly neutrophils. The epidermis at its cut edges thickens as a result of mitotic activity of basal cells and, within 24 to 48 hours, spurs of epithelial cells from both edges grow both downward along the cut margins of the dermis as well as beneath the surface scab to fuse in the midline and thus produce a continuous but thin epithelial layer. This epithelial response is amazingly fast, and epidermal continuity is reestablished long before the subjacent connective tissue reaction has begun to evolve. The processes involved in such reepithelialization are discussed in detail on p. 96.

By *day 3,* the neutrophils have largely disappeared and are replaced by monocytes busily scavenging necrotic debris and removing red cells and fibrin. Hypertrophy of subepithelial fibroblasts becomes visible at this time along with the initiation of fibroblastic replication and budding of capillary sprouts. This fibroblastic-vascular tissue progressively invades the incisional space. In time-lapse studies, Cliff (1965) has shown that this invasion advances at the remarkable rate of approximately 0.2 mm. per day into the blood clot which fills the incision. Such ingrowth is accomplished by mitotic division of both fibroblasts and endothelial cells. The major proliferative activity of the endothelium occurs just proximal to the growing tip of the capillary sprout, pushing the tip ahead. Demonstrable collagen fibers are now present in the margins of the incision but these are at first vertically oriented and do not bridge the incision (Ordman and Gillman, 1966). While this connective tissue response is taking place, epithelial cell proliferation and differentiation continue, thickening the epidermal covering layer.

By *day 5,* the incisional space is filled with loose vascularized fibroblastic connective tissue rich in ground substance. The newly formed capillary sprouts from both sides have joined to create continuous channels and, at this stage of wound healing, the vascularization is maximal. Collagen fibrils become more abundant and begin to bridge the incision. During this 5-day interval, the epidermis usually recovers its

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During the *second week* there is continued accumulation of collagen and proliferation of fibroblasts within the incisional connective tissue. Leukocytic infiltrate, edema and increased vascularity have largely disappeared, and the cellular connective tissue which fills the incision begins to compress the thin-walled, newly formed capillary channels. The surface scab is generally shed during this week.

At this time begins the long process of blanching, accomplished by the increased accumulation of collagen within the incisional scar, accompanied by shrinkage and disappearance of vascular channels. The tensile strength of the wound (see p. 97) is still well below that of normal skin and it will take months or even a year or more for the wound to attain its maximal mechanical strength.

By *the end of the first month,* the scar comprises a cellular, still excessively vascularized connective tissue devoid of inflammatory infiltrate, covered now by an intact epidermis. The slowed but continued proliferation of fibroblasts and the continued accretion of collagen build up the mechanical pressure on the vascular channels and, over the ensuing months, the vascularization is more and more reduced. It may require almost a year for the scar to be transformed to an acellular, avascular, pale, collagenous scar. The dermal appendages that have been totally destroyed in the line of the incision and the ensuing inflammatory response are permanently lost. Those that have only been injured or partially damaged along the lateral margins of the incision may regenerate.

In summary, *in the clean surgical wound, healing occurs within hours by the formation of a blood clot, the surface of which becomes dehydrated to create the scab. Epithelial continuity is restored within 24 to 48 hours. Fibroblastic bridging does not become evident until 3 to 5 days following the incision, and demonstrable collagenization only begins to appear in the latter part of the first week.* Therefore, the process is one of progressive proliferation of fibroblasts, the continued accumulation of collagen and the slow compression and devascularization of the newly formed connective tissue which fills the incisional space. Later, some of the details relating to the stimulation of proliferation, epithelialization and collagenization will be considered.

SECONDARY UNION

When there is more extensive loss of cells and tissue such as occurs in infarction, inflammatory ulceration, abscess formation or surface wounds which create large defects, the reparative process is more complicated. The common denominator in all of these situations is a large tissue defect which must be filled. Regeneration of parenchymal cells may occur in the margins but, with loss of the stromal framework, it cannot completely reconstitute the original architecture. Vascularized connective tissue grows in from the margin to complete the repair. The inflammatory reaction is quite intense in such large wounds. The young vascularized connective tissue bearing a leukocytic infiltrate is known as *granulation tissue,* and so these defects are said to "granulate in." This form of healing is referred to as *"secondary healing"* or *"healing by second intention."*

The healing of a large tissue defect on the surface of the body, such as an excised wound, basically resembles the primary healing already described. Epithelialization can take place only from the margins. The subepithelial repair depends heavily on the "fibroblast-capillary system" (Grillo, 1964). Here of course, the ingrowth of granulation tissue and subsequent scarring are on a much grander scale than in the incised wound (Figs. 3–23, 3–24 and 3–25). As in the case of primary healing, epithelialization advances down along and over the edges of the wound while the granulation tissue grows upward from the floor and margins, filling the defect.

