8. Wound Healing and Wound Care

Erle E Peacock

Introduction

During the course of human evolution a valuable defense mechanism - the ability to regenerate compound tissues - was replaced by a much less complicated and far less valuable process - the phenomenon of healing. Although ability to heal has been of enormous importance in natural selection, restoration of physical integrity by synthesis of scar tissue can be regarded, at best, as only a method of preserving homeostasis and cannot be compared to the more pristine formation of multi-germ-layer regeneration. Moreover, the fibrous tissue synthesis stage of healing can be detrimental even to the extent of destroying the organism which it sought to preserve. Examples are the potentially fatal deformity of valve leaflets incurred during healing of rheumatic fever valvulitis, development of posthepatic cirrhosis, and development of esophageal stenosis after swallowing a corrosive agent. The patient may survive the initial disease or injury only to succumb months or years later from complications of fibrous tissue synthesis during healing.

Posthepatitic cirrhosis is of special interest to students of biology of wound healing, because the liver is probably the only example of a compound organ in human beings in which almost embryonic propensity for secondary regeneration appears to be retained. Under most circumstances, the liver can be counted upon to regenerate about four-fifths of its preinjury mass; in fact, the failure of regeneration to occur with normal rapidity in severe nodular cirrhosis gives the distinct impression that only overgrowth of fibrous tissue may have prevented hepatic regeneration. The significance of this hypothesis is based upon the possibility that fibrous protein synthesis anywhere in the body chokes or overpowers cellular regeneration; from an evolutionary standpoint, such a hypothesis has some factual basis. The hydrozoan *Tubularia* will sometimes regenerate an amputated hydranth without forming a connective tissue scar; at other times the organism will merely heal the wound by formation of scar tissue. When scar tissue is found, only an abortive attempt at regeneration can be identified. There is a very critical time in the development of newts when the ability to regenerate is disappearing. If during this time connective tissue synthesis is blocked by pharmacologic agents the power to regenerate a new limb will be prolonged.

With the exception of the liver, regeneration in human beings is essentially limited to simple tissue such as epithelium; compound structures such as skin, deep organs, and nervous system can heal only by sealing the wound in a manner to be described. The sealing process varies, depending upon whether structural integrity is interrupted or tissue substance is removed. In both types of wounds, epithelization is the fundamental process which seals the wound, and fibrous tissue synthesis is the process which provides structural strength. When tissue is missing, an additional process - contraction - moves tissue edges into closer approximation so that epithelization and fibrous protein synthesis can accomplish their objectives. Simple as this description may sound, most of the mistakes made by physicians in treating wounds are attributable to failure to realize and understand the limitations and end results of each of these fundamental processes and how they differ from pristine regeneration. Thus optimal wound management requires detailed knowledge of epithelization, fibrous

protein synthesis, and the biology of wound contraction. Study of these processes requires, in addition, some knowledge of the milieu in which they occur - the ground substance.

Wound Contraction

In 1973 John Hunter wrote, "In the amputation of the thick thigh (which is naturally 7, 8, or more inches in diameter) ... the cicatrix shall be no broader than a crown piece." The essence of this quotation is that full-thickness wounds of organs (including skin) do not heal by synthesis of fibrous scar with the exact dimensions of the original defect. A crown piece in Hunter's time was 1.5 in in diameter, thus over 90 percent of the amputation wound was closed by centripetal movement of skin edges. This process is called *contraction* - a dynamic term denoting action, which should not be used interchangeably with "contracture", the term for the end result. Just as loss of brain or stomach produces a permanent defect in human beings, loss of skin also is permanent, and when a defect in the integument occurs, restoration of integrity is dependent largely upon stretching surrounding skin to cover exposed subcutaneous tissue. Obviously, stretching skin will distort movable features such as lips, eyelids, breasts, or digits. The fundamental process in contraction can be illustrated perfectly and the end result predicted positively by simply grasping the edges of a gaping wound and manually coapting them. Such replication of the contraction process produces the exact deformity that will result from natural wound contraction over a longer period of time. If it is not physically possible to coapt the edges of a wound by reasonable external force, one can be certain that natural processes also will not be effective, as the amount of skin present is all that will be available to be stretched over the wound. The area which remains uncovered will either remain as an open granulating wound or, if it is small, be covered by epithelium, which is a poor substitute for normal skin and establishes a potentially dangerous area for the development of epidermoid carcinoma.

Thus the effectiveness of the contraction process in producing complete wound closure and the cosmetic and functional deformity which closure by contraction produces are related to the amount of skin available in a given area of the body. Because the hands and face of a young person do not contain excess skin, closure of a defect by contraction causes distortion of facial features or restriction of joint motion. In areas where there is redundancy of skin, such as the cervical region or face of old people, wound contraction can be extremely effective in closing defects without producing cosmetic or functional abnormalities. Where an excess of skin is not present but flexion or extension of a joint will move wound edges together, wound contraction inexorably results in movement of the joint into an extreme position. After healing has occurred, the joint will be fixed because of a lack of a satisfactory envelope. When loss of skin occurs over an area such as the malleolar surface of the lower leg and angle, wound contraction simply cannot occur because there is not enough skin to stretch over the defect. In this instance the wound either becomes covered by a thin, almost gelatinous film of epithelium or remains open for an indefinite length of time.

Three questions immediately arise about the contraction process: What starts it? What stops it? What is the mechanism by which it occurs? On first consideration, the answer to the first question appears obvious, in that interruption of the integrity of skin always seems to be the initiating stimulus. Close examination of the series of events which occur following removal of a piece of full-thickness skin, however, reveals that wound contraction does not begin immediately and that about 4 days elapse before movement of the edges is measurable.

This so-called lag phase of healing seems to include the contraction phenomenon, and it can only be surmised that a set of conditions must be established or an assembly of cells or energy source completed before the actual work of mobilizing skin edges begins. One might surmise also that reestablishment of physical integrity is the stimulus which stops contraction; but again, measurement of the timing of other events reveals that contraction of a wound does not stop immediately with closure; indeed, wounds which were not caused by a loss of tissue and which have their edges approximated immediately will sometimes undergo considerable contraction. Even closure of a wound by the application of a free split-thickness skin graft or pedicle graft does not stop the contracting process once movement of wound edges has begun. An interesting observation is that the rate of wound contraction is not the same for all points on the circumference of a wound unless the wound is a perfect circle. The ultimate configuration of the scar produced by a contracting wound is the result of variations in the rate of movement of different segments as well as the firmness of attachment of different areas of the skin to both movable and immovable structures. From a practical standpoint, the surgeon may use such information to reduce the final extent of wound contraction. For example, a wound created by bringing ileum through the abdominal wall to form a permanent ileostomy can produce ileal obstruction of the skin opening undergoes contraction. One way to minimize skin wound contraction is to make the skin incision a perfect circle.

The first step in studying the mechanism of wound contraction is to try to define precisely where the fundamental process is located. In the crudest analysis it must be determined whether centripetal movement occurs because an energy or power source located outside the defect is pushing the skin edges in or whether a centrally located power source is pulling the skin edges to the center of the defect. Curiously, even after 25 years of intensive study, the answer is not entirely clear. There is good evidence that energy is being expended in both areas, and the question becomes whether both processes are effective or whether only one is effective and the other either is reacting to wound contraction or is insufficient to produce effective tissue movement.

Over the years most investigators have assumed either that central granulation tissue in a contracting wound was retracting and pulling the normal skin over the granulating base or that contents of the wound were being absorbed as the skin edges move toward the center. In 1958, Grillo et al awakened interest in this question by reporting some experiments designed to determine whether changes in the central mass of wound tissue were pulling the skin edges together or whether central wound tissue was merely adjusting the movement of wound edges propelled by peripheral force. The commonly held opinion that dehydration of wound tissue was responsible for contraction was destroyed by their measurements, which showed that water content of central wound tissue at the beginning of wound contraction had not changed significantly at the end of contraction. The assumption that collagen synthesis and contraction might be responsible for drawing wound edges together also was disproved by direct measurements of the collagen content of wound tissue during the process of contraction. Although collagen content increases markedly between the fifth and eighth day of healing, total collagen in the wound falls significantly after this period and cannot be correlated with rate of wound contraction. Moreover, the rate of wound contraction is not affected by suppressing collagen synthesis or interfering with cross linking.

The result of such studies was that attention was focused upon living cells as the motor units in the contraction process. Wound contraction occurs only in living organisms,

and the force producing migration of wound edges is generated by living cells. As might be expected, cytochrome poisons, such as potassium cyanide, can be shown to impair wound contraction although they do not abolish it completely. Migration of mesodermal cells in tissue culture also has been shown to be restricted by cytochrome poisons. These observations are readily reversible, which suggests an inverse relationship between inhibition of aerobic respiration and cell migration.

In an attempt to see if cells responsible for wound contraction were located in granulation tissue, Grillo excised all central wound tissue from wounds in guinea pigs every day during the contracting process. Curiously, excision of central tissue did not affect rate of wound contraction. Such data are not conclusive in localizing the mechanism of wound contracture, however, because they cannot be correlated with results produced by other manipulations of the central mass of wound tissue. For instance, if a square of granulation tissue in the center of a healing wound is outlined by tattoo marks and then separated from the rest of the wound tissue by circumferential incision during wound contraction, two interesting observations can be made: The centrally migrating wound edge will retract peripherally, and the centrally circumcised area of granulation tissue will contract centrally. This finding leads one to the inescapable conclusion that granulation tissue between two wound edges was not being compressed by peripheral skin moving inward but was under considerable tension produced by the advancing wound edges. Moreover, in other experiments, wounds which were splinted for several days and then released did not show marked acceleration of wound contraction following removal of the splint if central granulation tissue was incised. Additional evidence that tension in granulation tissue is causally related to wound contraction is found in the ingenious experiments of James and Newcombe, who measured the contraction force of granulation tissue and plotted it against the length of tissue elements and the cross-sectional area of granulation tissue. No significant correlation between wound tension and overall wound area could be shown, but a highly significant correlation was found between cross-sectional area of granulation tissue and the tension which was developed during wound contraction. Such studies suggest that granulation tissue under tension resembles stretched elastic tissue, in that the amount of tension produced is related to cross-sectional area and not to overall length or surface area. These data, plus the demonstration that granulation tissue contains cells of a type which can exert migratory force of a magnitude necessary to mobilize skin edges, strongly suggest that the machinery for wound contraction is located in the central granulating mass. A recent discovery by Majno et al of highly specialized cells (termed *myofibroblasts)* with smooth-muscle-like contracting powers lends additional support to this concept.

Grillo found that although wound contraction was not inhibited by excising the entire central mass of granulation tissue, it could be stopped decisively by excising a very limited zone of tissue just beneath the advancing dermal edge. The term "picture frame area" was developed to describe the strategic location of cells which appear to constitute the machinery for wound contraction. Histologic examination of the "picture frame area" reveals a collection of large, stellate, pale-staining cells which have been thought to be the cells responsible for moving the overlying dermis.

Presently it can be said that recent investigations have eliminated changes in nonliving materials as the cause of wound contraction and have established that the movement of wound edges requires a high order of energy transfer performed by living cells. No unifying

hypothesis exists by which all the available data can be explained or the exact site or mechanism of action of wound contracture identified. The apparently incompatible findings of Grillo and Abercrombie and James concerning the importance of the central granulation tissue can probably best be resolved by hypothesizing that the wound margin makes its way over the surface of movable granulation tissue, and as it does so, it forces it by counteraction in a centrifugal direction, thus putting central granulation tissue under enough tension to cause retraction when it is excised or divided. Regardless of the exact location, however, the phenomenon of wound contraction is one of the most predictable and powerful of all biologic reactions and must be positively reckoned with in the management of wounds where tissue has been lost. The process is carried out by myofibroblasts. Under the microscope, myofibroblasts show characteristics of fibroblasts and smooth muscle cells including a rough endoplasmatic reticulum, microfilament bundles similar to smooth muscle, and abundant microtubules that apparently perform a bracing function. In contrast to normal fibroblasts, myofibroblasts often are joined by hemidesmosomes, allowing the cells to "pull on each other". Histochemical studies indicate that the common contractile protein is actin. Wound contraction can be controlled by topical application of smooth muscle inhibitors such as Trocinate. Inhibitors of microtubule formation such as colchicine and vinblastine also inhibit wound contracture under experimental conditions. Colchicine presently is being utilized experimentally in the control of fibrous contractures in human beings.

Epithelization

An attempt to cover by regenerating epidermis any area of the body denuded of skin is the first irrefutable sign of wound repair and occurs long before any evidence of connective tissue synthesis. Factors which control movement of epidermal cells and the mechanism by which cells cover a denuded area are important to students of wound healing for two reasons. The first is that epithelization is necessary in the repair of all types of wounds if a water-tight seal is to occur. Protection from fluid and particulate-matter contamination and maintenance of an internal milieu are dependent upon the physical properties of keratin. It should be pointed out, however, that just as the plastic liner of a home swimming pool contributes only a watertight seal while structural stability is maintained by concrete blocks, the epidermis provides very little structural strength for the wound. It is the surrounding fibrous protein framework which gives strength to the scar. Actually, no cellular structure or globular protein can impart much strength in the repair of a wound. When structural strength is needed, fibrous protein must be synthesized. Thus highly cellular organs, such as liver, spleen, kidney, or brain, have almost no structural strength and cannot be sutured as effectively as fibrous tissue organs, such as dura, dermis, fascia, or peritoneum. A wound healed only by epithelium will stop "weeping" and be safe from bacterial invasion as long as the epithelium is intact, but the slightest trauma will literally wipe off what is hardly more than a gelatinous film; thus no degree of permanent protection has been achieved.

Second, epithelization is of great importance in the study of wound healing, because when certain variations in the control of cell division and cell movement occur, normal epithelization becomes uncontrolled growth, with awesome invasive potential. The recognized propensity to development of cancer in certain types of wound scars (radiant-energy-induced wounds particularly) and in all wounds which are prevented from healing emphasized the close similarity between cancer and the healing process. Actually, a histologic section from a 5-day-old healing wound can be interpreted easily as fibrosarcoma if none of the historical

details are available. Healing is dependent upon what may be though of as a return to embryonic status; at certain times in the healing process the overall picture - characterized by mitosis, pleomorphism, disorganization, and loss of polarity - resembles uncontrolled growth of a malignant neoplasm. A major difference exists, however: the factor of control. In a healing wound, the embryonic state is temporary and some controlling influence brings order out of disorder, a resting state to rapidly multiplying cells, and a remodeling of recently synthesized fibrous tissue to produce purposeful structural patterns. In a neoplasm, however, the situation is similar to a healing wound in which the factor of control never reappears, so that healing continues without purpose or control until the entire organism is consumed by direct extension or metastasis of the products of regeneration. Considered in this way, there may be only a fine distinction between healing and malignant growth; it may be that when we understand all the factors which influence cells to return to embryonic activity during healing, and even more important, the factors which control their growth and movement after healing has been accomplished, an important step will have been taken in solving the riddle of cancer. For now, however, it is important to remember that the stimulus following injury to overcome entropy and develop embryonic kinetics is one of the most powerful and predictable phenomena in biology.