Secondary healing differs from the primary healing in several important respects. *Inevitably, large tissue defects have more necrotic debris and exudate which must be removed.* Consequently, the inflammatory reaction is more intense than in the incised wound. Healing cannot be completed until this inflammatory response has controlled the injurious agent and the necrotic debris and exudate have been removed at least sufficiently to permit ingrowth of the granulation tissue from the margins. The mechanisms of "cleanup" comprise proteolysis and resorption of the digestate, phagocytosis by scavenger cells, or drainage to the surface. The persistence of exudate in a tissue defect, as in an abscess in the liver, represents a serious obstacle to healing.

Other distinctive features of the secondary closure of surface wounds are: (1) ingrowth of granulation tissue and (2) wound contraction. When the large defect occurs in deeper tissues such as in a viscus, the fibroblastic-vascular system bears the full responsibility for its closure, since drainage to the surface cannot occur. Not only is the quantity of granulation tissue greater in secondary healing, it is also more heavily infiltrated with leukocytes as a result of the greater intensity of the inflammatory response.

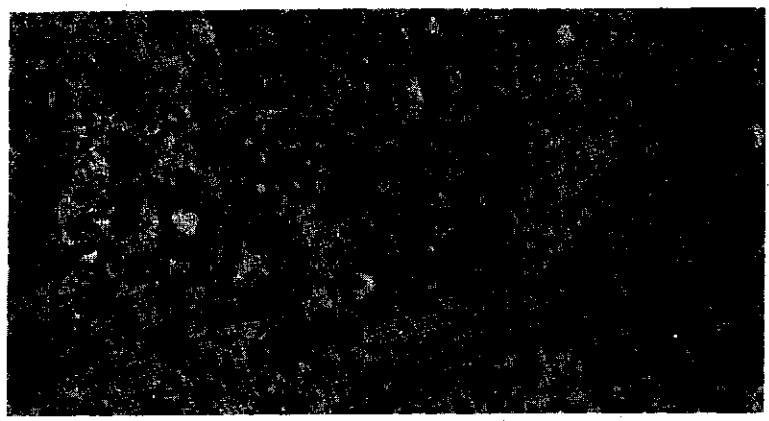

Figure 3–23. Active granula tion tissue containing numerous di lated vascular channels and inflam matory white cell exudate in a loos fibrous tissue stroma.

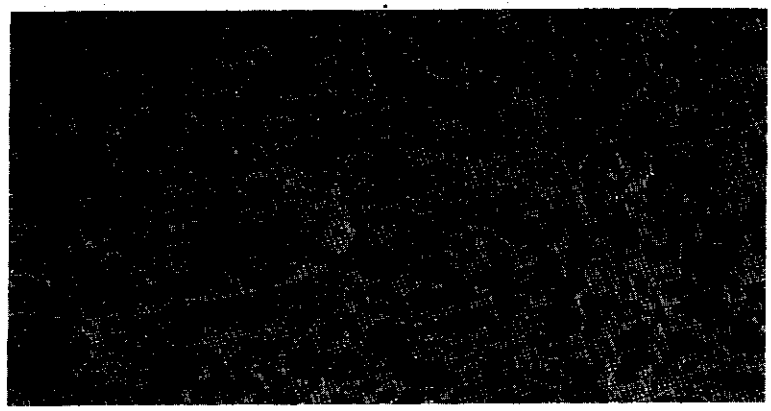

Figure 3–24. Cellular sca composed of packed fibroblasts wi only scattered white cells and vasc lar channels.

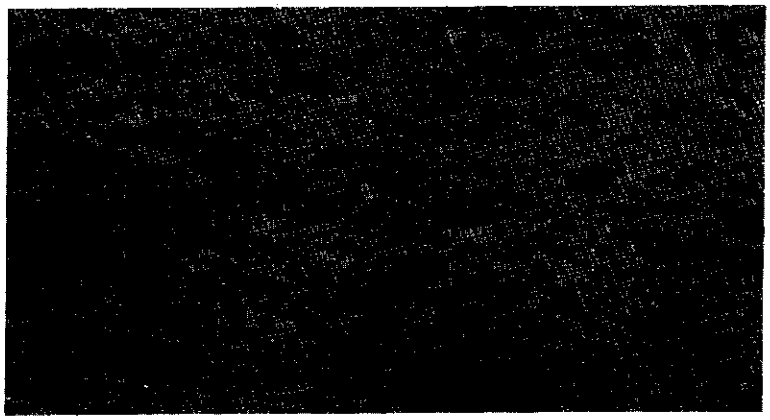

Figure 3–25. Dense collage ous scar. The widely scattered fibr blasts are separated by dense colla gen. Only a few inflammatory whi cells remain.

Perhaps the feature which most clearly differentiates primary from secondary healing is the phenomenon of *wound contraction* which occurs in large surface wounds. It can only occur in those sites where the skin is mobile. It has been shown by Billingham and Russell (1956) that a defect of about 40 cm.^{2} in area in the skin of a rabbit is reduced in approximately six weeks to 5 to 10 per cent of its initial size largely by contraction. The margins of the wound are literally drawn together. It is estimated that all open skin wounds halve their surface area at the same rate and so all tend to approach the same size. Indeed, such contra tion is largely responsible for the closure skin wounds, and the granulation tissu sprouting from the base essentially provides temporary covering which may, in fact, need be resorbed in part to accomodate for th shrinkage in the size of the defect (Harknes 1964).