Apparently cell division and ameboid movement cease only when cells are surrounded by other cells of their own type, and this characteristic of individual cells has something to do with determining the direction in which a mass of cells will move. Weiss observed that when epithelial and mesenchymal cells are mixed and suspended in a proper medium, random movement of cells will occur, causing numerous collisions. Collisions of dissimilar cells (ie, epidermal and mesenchymal) result in repulsion, whereas collision of similar cells results in two cells sticking together and later developing protoplasmic bridges and protofibrils. Thus random movements and collisions over a sufficient period of time invariably result in cells of similar type becoming agglutinated on one side of the medium and the remainder becoming agglutinated on the other side. As increasing portions of the circumference of a cell membrane become satisfied by attaching to cells of similar lineage, the remaining unsatisfied sides become the exploring or searching surface; thus some degree of polarity for the whole mass is established. Failure to achieve complete surface contact with other cells results in a continued state of embryonic activity. One does not have to use much imagination to predict that as the cells continue to be driven by an insatiable desire to contact cells of their own types, the risk of loss of control over replication and locomotion increases with time. Until more is known about the factors involved in the control of cell growth and movement, however, one can only take cognizance of the fact that any wound which is prevent from healing is potentially a malignant neoplasm.

Wounds caused by certain agents such as radiant energy or specific chemicals have unusual propensity for developing cancer in scars or unhealed wounds. In wounds induced by radiant energy, the length of time before cancer develops appears to be directly proportional to the wavelength of the damaging ray. Thus thermal burn wounds and scars may require 20 years for invasive cancer to develop, while in gamma- or x-ray wounds cancer may develop in a matter of months. Solar and cosmic radiation, a causative agent in most human skin cancer, is short-wavelength radiation, but because it is filtered by atmosphere and melanin, human development of epidermoid cancer from this source usually does not occur until late in life.

The development of cancer is more rare in surgical or traumatic wounds than in radiant-energy or chemical-induced wounds. No type of wound is exempt, however, when healing has been prevented by constant reinjury or inadequate skin replacement. Even in postphlebitic leg ulcer (a common chronic ulcer) cancer may develop over a long period of time.

The mechanism by which epithelium attempts to close a wound has caused considerable speculation. Previous descriptions of the process, based on the assumption that mitosis was not a prominent occurrence, are not correct. Although it is difficult to find mitotic figures in the advancing margin of epithelium, the works of Bullough and of Gillman and Penn have shown conclusively that mitosis does occur in several layers of epithelium and that it is a recognizable part of epithelization. Theoretically, it should be possible for a wound of any size to be epithelized, although there is a practical limit in clinical practice to the size of the area which will become epithelialized naturally.

Two important gross and histologic differences between normal epithelization in a healing wound and abnormal epithelial growth in epidermoid cancer are the size and the shape of the peripheral cell mass. A striking feature in a normally healing wound is diminishing thickness to monolayer proportions of the advancing cell front. In carcinoma, cells pile up and tumble over one another to produce a grossly umbilicated appearance. Recent investigations suggest that loss of surface protein may be a key factor in changes in cell adhesiveness. Thus in normal epithelial regeneration, even though mitosis does occur, the most fundamental process is dedifferentiation and cell movement by development of ruffled membranes and pseudopods. The process begins early (within hours) and results in flat, thin, resting cells at the margin of the wound. These cells develop ruffled membranes and move across the center of the wound. When this occurs, the cell seems to adopt the characteristics of a typical basal cell; if it comes to rest in a more superficial position, it becomes a typical prickle cell.

In incised and sutured wounds, epithelization produces a watertight seal in 24 hours even though there is a dip where the cells have migrated into the crevice. Although the area of regeneration thickens with addition of more cells, the center of the wound remains somewhat inverted until underlying connective tissue synthesis pushes the epithelium into an everted position. Gillman and Penn have pointed out that the cutaneous tract of a skin suture on either side of the scar is also a wound of the epithelium, and that the inverted contour of epithelium over the would also occurs along the path of a suture to the extent that a completely epithelized tract may be produced or a small cyst formed after a suture is removed.

Epithelization of a surface wound (whether partial thickness of skin such as an abrasion, or split-thickness skin-graft donor site, or full-thickness wound such as postphlebitic ulcer of the ankle) involves similar movement of epithelial cells but over a much more hazardous terrain and greater distance than incised and sutured wounds. The early escape of blood and serum in open wounds produces a scab, and the regenerating epithelium moves beneath the scab, literally detaching it from the underlying surface as it seals the wound. Actually, epithelium does not move along the interface between dermis or fat and the scab but seems to prefer to infiltrate or actually cut through the fibrous tissue substrate by elaborating an enzyme which renders collagen soluble. This mysterious behavior has been somewhat clarified recently by identification of tissue collagenase at the interface between

epithelium and mesenchymal tissue. Confirmation of the observation that epithelium literally cuts its own path through fibrous tissue may be extremely important in understanding the remodeling of deep fibrous tissue to produce a new dermal-epithelial interface.

The protective influence of a scab or other cover (eschar, surgical dressing, etc) to prevent physical trauma, drying, hemorrhage, contact with caustic materials, and the like is the basis for medical care of secondarily healing wounds. In the final analysis, successful epithelization occurs only if the cumulative effect of physical manipulation, drying, bacterial enzymes, wound area, etc, does not exceed the finite capacity of available cells to divide, dedifferentiate, and move across the surface. Considered in the simplest analysis, it may be that interruption of epidermis merely allows the epidermis to do what it normally would do if it had room, since cell movement and cell division are to a large extent prevented in the intact epidermis by the compression effect of surrounding cells.

Ground Substance

Even as late as 1952, some treatises on wound healing made no mention of the role of ground substance. The mystery surrounding ground substance is nowhere better exemplified than in the name itself, a mistranslation of the German *grundsubstance*, which referred to a mysterious matrix from which all the formed elements of connective tissue were believed to originate. A similar connotation was expressed by the French *substance fondamentale.* Modern definitions have done little to clarify the true nature of this amorphous material, and the best that can be said, even now, is that the term "ground substance" usually refers to a continuous nonfibrillar matrix including water and electrolytes through which metabolites diffuse between blood vessels and cells. Histologically, ground substance is identified by a remarkable propensity to absorb certain dyes such as toluidine blue and to undergo characteristic reactions with periodic acid. By such staining reactions it can be seen that ground substance is relatively organized in some areas, such as basement membrane, and undergoes, during inflammation and healing, characteristic changes in staining reaction called *metachromasia.* Such histochemical reactions seem to be due to reactions with mucopolysaccharides, many of which contain hexosamine. Because of characteristic staining reactions, attention has been focused on the acid mucopolysaccharides, even though it must be remembered that they account for only a small portion of ground substance. As a result, errors have been made by measuring hexosamine in connective tissues and drawing conclusions about the relative amount and importance of ground substance.