The mechanism of wound contraction still obscure and has excited great interes Shortening of collagen fibers has been large ruled out. The best evidence, provided b Majno and Leventhal (1967), indicates tha

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ibroblasts within the granulation tissue develop characteristics of smooth muscle cells and shorten to provide the contractile forces (Gabbiani et al., 1972). These fibroblasts have considerable pull and it is of interest that efforts have been made to harness such forces as a source of energy (Higton and James, 1964). Whatever the mechanism, wound contraction contributes heavily to the repair of large surface defects, making it clear that whatever the dimensions of a scar the initial area of necrosis or tissue loss must have been much greater.

In summary, *second intention healing differs from first intention in the following respects:*

1. Loss of a greater amount of tissue.
2. Necessity for removal of greater amounts of inflammatory exudate and necrotic debris.
3. Formation of larger amounts of granulation tissue.
4. Contraction of surface wounds if there is mobility of the wound margins.
5. Production of larger amounts of scar.
6. Greater loss of skin appendages such as hair, sweat and sebaceous glands.
7. Slower completion of the entire reparative process.

As is the case with everything in life, sometimes things go wrong in the healing of wounds. Many of these aberrations (discussed on p. 99) relate to the management of the wound and the state of health of the wounded person. Two, however, may occur in the completely normal individual who received optimal care. The first comprises the formation of excessive amounts of granulation tissue. The excess, referred to as *"exuberant granulations"* or more grandiloquently as *"proud flesh,"* may protrude above the margins of the closing defect and block reepithelialization. Happily, the problem is readily managed by either surgical excision or chemical cauterization of the excess. The second abnormality, for mysterious reasons encountered most often in blacks, is *keloid* formation. Here, an abnormal amount of collagen is formed in the connective tissue, producing a large bulging tumorous scar (Fig. 3–26). The tendency to form keloids appears to be an individual genetic characteristic. It has only been recognized in skin wounds but the same excessive scarring may occur in deeper tissues as well, although we do not have substantial evidence that it does. Keloid formation can be a troublesome problem, particularly on exposed skin areas, since it is disfiguring and exceedingly difficult to manage medically; excision may be followed only by recurrence. It is encountered in both primary and secondary healing.

Figure 3–26. Keloid. Deep to the overlying regenerated epithelium there are interlacing broad bands of dense collagen.

INTEGRATION OF PARENCHYMAL REGENERATION WITH CONNECTIVE TISSUE SCARRING

Most bodily injuries are repaired by the regeneration of parenchymal cells, accompanied by more or less connective tissue scarring. Both of these processes have been considered separately, but it would be well to consider their respective contributions to the reparative process of most injuries. An abscess in the cortex of the kidney resulting from a bacterial infection might be used as an example. Reconstructive activities are initiated soon after the inflammatory phase has begun. Even during the acute stages of the response, there is proliferation of the marginal cells beyond the range of the toxic action of the microbial invader. At some point in the margin, there will be a zone where the epithe-

to the basement membrane and to each other by desmosomes. Are these altered, detaching the cell from its anchorages, and are factors liberated which attract the cell? This question has not been resolved and, as Abercrombie and Ambrose (1962) put it: "It is likely to be difficult to decide whether when cells are mobilized, there is a primary change in their surfaces (or in the surfaces to which they are adhering) that is a decrease in the intensity of adhesion, or whether the primary change is the activation of the mechanism of movement." Within hours of the onset of migration, replication of cells commences. It is important to note that this proliferative reaction in the epidermis extends only about 1 mm. from the wound margin (Bullough, 1962). It is, therefore, a local phenomenon and not likely to be related to loss of circulating factors. Moreover, proliferative activity in the epidermis precedes, by several days, evidence of mitotic division in the subepithelial connective tissues, further suggesting some alteration in intracellular controls specific for cell types. *These observations have led to the general thesis that "control of mitotic activity, particularly in regeneration and repair, has swung away from the concept of stimulatory substance to one envisaging control by feedback mechanisms"* (Johnson, 1964).

The nature of the intracellular feedback control is still highly hypothetical and several postulations have been offered. Weiss (1955) proposes that cellular growth is dependent on cell-specific catalysts or *"templates"* which dictate the genetic programs for the reproduction of the living mass of new cells. Each cell also produces specific "antitemplates" which, unlike the templates, are free to diffuse into or out of the cell. The antitemplates block the action of the templates. With injury, loss of cells and the consequent inflammatory response, there is diffusion of the antitemplates out of the extracellular tissue spaces. The extracellular-intracellular concentration gradient then leads to diffusion of antitemplates from the cell, releasing the feedback controls on cell replication. As new cells are formed, antitemplates are synthesized by this progeny until the equilibrium is once again established.

Bullough (1962) refers to the intracellular control as a *chalone* (derived from a Greek marine term implying "to reef the sails"). This thesis proposes that each tissue produces and contains its own specific inhibitor. With injury, chalones diffuse out of the cell, permitting regeneration. Iversen (1968) has extracted chalones from the skin of man and animals and has reported suppression of the mitotic rate of epidermal cells in tissue culture when this extract was added. The factor appears to be tissue specific since it has no effect on fibroblasts or liver cells, for example, but not species specific since an extract derived from human skin will act upon epidermal cells from lower animals.

Abercrombie (1966, 1967) has suggested another form of intracellular control of mitotic activity. He speaks of *contact inhibition* in which cells are inhibited from mitotic division by the interchange of signals or substances at their points of contact. It can be readily demonstrated in tissue culture. When cells grow out from two separate explants they expand centrifugally until the two populations come into contact at some point. When contact is established, further migration and division ceases only at these points of contact. The nature of the message which passes from one cell to the other is still unclear. It could be the flow of electrochemical charges, soluble factors or modification of membrane receptors. More details on this interesting problem are available in the reports of Loewenstein (1969). Here this unsettled matter must rest for the present, but release of intracellular controls appears to be the initiator of cell replication in the reparative response.

Available evidence suggests that control mechanisms are tissue specific. What initiates the fibroblastic vascular response beneath the epidermis? Much less is known about this problem and, indeed, we cannot at the present time exclude the possibility that controls similar to those postulated for parenchymal cells also operate on stromal and vascular elements. Alternatively, it has been suggested that the blood vessels and fibroblasts may respond to local hypoxia. Conceivably, in the center of a wound, there is lower oxygen tension which stimulates proliferation in the marginal fibroblasts and blood vessels (Remensnyder and Majno, 1968). It must be apparent that the nature of the stimuli which initiate cell proliferation and regeneration in wounds is of utmost importance to the understanding of the nature of cancer. It is entirely conceivable that the mechanisms or stimuli which activate the controlled growth in repair may be further dislocated or permanently turned off or on to permit emergence of an uncontrolled cancerous growth.

DEVELOPMENT OF WOUND STRENGTH

It may come as a surprise to learn that, despite decades of study, there are still many gaps in our knowledge and numerous disagreements about several of the fundamental

features of wound healing. There is still controversy over such basic issues as the following: What substances or structures within the wound impart to it its tensile strength in the first weeks of healing? What is the origin of the fibroblast, the backbone of all connective tissue repair? How is collagen synthesized? How rapidly does an incised wound regain the tensile strength of unwounded skin? These issues are examined in the following discussion.

Two viewpoints as to the origin of the fibroblast in the healing wound are still stoutly defended. The first proposes that some or many of the fibroblasts are derived from hematogenous cells, particularly monocytes and macrophages (Allgöwer, 1956) (Allgöwer and Hulliger, 1960). Alternatively, it is held that fibroblasts are derived from local fibroblasts or their immediate precursors. Underlying this problem is the well known fact that, in wound margins, the mature spindle-shaped fibroblast undergoes striking enlargement and becomes stellate or polymorphous, while the monocyte and macrophage develop larger pseudopods so that both cell types come to resemble each other to a considerable extent. Most of the evidence stems from in vitro cultures of mononuclear blood cells and the demonstration of collagen or collagen precursors in the culture flask. Opponents of this view contend that such cell cultures may well have been contaminated by connective tissue cells in the process of securing the blood cells (Grillo, 1963) (Ross, 1968). Most of the evidence supports the view that the fibroblast is derived from local fibroblasts (Grillo, 1964). Local irradiation of wounds suppresses collagen synthesis, which would not be anticipated if fibroblasts were derived from the circulating blood. Electron micrographic studies of the ultrastructural details of the cells in question reveal morphologic details of the cells consonant with the features of classic fibroblasts. Isotopic labeling experiments also indicate that newly formed cells are derived from local fibroblasts.

The amino acid composition of collagen is unique among the proteins of vertebrates. It is the only protein having significant amounts of hydroxyproline and hydroxylysine. Elastin may be a possible exception since it possesses small amounts of hydroxyproline. Three polypeptide chains possessing these hydroxylated amino acids are wound about each other in a helical fashion to form the tropocollagen macromolecule, the soluble precursor of collagen. The classic fibrillar structure of collagen results from the aggregation of these macromolecules to form fibrils which have periodic banding at approximately 600 to 700 Å intervals. Further details on the ultrastructure of collagen can be found in the review by Ramachandran (1963). The polypeptides, like a... others, are synthesized on the ribosomes of th... well developed, rough endoplasmic reticulu... in the fibroblast.

There is general agreement that the ... broblast is responsible for the production ... collagen, but the biomolecular pathways i... volved in its production are still debatable (V... Winkle, 1967). A major issue relates ... where the collagen fiber is elaborated. O... school of thought proposes that the tropoco... lagen macromolecules are aggregated into th... collagen fibril in the peripheral cytoplasm ... the fibroblast, and the fibrils are then extrude... by some process that involves shedding ... peripheral cytoplasm (Porter and Pappa... 1959). Another view proposes that the tropo... collagen monomers are secreted outside of th... cell, and aggregation into fibrils occurs in th... extracellular ground substance (Ross, 1968...