Meyer's division of the acid mucopolysaccharides into two major groups has been useful in the study of wound healing. These groups are nonsulfated mucopolysaccharides, of which hyaluronic acid and chondroitin can be easily identified, and sulfated mucopolysaccharides, of which chondroitin sulfate B, chondroitin sulfate B, chondroitin sulfate C, heparatin sulfate, and keratosulfate have been identified. Presently it seems that the nonsulfated group is the main component of the structureless gel fraction of ground substance and that the sulfated group is most closely associated with the fibrillar elements of connective tissue. Thus changes in sulfated acid mucopolysaccharides are most likely to be of significance during the healing process, and, indeed, such substances are found to be increased during early stages of wound healing. Determination of actual amounts of any of the components of ground substance may be misleading, however, as synthesis and deposition

involve polymerizing reactions and formation of giant molecules with molecular weight varying between 10.000 and 10.000.000.

Because the healing process is characterised by polymerizing aggregating reactions, it is interesting to speculate upon the role of mucopolysaccharides. Discovery that acid-sulfated mucopolysaccharides accumulate during healing raises the question of whether linkages between fibrillar proteins and ground substance occur. The same question has been raised about normal tissues such as tendons, where chondroitin C is a prominent portion of the ground substance; stabilization of tendon by cross linkages between collagen fibrils and chondroitic C has not been demonstrated conclusively. Chondroitin A protein complex seems important in stabilization of cartilage, and destruction of this complex by local injection of papain in a rabbit's ear will produce a lop-ear deformity which will return to normal as soon as the complex is reconstituted. It seems likely that ground substance is most important in the phenomenon of healing because of its relation to collagen synthesis and remodeling. Although chemical linkages between mucopolysaccharides and collagen have been extremely difficult to identify, chemical bonds are present which may be important in the development of strength or orientation of collagen fibers and fibrils. Certainly the assembly of collagen subunits into fibrils and fibers is dependent upon many environmental conditions, including a purely physical template or lattice. Variations in the relative amounts of sulfated fractions are believed by many to be instrumental in determining the configurations of collagen fibrils, but how much this complicated substance actually participates in other aspects of the healing process awaits further investigation.

Collagen

As far as the questions which patients ask their physicians following repair of wounds are concerned, fibrous protein synthesis is the essence of healing. Accurate answers to such questions as "When do the stitches come out?" "When can I go back to work?" "How bad will the scar be?" and others are dependent upon a thorough knowledge of collagen synthesis, collagen degradation, and the factors which influence the equilibrium between the two. Unfortunately, there are gaps in our knowledge about collagen metabolism; but enough is known so that the care of wounds does not have to be a mixture of craft and religion, as Paré expressed it, but can be, in most instances, a scientific exercise with a predictable outcome. Even such seeming trivia as the selection of a suture or dressing material can be the result of logical reasoning based upon factual knowledge.

Collagen is an extracellular secretion from specialized fibroblasts, and the monomeric particles or basic molecules which fibroblasts synthesize are frequently called *tropocollagen.* The tropocollagen molecule is one of the largest biologic macromolecules, with a molecular weight of about 300.000 and dimensions of 15 A in width and 2800 A in length. It is a stiff, elongated rod which can be visualized by an electron microscope and is soluble in cold salt solution. Thus tropocollagen is sometimes referred to as saline-extractable, or salt-soluble, collagen.

Recently it has become evident that genetic pleomorphism is expressed in subtypes of collagen molecules. Three types of collagens can be recognized by analyzing the composition of alpha1 and alpha2 chains. Type I collagen is the most prevalent type in the mature vertebrate organism. Type II collagen appears limited to cartilage and is found

primarily in human articular and costal cartilages and in chick embryo bones. Type III collagen is found in association with Type I collagen and is most prevalent in tissue undergoing remodelling or fetal organogenesis. Type III collagen also appears to be an important component of tissues with an unusual degree of elasticity, such as those of the aorta, esophagus, and uterus.

The amino acids found only in collagen, and used to identify it in analytical procedures, are hydroxyproline and hydroxylysine. The amount of collagen in a specimen of tissue is determined by measuring the amount of hydroxyproline and multiplying the result by a factor of 7.8. Other fibrous tissues such as elastin do not contain significant amounts of hydroxyproline. Formerly it was believed that hydroxyproline in collagen had much to do with the formation of various intra- and intermolecular cross links which give collagen molecules, fibers, and fibrils their characteristic rigidity. The three-plane fixation of the triple-helix structure results, teleologically speaking, in being able to rely on collagen to transmit energy accurately in tendons or to support nonfibrous structures such as muscle. The supporting nonelastic properties of collagen can be destroyed by rupturing cross links within and between molecules, but fortunately, the destruction of cross links to this extent requires rather harsh treatment for mature collagen, such as temperatures over 70 °C or exposure to strong acids or alkalies. Under these circumstances, what is produced is gelatin, which, of course, has no structural strength even though the essential amino acids are present. Hydroxylation of proline and lysine also are important in transport of collagen molecules across cell membranes.

Synthesis of collagen is an intracellular phenomenon which occurs on polysomes; a critical stage in construction of the molecule is the hydroxylation of proline to produce hydroxyproline. Externally administered hydroxyproline is rapidly excreted in the urine and apparently cannot be utilized by fibroblasts to synthesize collagen. Among other things, one of the metabolic defects which can be identified in collagen-deficiency diseases such as scurvy is accumulation of proline-rich precursors and deficiency of hydroxyproline-containing peptides. During active collagen synthesis, rough endoplasmic reticulum in fibroblasts forms characteristic parallel lines, or canaliculi, and it appears that monomeric molecules are excreted into the extracellular milieu through these canaliculi. In ascorbic acid deficiency, the microsomes do not form parallel lines of canaliculi but are arranged, instead, in large cystic spaces. It is from these areas that proline-rich and hydroxyproline-poor amorphous material is found.

Before aggregation and normal assembly can occur, a specific extracellular enzyme, procollagen peptidase, is needed to remove nonhelical terminal extensions from both the N-terminal and C-terminal ends of collagen molecules. Recent evidence suggests that the terminal peptide extensions of the collagen molecule are registration peptides facilitating triple-helix formation. They interfere with subsequent fibril aggregation, however, and failure to remove the registration peptides because of congenital absence of procollagen peptidase results in poorly assembled collagen with marked structural abnormalities. A type of Ehlers-Danlos syndrome has been found to be the result of persistent pro-alpha-chains. A similar condition appears to be responsible for the structural malformations in a disease of Belgian cattle called dermatosparaxis.

Monomeric collagen particles exposed to proper pH, temperature, osmotic conditions, etc, in the intercellular milieu aggregate or polymerize rapidly by the formation of cross links of various types. The most important such cross links are covalent ester bonds such as a Schiff's base between an amino group of one molecule and an aldehyde group of another. Oxidative deamination of lysine by an important enzyme, lysyl oxidase, is a necessary first step to formation of covalent ester cross links. In addition, other types of cross links, such as oppositely charged electrostatic groups and Van der Waals interactions, are involved in assembling monomeric particles into polymerized aggregates.

The rodlike collagen molecules appear to lie in staggered, overlapping, parallel formation, with one-quarter-length overlap. It is this staggered one-quarter-overlap arrangement of tightly packed units which gives collagen its typical repeating axial periodicity of 640 A. Whenever collagen molecules are assembled under physiologic conditions such as those provided by the extracellular ground substance, typical fibrils with 640 A repeating periods are produced. In certain laboratory preparations, however, it is possible to alter the characteristic 640 A periodicity by forcing the monomeric particles to line up exactly parallel or end-on. This can be accomplished by adding glycoprotein to the milieu or by charging the preparation with a high-energy system such as adenosine triphosphate. Under these conditions, fibrils with band widths of 2000 A can be produced; such atypical fibers are called *segment long-spacing fibers,* or *fibrous long-spacing fibrils.* These preparations have been extremely valuable in the laboratory, as they have revealed much about the size and method of polymerization of collagen molecules; they are not of any physiologic importance, however, as far as is known.

Although the collagen molecule is basically a triple helix with a spiral configuration, heat-sensitive intramolecular cross links prevent it from having elastic or recoil properties. However, if a collagen fiber or fibril is placed in a water bath with a small weight suspended from one end and the temperature of the bath is elevated, a point will be reached when the heat-sensitive intramolecular cross links will be destroyed and recoil of the spiral polypeptide chain will occur. The temperature at which this phenomenon occurs is called the *thermal shrinkage temperature,* and the magnitude of this reaction is such that a fiber or fibrils will shrink to one-third physiologic length. The thermal shrinkage temperature of collagen, therefore, is an excellent indicator of the strength and degree of inter- and intramolecular bonding. By measuring the thermal shrinkage temperature of various types of collagen, it has been possible to learn something about variations in bonding under physiologic conditions and, in some instances, to correlate the development of physical properties of collagen with the extent of cross linking. From such studies it has become clear that cross linking, among other factors, is a function of aging; the older a specimen of collagen becomes, the firmer and more numerous the cross links are. Thus, collagen gel which is only a few minutes old has relatively few cross links and a low thermal shrinkage temperature and is so flimsy that cold salt solution solubilizes it. If the gel is allowed to mature for 24 hours, the number and strength of the cross links increase to the extent that a weak acid may be needed to depolymerize even a portion of it and a higher temperature will be required to cause it to undergo thermal shrinkage. If the aggregate is allowed to polymerize for several weeks, the maximum number and firmness of cross links will be realized, with the result that a strong acid may be needed to get even a portion of the collagen into monomeric units and the thermal shrinkage temperature will be the highest yet. In summary, therefore, both solubility

and thermal shrinkage temperatures can be used to measure the age of collagen as represented by the effectiveness of the cross-linking process.

In addition to naturally occurring cross links such as ester bonds, artificial cross links can be added to change the physical properties of collagen. Just as adding an agent which shares electrons easily, such as a sulfur molecule, will increase the strength of rubber (vulcanization) sevenfold, addition of a similar agent such as the methyl group in formaldehyde will increase the number and kinds of cross links in collagen. Just how much the addition and destruction of cross links has to do with the physical properties of wound-repair collagen in scar tissue is not known. It has been shown, however, that addition of methyl or amide cross links will increase the tensile strength of scar tissue in incised and sutured wounds in rats as much as threefold on the eighth postwound day. That variations in cross linking are partially responsible, however, for the final appearance, texture, or elasticity of human scars is becoming more certain.

At this point, other factors involved in tensile strength must be considered, for cross linking may have very little to do with tensile strength after fibrils and fibers have been formed. It is highly unlikely, in the opinion of the author, that fibrils and fibers are cross-linked very efficiently, because the average distance between fibrils is of the order of 1 microm. Chemical cross links are approximately 2.8 A, which means that the distance is roughly 500 times too great for the usual types of cross links to span the distance between fibrils. However, because addition of cross links such as methyl or amide bonds definitely increases tensile strength in wet scar tissue, the inescapable conclusion seems to be that rupture of scar tissue must occur, to some extent, along inter- and intra-molecular planes. There is no uniform agreement on this point, and the question of the importance of cross linking in the development of strength in scar tissue must be investigated further.

After a certain amount of collagen has been synthesized, the most important factor in gain of strength may be the physical weave of fibrils and fibers. Certainly it is possible to vary the physical properties of other fibrous materials by varying the weave of the small components exclusive of any chemical bonds. A good example of this principle is to be found in the physical weave of a nylon stocking. Nylon thread is nonelastic, yet a nylon stocking can be made elastic by properly weaving the fibers. Transposed to a biologic system, nonelastic tendon or fascia shows physical characteristics similar to nylon thread, while elasticity of the wall of the aorta is similar to that of a nylon stocking.

The old concept of collagen as a static, adynamic substance - the excelsior of the body - is erroneous. Actually, as will be shown later, collagen in wound scar is a relatively dynamic structure which, like other tissues, is undergoing constant remodelling and replacement. After the forty-second day of wound healing there is no measurable increase in the amount of collagen in a healing wound, and yet the scar continues to gain strength for at least 2 years. Thus changes in collagen, such as increased cross linking and rearrangement of fibers and fibrils, must be occurring.

Before leaving the subject of remodeling, it is important to mention a disease, lathyrism, which has been useful in study of collagen metabolism and which is beginning to have far-fetched implications for control of human scar tissue. The disease, recognized by Hippocrates, is caused by excessive ingestion of certain peas of the genus *Lathyrus.*

Considerable differences exist between the human form of the disease, which is manifested by spastic paralysis, and the disease in laboratory animals, which is characterized by skeletal and cardiovascular abnormalities secondary to altered collagen metabolism. The active and highly potent fraction which produces altered collagen metabolism is beta-aminopropionitrile. Considerable data are available on the effect of this substance on both developing and mature tissues. Most such data support the hypothesis that the primary effect of beta-aminopropionitrile is to block the formation of inter- and intra-molecular cross links during all stages of collagen aggregation. Thus beta-aminopropionitrile affects growing tissue more than adult tissue. Characteristically, beta-aminopropionitrile produces an enormous increase in saline-extractable collagen, as it seems to block the assembly of monomeric collagen units into stable fibrils and fibers. There is some evidence to indicate that fibril formation is not stopped during lathyrism but that cross linking in fibrils is so unstable that cold saline will solubilize most of the collagen which was assembled during beta-aminopropionitrile poisoning. Growing embryos literally become saline-soluble under the effect of beta-aminopropionitrile, and mature animals will develop hernias or die suddenly of dissecting aneurysms. Wound healing, as might be predicted, is affected by beta-aminopropionitrile; there is a cessation of gain in tensile strength within hours after the agent is administered, while saline-extractable collagen increases approximately ten times. Clinical implications of the beta-aminopropionitrile effect are exciting, for it is a clear-cut demonstration that it is possible to alter the physical properties of collagen in dramatic fashion. Because some of the effects of fibrous tissue healing in specialized organs, such as the liver or heart, can be more ruinous to the health of the individual than the disease or injury which preceded healing, the demonstration that some control over deep scar formation is possible is an exciting one. If, in addition, mature recently synthesized collagen also could be solubilized selectively, a major breakthrough in many diseases processes could evolve. Highly purified beta-aminopropionitrile has been administered to human beings with scleroderma, urethral stricture, and keloid. It can be given safely to human beings, and it is anticipated that clinical trials presently being performed will establish the effectiveness of induced controlled lathyrism as a therapeutic modality. In the meantime, penicillamine, a lathyrogenic agent as well as a copper chelater previously utilized to treat Wilson's disease, is being used to control collagen synthesis and deposition in human beings.