It has been established that collagen fibr... can be created in the flask independent of cel... from soluble precursors (Gross et al., 1955). ... has been further shown that fibrils in extracel... ular locations enlarge in diameter with i... creasing age, strongly suggesting that the fibr... develops outside of cells and is not born fu... grown within the fibroblast (Ross and Bendi... 1961). Most of the evidence therefore suppor... the notion that soluble collagen precursors a... secreted by the fibroblast and that final a... gregation or polymerization occurs extracell... larly.

The ground substance of connective tissu... is believed to play some important role in th... production of collagen (Wagner and Siew... 1967). The substances found in connective ti... sue ground substance are derived from eithe... the plasma or local cells, principally fibroblast... They include a host of relatively water-solubl... and water-insoluble components, the most im... portant of which are mucopolysaccharides an... glycoproteins (Spiro, 1966). The most impo... tant mucopolysaccharides are acidic and com... prise two groups—those bound to sulfate an... those which owe their acidity to carboxy... groups (hyaluronic acid and chondroitin). Be... cause of their acidity, all have metachromasi... when stained with toluidine blue. The muco... polysaccharides are largely synthesized locall... in the wound area by connective tissue cells... The glycoproteins are elaborated principally i... the liver and elsewhere. One might anticipate... therefore, that with the fibroblastic response o... repair, increased amounts of acid mucopoly... saccharides would, in the course of time, de... velop in the wound (White et al., 1961). It is... postulated that this change in the composition... of ground substance is important in the extra... cellular polymerization of collagen precursors... into fibrils (Schilling, 1968).

We may now turn to the crucial clinical question: How long does it take a skin wound to achieve its maximal tensile strength? At the same time, consideration should be given to the factors or substances which contribute to this tensile strength. (Both issues are highly controversial at the present time.)

Observations in the literature vary widely on the rate and extent of recovery of wound strength. On the one hand, Adamsons et al. (1964), in studies of paramedian abdominal incisions in adult male guinea pigs, report that the tensile strength of a wound reached the strength of the control side by the end of the fourth week." At the other end of the scale is the report of Douglas (1969) that, in both guinea pigs and man, skin wounds remain weak for many years and regain only about 30 per cent of their original strength at the end of the year. He further states that, in man, wounds have regained only about 50 per cent of their original strength at the end of three years; and (even at the end of 14 years, a deficiency still exists.) It is difficult to reconcile these startlingly different results, but perhaps the explanation may be found in a host of factors such as variations in the age of the animals, their diet, the depth of the skin incision, its length, methods of measurement and methods of suturing the original incision.

From the welter of opinions, a general impression emerges. Immediately after injury, there is a short lag phase perhaps lasting a few days and possibly lasting up to 10 to 14 days. Thereafter, there is a rapid increase in wound strength over the next four weeks. This rate of increase then slows and virtually plateaus at approximately the third month after the original incision. This plateau is reached at about 70 to 80 per cent of the tensile strength of unwounded skin and indeed, the plateau may persist for life.

Thus, Dunphy (1967) reports that *"most wounds involving skin, fascia or tendon never regain the initial strength of the tissue divided."* The recovery of tensile strength comprises, therefore, a sigmoid curve terminating in a plateau below the original level of the unwounded skin (Levenson et al., 1965). The structural or biochemical explanation of this curve still eludes us. It is not merely a function of collagen synthesis since the curve of tensile strength does not parallel that of collagen increase in the wound. Immediately after injury, there is resorption of collagen. Thereafter, fibroplasia commences and the period of exponential rise in tensile strength is associated with a rapid increase in the number of fibroblasts as well as the synthesis of collagen. But the later linear rise in tensile strength is not associated with a significant increase in the collagen content of the wound. Perhaps the collagen fibers are maturing or polymerizing at this time or there is remodeling of collagen to reorient the fibers across the wound, thereby increasing tensile strength. But collagen content alone cannot explain the curve.

In the light of these findings, one may properly ask: How can patients be discharged from the hospital within a week of surgery? An interesting study bears on this question. It has been shown that carefully sutured wounds have approximately 70 per cent of the strength of unwounded skin immediately following surgery (Lichtenstein et al., 1970). Indeed, (eight weeks later there was no significant increase in tensile strength despite the presumed proliferation of fibroblasts and synthesis of collagen. The obvious conclusion is that, in the fresh wound, most of its tensile strength depends on surgical skill and the placement of sutures.) When the latter are removed at the end of the first week, wound strength is only at approximately the 10 per cent level. But, in addition, it is reasonable to propose that reepithelialization which occurs within the first days of wounding provides some strength, and perhaps the early granulation tissue in some way serves as a binding agent or adhesive material. We must rest this discussion at this unsatisfactory point, recognizing that there is still much to be learned about this seemingly simple yet important surgical problem.