Several times in this chapter the term "remodeling" of scar tissue has been used. The thoughtful student is likely to be concerned over such a term, as it connotes not just synthesis of collagen but collagen breakdown as well. Because no enzyme able to lyse collagen had been identified in human beings until approximately 20 years ago, collagen turnover in either normal tissue or wound scar was suspect. Even though no such mechanism could be demonstrated, however, indirect evidence has been abundant that some enzyme or mechanism for solubilizing collagen must exist. There is always some extractable collagen in the skin of even the oldest and most depleted individuals. Obviously, if all tropocollagen were going into the skin, the dermis would soon be as thick as elephant hide. Some collagen must be coming out of the dermis, and the relatively constant thickness of skin only attests to an equilibrium which exists between collagen synthesis and degradation. Surface scars are raised above the surface 2 to 4 weeks after injury; yet they usually soften, become pliable, and decrease considerably in size with the passage of time. The loss of 50 percent of collagen from the gravid uterus 36 hours after parturition and the rapid disappearance of dermis when tetraplegic patients are allowed to lie unattended attest that human beings possess an effective enzyme capable of degrading mature collagen. In 1963, Gross, Lapiere, and Tanzer in 1963

hypothesized that collagenolytic enzyme was the product of living cells and that contact with a living cell was necessary in order for collagenolysis to occur. In one of the most important experiments performed in the wound-healing field during the last decade, the hypothesis was tested by preparing culture plates of reconstituted collagen and amphibian Tyrode culture medium. Specimens of tissue from the rapidly absorbing tail of a metamorphosing tadpole (a structure containing mostly collagen which is absorbed and broken off during metamorphosis) were placed on the collagen-Tyrode substrate, and the culture plates were incubated under tissue culture conditions. After several days a clear zone appeared around each implant, and if the tissues were kept alive long enough, the entire substrate became lysed by collagenolytic activity. Failure of the cells to survive stops collagenolytic activity immediately; even after lysis has begun, it can be stopped by killing the cells. Thus Gross and Paliere demonstrated that collagenolytic enzyme is a product of living cells and that cells which produce enzyme need to be in close contact with collagen fibers for lysis to occur. Riley and Peacock cultured a variety of normal and pathologic human tissues and found collagenolytic enzyme to be widely distributed, particularly in epithelium-containing structures.

The most uniformly positive tissue for collagenolytic enzyme in human beings is cutaneous scar. Scar tissue reveals positive lytic activity approximately 10 days after closure of a cutaneous laceration, and a high level of activity has been found in dermal scars as long as 30 years after injury. Granulation tissue is only slightly active; burn eschar does not show any activity for about 2 weeks. Between 2 and 3 weeks after a third-degree burn, however, cultures of separating dermal eschar are strongly positive for collagenolytic activity. These findings suggest that invasion of dead eschar by underlying connective tissue cells or undermining epidermal cells is necessary for contact between cells and heat-tanned collagen. Retarded wound healing may be the result of excessive collagenolysis. Serum, cysteine, and progesterone have been shown to inhibit tissue collagenase acting at neutral pH. Progesterone in ophthalmic concentrations may be the agent of choice in treating corneal injury, particularly alkali burns in which delayed tissue collagenase activity is the cause of rupture of the globe.

By measuring collagen synthesis and collagen breakdown, it is now possible to study healing from the standpoint of variations in metabolic equilibrium. Considered as such, scar tissue becomes a product of opposing forces of collagen synthesis and collagen destruction, and the result of such forces will vary according to the relative rate and effectiveness of each. The maximum amount of total collagen in a healing wound is found by the forty-second day. Although increased amounts of saline-extractable collagen (compared with nonwounded resting dermis) can be extracted from scar tissue for as long as 18 months, there is no further gain in insoluble (or mature) collagen. The conclusion would seem to be that, even though remodeling of the collagen continues, equilibrium has been established between collagen synthesis and collagen destruction. Recent demonstration by Cohen of accelerated collagen synthesis and deposition and collagenolytic activity in human keloids probably represents an abnormality of such an equilibrium.

The concept that all collagen to some extent, and healing wound collagen particularly, is undergoing simultaneous construction and destruction can serve as a basis for speculation concerning some of the previously unexplained findings in the healing process. One such enigma is the behavior of wounds during ascorbic acid depletion. In the classic descriptions of scurvy it is important to remember that sailors' wounds did not just fail to heal; they actually disrupted months after they had healed perfectly. This observation has been verified

in animals and raises the question of whether collagen is dependent upon ascorbic acid for structural integrity. It is known that collagen can be repeatedly depolymerized and reconstituted in the laboratory without contact with ascorbic acid, and artificially reconstituted collagen does not lose tensile strength. Therefore, the notion that vitamin C has anything to do with strength of mature scar tissue is untenable. Because synthesis of new collagen is blocked during ascorbic acid deficiency, and because collagenolytic activity probably proceeds normally, a possible explanation for old scar dehiscence would seem to be that tissue previously in equilibrium becomes unbalanced by having synthesis knocked out and lysis continue. Inexorably, the scar will become weaker until a point is reached where normal tissue tension produces complete disruption.

Although to some extent hypothetical (actual quantitative measurements of lysis and synthesis are not sensitive enough now to prove or disprove the equilibrium hypothesis), the theory is important as it relates to the whole field of conditions erroneously referred to in the past as "collagen diseases". The collagen in these diseases is precipitated under physiologic conditions and, as might be predicted, is normal as far as can be determined by electron or light microscopy, x-ray difraction, or amino acid analysis. Thus all the evidence supports the idea that so-called collagen diseases represent abnormal amounts of collagen in abnormal places but are not specific diseases of the collagen molecule or fibril. Such an explanation is entirely logical, as one cannot have a disease of a nonliving structure. Collagen is a crystalline protein in which the nearest thing that could be classified as a disease process is the abnormal construction of collagen during lathyrism. The collagen in such diseases as rheumatic fever, dermatomyositis, and scleroderma is probably much more accurately considered as the ash or scar from a burnt-out primary wound or inflammatory process. In the other direction, destruction of collagen in diseases such as rheumatoid arthritis is, at least partially, the result of excessive tissue collagenase activity. The concept of the collagen system as a dynamic, constantly remodeling one opens the door for investigation of a large number of diseases of unknown cause which are characterized by deficient or excessive collagen formation.

Sequence of Events: Summary

Once the basic processes in the healing phenomenon have been mastered, the student has only to relate them to one another in proper sequence to be ready to start the study of what physicians can do to aid healing. The most important concept in this regard is the understanding that healing is not a series of events but is a concert of simultaneously occurring processes, some of which continue for many years after physical integrity of wounded tissue has been reestablished. The most dramatic events, such as sealing the wound, regaining tensile strength sufficient to permit normal stress, and acquiring a scar which is cosmetically and functionally acceptable, occur in a relatively short period of time. Long-term processes, such as remodelling of collagen and development of cancer in scar tissue, fortunately are not processes which cause patients much concern. Although the basic processes are much the same in an incised and sutured wound properly coapted (healing by primary intention) and a wound in which tissue has been lost so that healing must occur by contraction and epithelization (secondary healing, or healing by secondary intention), the time required for secondary healing is so much longer and the area involved usually so much greater that it is convenient to study the secondary healing process to see how the basic steps in wound healing relate to one another.

The first thing which happens after full-thickness skin loss is that normal elasticity of the skin and external tension produced in some areas by muscle pull enlarge the defect according to the amount of force exerted and the direction over which it acts. Thus the shape of a skin defect may have little relation to the size or shape of the fragment of tissue which was removed. If hemorrhage is not too severe, a clot forms quickly, then contracts and dehydrates to form a scab. Because a scab is essentially a dehydrated, fully contracted blood clot, it is less durable and effective in closing the wound than collagenous eschar. Nevertheless, a scab serves a useful purpose in providing limited protection from external contamination, satisfactory maintenance of internal hemostasis, and a surface beneath which cell migration and movement of the wound edges can occur. Classically, the beginning of wound healing is described as the "lag" phase - an inaccurate term which carries the connotation that there is a period when nothing of importance is happening. Actually, a great number of important things are happening even though they usually are not considered part of the healing process. One soon recognizes, however, that almost instantly following infliction of an injury the stage for healing is set, and the props and background for the events which are to follow are essentially those of controlled inflammation. Study of the biology of repair has emphasized that the most successful reparative processes occur against a background of inflammation and that, up to the point of necrosis, how well the wound heals is directly related to the amount of inflammation present. Specifically, the release of various amines from connective tissue mast cells, perfusion of capillaries surrounding the defect, change in permeability of capillary wall, release of enzymes, fluid, and protein into extracellular spaces, accumulation of white blood cells and connective tissue cells, and formation of thrombi in peripheral lymphatic channels are all well-known changes in general inflammation which are important in providing the best milieu for repair to proceed. It is only when bacteria, foreign bodies, medications, or accumulation of destructive enzymes cause necrosis of tissue that inflammation becomes a deterrent to healing. Therefore the author prefers to see the term "lag" phase replaced by strong emphasis on inflammation as an active part of the reparative process.

Approximately 12 hours after injury has occurred, and at a time when inflammation has been established, epithelial migration - the first clear-cut sign of rebuilding - occurs. In a primary wound, epithelization is complete in a few hours; in a secondary healing wound, migration of cells is rapid at first, but as the line of cells from the wound margins becomes extended and the epithelial probe dwindles to a monolayer, progress becomes slower, so that days or even weeks elapse before epithelization is complete. After 4 or 5 days, however, epithelization is assisted as the machinery of wound contraction begins, and the wound margins begin central movement.

A great amount of activity takes place in the center of the wound after a scar or eschar has been removed and before epithelium has covered the surface. Grossly, the surface which was once gray or yellow-brown and smooth becomes bright red and granular. The reason for this is an extravagant proliferation of richly perfused capillary loops. The knuckles or loops of blood vessels impart a granular appearance to the surface, and it is because of them that the wound is often described as granulating or showing granulation tissue. Granulation tissue provides a good defense against invasion by surface contaminants, but it is fragile and produces a difficult terrain for advancing epithelial cells. This is particularly true if surface infection, edema, or deep fibrous tissue interferes with return circulation. When this happens, the fiery red granular dots will change to a purple, soggy, gray-black cluster which may fill

the entire wound cavity and spill over the wound edge, thus eliminating the possibility of epithelization.

Although no visible signs of collagen synthesis can be found until the fourth to sixth day, biochemical evidence of collagen synthesis can be found between the second and fourth days. The level of hydroxyproline in wound tissues rises rapidly, and the saline-extractable-collagen level becomes elevated shortly thereafter. Before signs of collagen synthesis occur, the ground substance changes, as evidenced by accumulation of sulfated mucopolysaccharides and development of metachromasia. On or about the seventh day wounds will show a delicate fine reticulum of young collagen fibrils. Actually, the gelation which is occurring at this time is so random that polymerization of new collagen fibrils is much like that of a new gel in a laboratory beaker - without purposeful orientation or polarity. There is a short period when young fibrils and fibers take silver stains selectively, and it is thought that this property reflects the presence of large numbers of unsatisfied bonding sites; mature collagen fibers do not stain selectively with silver. As fibrogenesis proceeds, purposefully oriented fibers seem to become thicker, presumably because they are accruing more collagen particles; nonpurposefully oriented fibers seem to disappear. The overall effect appears to be one of lacing the wound edges together by a three-dimensional weave. In secondary wounds the mass of scar tissue becomes dense, compact, and smaller in circumference but shows little in the way of purposeful organization. The overall direction is one of replacing granulation tissue, allowing the surface to become covered with epithelium, and filling in the remaining skin defect with scar tissue after contraction is complete. As far as filling the defect is concerned, contraction is the major influence; it exerts full potential before scar-tissue synthesis is complete. The central scar seems to remodel itself to fill the defect after contraction is over. Thus wounds surrounded by mobile and redundant skin will have a small central scar, while wounds surrounded with tight nonmovable skin will have relatively large central scars regardless of the size of the defect.

Development of tensile strength (strength per unit of scar tissue) and burst strength (strength of the entire wound) is the result initially of blood vessels growing across the wound, epithelization, and aggregation of globular protein. Later, collagen synthesis is important. The effect of vascularization and epithelization, although relatively small, is adequate on the fifth day to hold wound edges, if not under excessive tension, coapted without sutures. The really significant gain in tensile strength begins about the fifth day, however, when collagen synthesis becomes apparent; tensile strength measurements in laboratory animals usually are recorded from that day. Increase in strength is rapid for 17 days and slow for an additional 10 days; there is an almost imperceptible gain in tensile strength for at least 2 years. In spite of the measurable increase in tensile strength for such a long period, strength of scar in rat skin never quite reaches that of unwounded skin.

Collagen content of the wound tissue rises rapidly between the sixth and the seventeenth day and none at all after the forty-second day. Gain in strength after the seventeenth day, therefore, is due primarily to remodelling of collagen and, hence, is not correlated with total collagen content except for a very short portion of the healing curve.

When a normally healing wound is disrupted mechanically after the fifth day and immediately resutured, the return of tensile strength is so rapid that within 2 days the burst strength is nearly what it would have been had the secondary wound not occurred. This

phenomenon, commonly called the *secondary healing effect*, has been studied intensely to determine the exact mechanism of rapid gain of tensile strength following a secondary wound. Curiously, it is neither more rapid collagen synthesis nor more rapid assembly of collagen subunits; secondary wounds contain slightly less collagen than primary wounds of the same age. Because the thermal shrinkage temperature of secondary wound collagen is significantly higher than that of primary wounds of the same age, it has been suggested that more effective cross linking or better physical weave of collagen subunits is responsible for the rapid gain in strength of secondary wounds. The demonstration by Madden and Smith that secondary healing is really nothing more than continued primary healing (without a lag phase) invalidates previous cross-linking theories of secondary wound healing. Whatever the explanation, however, the machinery for producing rapid gain in tensile strength in secondary wounds is limited to an area of 7 mm around the first wound. Excision of skin edges more than 7 mm circumferential to the primary wound results in secondary wound healing at the same rate as in a primary wound.

Wound Care

From a treatment standpoint, there are essentially two types of wounds: those which are characterized by loss of tissue and those in which no tissue has been lost. Lacerations are an example of wounds without tissue loss, and avulsions or burns are examples of wounds which, in addition to interruption of surface continuity, result in loss of tissue. A question which must be answered for both is whether immediate closure can be performed safely. Whether the wound can be closed by suturing the edges together or a graft of some sort is required, a decision must be reached about whether closure can be immediate or should be delayed until the danger of infection is past.

The key to deciding when a wound should be closed is an understanding of the d difference between contamination and infection; the trick to determining when one has become the other is the ability to recognise and interpret signs of inflammation. A contaminated wound can be converted by skillfully performed surgery into a clean wound which can then be closed safely; an infected wound cannot be surgically debrided without high risk of failure, including the potentially lethal complications of interfering with natural localizing processes. The history and physical examination contribute valuable information, because the length of time needed for contamination to become infection reflects, among other things, the strength of the bacterial inoculum and the ability of the substrate to combat invasion. A clean razor slice of highly vascular skin of the face might be closed safely 48 hours after injury, whereas a stable-floor-nail penetration of the foot of an elderly person might not be closed safely 1 minute after injury. Quantitative measurements of the number of bacteria in tissue samples have shown that concentrations greater than 10^5 organisms per gram of tissue are likely to cause abscess and wound breakdown following secondary closure. If the concentration of bacteria is significantly less than 10^5 organisms per gram of tissue, the chances of successful wound closure are much improved. Because contaminated wounds have bacteria only on the surface and ideally the surface will be mechanically or hydrodynamically cleansed, quantitative bacteriology is reserved primarily for diagnosis of granulating previously infected wounds.