FACTORS MODIFYING THE QUALITY OF THE INFLAMMATORY-REPARATIVE RESPONSE

Many host factors influence the adequacy of the inflammatory-reparative response. Only a few of the more important will be discussed here under the headings of systemic and local influences.

SYSTEMIC INFLUENCES

Age. Age is probably not a major factor in the inflammatory-reparative response. It is mentioned here because there is a prevailing "general wisdom" that the elderly heal more slowly than the young; yet there is very little controlled data in the experimental animal to support this notion. Some years ago, it was reported that fibroplasia and collagenization occur more slowly in old rats than in young (Howes and Harvey, 1932). The validity of these observations when applied to man has not been established. It has been virtually impossible to rule out either the altered vascular supply due to the inevitable senile arterio-

Tissue in Which the Injury Has Occurred. It is apparent that perfect repair can occur only in tissues made up of stable and labile cells, whereas all injuries to tissues composed of permanent cells must inevitably give rise to scarring and, at the most, very slight restoration of specialized elements. The location of the injury, or the character of the tissue in which the injury occurs, is also of considerable importance from yet another standpoint. There are many situations in the body in which inflammations may arise within tissue spaces or cavities and develop extensive exudates that fill these spaces. Despite these widespread extensive inflammatory responses, there may be no associated necrosis of fixed tissue cells. Under these circumstances, repair may occur by liquefactive digestion of the exudate, initiated by the proteolytic enzymes of leukocytes, and resorption of the dissolved exudate. This mechanism of dealing with an exudative inflammation is called *resolution.* Since no necrosis of fixed tissue cells has occurred, perfect restitution of the preexisting architecture is attained.

An example of resolution may make its meaning more clear. Bacterial infections in the lung cause inflammations which may solidly fill the alveolar spaces with exudate. In many instances, the alveolar septa are not damaged, although the lung becomes totally solidified by the inflammatory exudation. Proteolytic digestion of the exudate and resorption or coughing up of the watery digestate permit resolution of the pneumonia and restoration of normal lung structure and function. This same sequence of events is not inevitable in all pneumonias, since infections with more virulent pathogens may cause necrosis of alveoli and result in fibrous scarring and permanent pulmonary damage. Moreover, for completely obscure reasons, certain pneumonias with or without necrosis sometimes fail to resolve but, instead, granulation tissue grows from the septal walls into the exudate and converts it into masses of fibrous tissue, referred to as *organization* of the pneumonia (Fig. 3–27).

These processes of resolution or organization of inflammatory exudates are also observed in inflammations within other tissue spaces of the body—i.e., peritoneal, pericardial and pleural cavities and joint spaces. In the overall viewpoint, most injuries of the body do not resolve without tissue necrosis, and result in some connective tissue proliferation and therefore some degree of scarring. Finally, even when scarring is complete, there is another hazard consequent upon a lag in the return of tensile strength of the collagen fibers. A rise in tension may bring about undue stretching of the scar, with hernia formation when the dominal wall is affected. So, too, the walled scar of syphilitic aortitis yields to bl pressure and fathers an aneurysm.

Figure 3–27. *Organized pneumonia. Large masses of fibroblastic scar tissue are visible in the veolar spaces.*

In concluding this discussion of host tors, it is hardly necessary to point out many involve issues of considerable clinical portance. The correction of nutritional d ciencies, avoidance of steroid therapy, wise of sutures, careful debridement and rem of foreign bodies and, in general, scrupul attention to all of the influences which hamper the inflammatory response are all sponsibilities of the clinician.

PERSPECTIVE ON THE INFLAMMATORY-REPARATIVE RESPONSE

The full spectrum of events, from the tial reaction to injury to the ultimate tis repair, has been presented. It must be obvi that an injury may have little consequence

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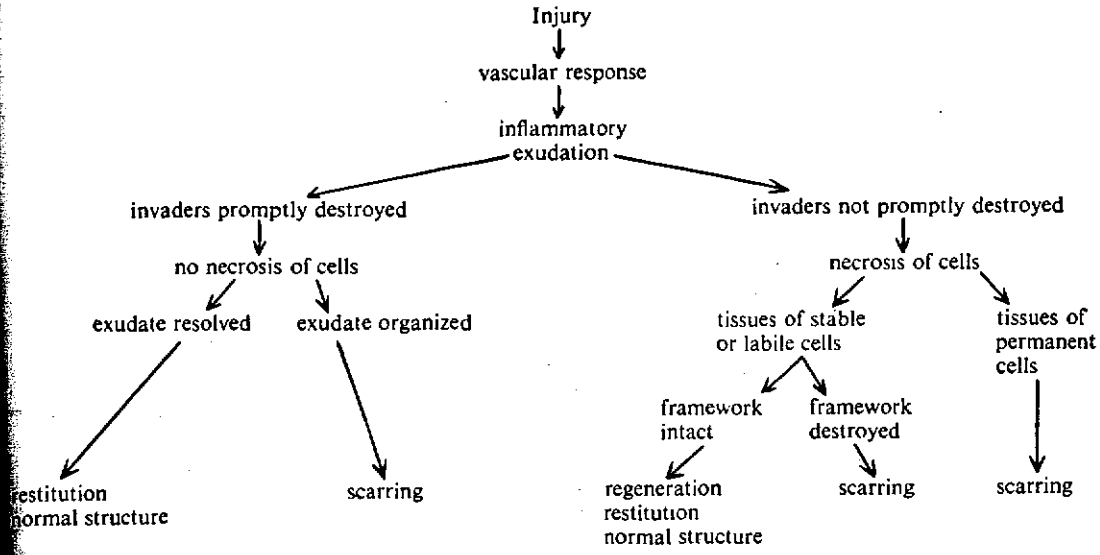

Figure 3–28. *Pathways of reparative response.*

be dealt with readily or may culminate in
re destruction and damage. A perspective
he various pathways is offered in Figure 3–
This overview makes clear that not all inju-
result in permanent damage; some are
lved with perfect reconstitution of the na-
tissue. However, most often some residual
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Connective Tissue Cells. *Connective tissue cells,* such as fibroblasts or their more primitive mesenchymal progenitors, are not only highly resistant to injury, but are also multipotential cells capable of proliferation throughout life. Connective tissue scars result from the proliferation of fibroblasts, with the subsequent deposition of intercellular collagen. Since most injuries destroy stromal as well as parenchymal cells, fibroblastic proliferation and scarring are consequences of almost all reparative processes. The multipotential fibroblast is further capable of differentiation into any other type of supporting tissue cell. By metaplastic transformation, it may be converted to an osteoblast or chondroblast and form bone or cartilage. By the accumulation of lipids, it or its progenitor becomes transformed into a lipid cell and so constitutes injured fatty tissue.

Muscle Cells. There is a growing body of evidence that *skeletal, cardiac, and visceral (smooth) muscle cells* are capable of regeneration (Moznik, 1969) (Hay, 1971). Most of the evidence is derived from studies of lower animals, but a number of reports dealing with human muscle cells confirm the applicability of these observations to man. The precise mode of regeneration of skeletal muscle is still somewhat uncertain. It appears that regeneration of skeletal muscle may occur: (1) from the budding of old fibers, (2) by the fusion of myoblasts or (3) by transformation of the mononucleated satellite cells found attached to the sheath of all multinucleated skeletal muscle cells (Shafiq et al., 1967).

The evidence in support of the regenerative capability of cardiac muscle and smooth muscle is less substantial and we must conclude that further study is necessary. Robledo (1956) reports that he has observed both sprouting and longitudinal splitting of cardiac muscle fibers at the edge of necrotic areas in the heart in man. However, it must be pointed out that the heart also contains an abundant fibroblastic stroma and the precise identification of the regenerative cells may be difficult. It is probably safe to state that if cardiac muscle has regenerative capacity, it is limited, and most large injuries to the heart are followed by connective tissue scarring (Fig. 3–22).

Certainly, scarring follows the all-too-common myocardial infarction (ischemic necrosis of the myocardium) in man. This point is stressed because of its great clinical importance. Heart attacks are the most common cause of death in industrialized nations, and every heart attack implies some permanent loss of myocardial reserve. Regeneration of smooth muscle has been observed in the wall of the gut, urinary bladder, uterus and blood vessel walls (McMinn, 1967). Here again, most injuries to smooth muscle inevitably induce some scarring. The regenerative capacity of the smooth muscle, therefore, must be considered to be limited.

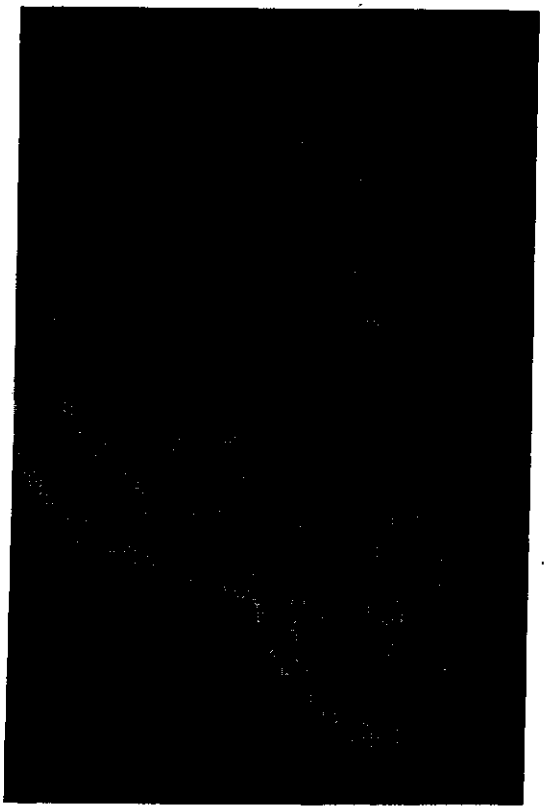

Figure 3–22. *Myocardial fibrosis. The cross section of the ventricular myocardium is studded with pale scars of fibrous tissue that have been caused by ischemic necrosis of foci within the myocardium.*

PERMANENT CELLS

These highly specialized cells *cannot undergo mitotic division in postnatal life* presumably because the genetic programs involved in their division are irrevocably repressed. Severe injury in such tissue inevitably implies loss of specialized function.

Nerve Cells. Nerve cells, when destroyed in the CNS (central nervous system), are permanently lost. They are replaced by the proliferation of the CNS supportive elements, the glial cells. The situation is somewhat more complicated with respect to the neurons of the peripheral nerves (Lumsden, 1957). When the cell body is destroyed, the entire structure (i.e., the cell body and extended axon) totally degenerates. If the cell body is spared and only

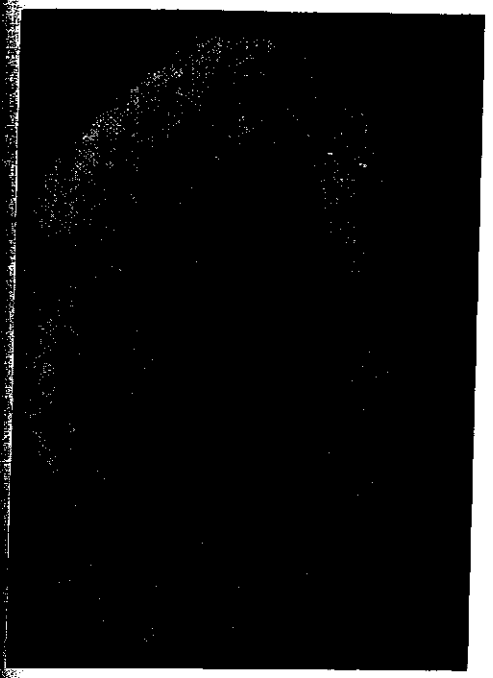

Figure 31–37. Chronic bursitis on cross section show the markedly thickened wall and shaggy, trabeculated interior.

oid fluid. As the chronic stage is reached, the ge at which the lesion is usually excised, the bur- space is filled with a granular, brown, inspis- ed changed blood heavily admixed with gritty cific precipitations. The wall is thick, tough and ous and is often pigmented by the contained morrhage and hardened by calcification. The er surface is usually shaggy and trabeculated, often thick, fibrous bridging cords traverse the er space (Fig. 31–37).

Histologically, the walls are composed of ise, fibrous tissue focally infiltrated by lympho- es, plasma cells and macrophages. The lining of bursa is usually composed of granulation tissue precipitated fibrin. Characteristically, there is rked focal vascularization of the wall of the cyst t often produces small hemangiomatoid collec- ns of capillary channels. Basophilic calcium de- sits may be found trapped within the fibrinous ng material and within the wall.

These conditions are more painful than ious and presently are treated by supportive easures, the local instillation of cortisone or ilar steroids and, in the calcific stages, by rgical excision.

NOSYNOVITIS

Tenosynovitis denotes an inflammation of e tendon sheaths and contained tendons. This condition is most often encountered in persons who place great stress upon certain tendons in the course of their occupation. Thus, tenosynovitis is most often encountered in the upper extremities of laborers and artisans, and in the wrists and hands of stenographers. On the basis of this clinical distribution, trauma is believed to play an important role. However, occasionally tenosynovitis may be caused by direct bacterial seeding.

Several anatomic forms of this inflammation are produced by these various causations. *Traumatic synovitis* consists of the accumulation of synovial fluid and fibrin within a tendon sheath. The fibrin may cause a grating sound on motion and may also, in time, become organized to produce fibrous adhesions. Direct bacterial invasion gives rise to a *suppurative tenosynovitis.* The most common offending organisms are the pyogens. Such pyogenic infection may also be initiated by penetrating injuries, as when a surgeon accidentally punctures a tendon sheath in the course of placing sutures. *Tuberculous tenosynovitis* is a very uncommon pattern that usually represents a hematogenous focus of seeding but may occur by direct inoculation of infective material through the skin. These tuberculous infections are characterized by the development of small granulomas on the synovial lining that often protrude and are sloughed off into the fluid of the tendon sheath to produce the characteristic *"rice bodies."* These conditions are extremely painful on motion and cause some disability because of this pain. Adequate rest and other supportive measures usually promote healing. However, sometimes residual fibrous adhesions limit, to some extent, the movement of the tendon. In time, these adhesions usually stretch sufficiently to restore function.

NODULAR FASCIITIS

This is an uncommon but very distinctive tumorous nodule that occurs in any part of the body, principally in the subcutaneous fat and fascia, but may also arise in the deep fascia and contiguous muscle. The major importance of this lesion can be deduced from another of its designations, *"subcutaneous pseudosarcomatous fasciitis."* This lesion is actually a curious, localized overgrowth of fibroblasts that appear to infiltrate. It is therefore apt to be mistaken for a sarcoma. In the words of Price et al. (1961), "the unwary, however, seeing a moderately or highly cellular nodule composed of plump or spindle-shaped connective tissue cells, with nuclei that are often hyperchromatic or in mitosis, lacking a capsule, and sometimes seem-