Once the decision has been made to close a laceration, the surrounding skin should be prepared with suitable antiseptic and local anesthetic injected. A guide to application of

antiseptic is never to put anything in a wound that could not be tolerated comfortably in the conjunctival sac. Any caustic solution which is capable of sterilizing the surface of the skin will also destroy delicate cells on the surface of the wound. Therefore, harsh antiseptics should be applied only to the edge of the wound, never within it. Recent popular use of povidone iodine solution to irrigate or soak wound tissues may offer some advantages over saline irrigation, but data presently are not convincing. Moreover, absorption following prolonged use in large wounds such as burns or in wounds containing serous membranes such as peritoneum or pleura has caused significant complications. Debridement of a wound can be done either hydrodynamically or mechanically. When the wound contains only surface contaminants not attached to wound tissues, a copious stream of saline solution will flush foreign bodies and undesirable organisms out of the wound cavity. When devitalized or contused tissue fragments are still attached to the wound tissues and external contaminants are partially driven into the tissues, however, surgical excision of affected tissues must be performed. When there is a redundancy of tissue and there are no important structures in the depth of the wound, such as nerve or tendon, the best type of debridement is excision of the entire wound to produce a new wound which is surgically clean. When there is a shortage of tissue or when a wound involves important structures which cannot be sacrificed without producing disability, damaged tissue must be carefully dissected until all dead tissue and extraneous material have been removed. In a wound of the hand involving numerous tendons and nerves, this type of debridement may be tedious and require several hours to perform.

After the wound has been debrided, proper suture material must be selected for closure. There are two major types of sutures, absorbable and nonabsorbable, and selection of the proper suture should be based on what has been learned about the biology of the healing process. For the most part, absorbable sutures, which are made of sheep intestines or synthetic polymers, are used when infection is known to be present or when debridement has been difficult and thoroughness is in doubt.

Plain gut sutures will be solubilized by tissue collagenase in less than 10 days, while gut which has been tanned lightly with chromium salts will remain structurally intact for approximately 3 weeks. Absorbable sutures are usually not used when they can be avoided, because the reaction to a foreign animal protein is considerably greater than the reaction to such substances as cotton, silk, and nylon. Synthetic absorbable sutures may not be as locally irritating as animal proteins. Because the collagen-synthesis stage of wound healing is barely under way at 10 days and the scar tissue is far from mature even at 3 weeks, a more permanent material may be needed. Chromic gut sutures produce less soft tissue reaction than plain gut sutures, possibly because more available cross-linking sites have been satisfied by the tanning agent.

Nonabsorbable sutures are usually preferable because they produce less tissue reaction and can remain permanently below the surface of the integument. The major disadvantage of permanent sutures is that if they are placed in areas where infection develops, the suture material can harbor organisms; hence infection will not subside until the sutures are removed. A nonabsorbable suture of steel or some alloy may be mechanically irritating, and sometimes and inflammatory reaction develops around nonabsorbable sutures which resembles a local allergic phenomenon. Sutures are placed in different types of tissue for different reasons; before selecting and placing a suture in a wound, the questions should be asked: What is the suture required to do? and How long does it need to do it? Sutures which are placed in tissues

to hold wound edges together under tension should be placed in fibrous tissue. Sutures placed in cellular tissues such as fat, epidermis, liver, or kidney provide little structural strength, as they tend to cut through tissues, having no appreciable strength. Sutures in weak tissues usually are used to obliterate a potential cavity (dead space), provide hemostasis, or act as a fine-adjustment leveling device on the surface of the skin. Objectives for such sutures are met in a few hours; thus absorbable sutures can be used satisfactorily if they are desirable.

A typical facial wound involving skin, subcutaneous fat, fascia, and superficial muscle might be repaired in the following way: After local anesthesia has been administered, the skin prepared, contaminants flushed out with saline solution, and any dead fragments of tissue excised, closure is performed. The muscle, being primarily cellular, does not hold sutures well. Muscle is closed primarily to stop hemorrhage and to obliterate dead space. An absorbable suture is satisfactory for these purposes. Fibrous tissue surrounding muscle has significant strength, however, and should be closed with a permanent suture of silk or cotton. If the skin is closed in a single layer, the retracted subcutaneous fat might not come together completely, thus producing a cavity which would become filled with blood and possibly infected. A loosely tied suture in subcutaneous fat, although it contributes almost nothing to tensile strength because it does not pass through fibrous tissue, may be utilized to obliterate a subcutaneous cavity and discourage hemorrhage. After the subcutaneous tissue has been closed, a decision should be made about the desired final appearance of the surface scar. The width of the wound following closure of the subcutaneous tissue will be an accurate indicator of how wide the final cutaneous scar will be if the next sutures merely approximate skin edges and are tied on the outside. The reason is that, if suture marks are to be avoided, silk sutures should be removed in 6 to 8 days because of development of inflammatory reaction, epithelial lined tracts, or small stitch abscesses. Although the wound edges may be accurately coapted with only a hairline scar at the time that such sutures are removed, the wound is held together only by epithelium, blood vessels, and globular protein. Even though it usually will not dehisce before collagen production takes over, the scar will stretch and widen during the ensuing 21 days while collagen formation and remodelling occur. The result usually is that a 7-day-old 1-mm-wide scar may become a 1-cm-wide scar 3 weeks after the sutures have been removed. One way to reduce widening of a scar after skin sutures are removed is to place permanent sutures in the fibrous protein layers of the skin to bring the edges together. This is accomplished by a subcuticular or intradermal suture of fine silk or cotton. The overlying epidermis is gently retracted, and sutures are placed in the lower part of the dermis. The knot is sometimes placed deep in subcutaneous tissue but can be tied superficially provided that the ends of the suture are cut close and the know and suture ends are covered by overlying epithelium. It is important to use a very fine suture that will not be palpable beneath the epithelium and a clear or light-colored suture material that will not show through translucent epithelium. It has been shown recently that permanent subcuticular sutures will not eliminate completely secondary widening of a scar; such sutures will reduce the extent of transverse remodelling in many wounds, however.

After subcuticular sutures have been placed, the skin edges will be as close together as it is possible to bring them; yet the overlying epithelial edges may be vertically uneven. A final row of sutures of fine silk or nylon which serve as a fine adjustment or leveler of the epithelial edges is frequently utilized to produce an even surface. Because these sutures are in cellular tissue, the contribute little to the strength of the wound and should not be placed more than 1 mm away from the wound edge. They should be tied loosely and removed before

any epithelial reaction develops. Actually, external sutures in a wound closed in this manner probably can be removed in a few hours or as soon as the plasma clot seals the epithelial edges. For practical purposes, however, they are not removed until the first dressing, whenever that may be. In recent years the use of external cutaneous sutures has been partially eliminated by the development of various types of adhesive strips which can be used to hold skin edges together without producing epithelial sinuses or reaction.

When do you remove stitches? is a question frequently asked of surgeons. The answer is simple: when they have done the job they were put in to do, namely, hold the wound edges together until adequate tensile strength has developed. To set a finite period of time for removal of sutures it to imply that wounds heal at a standard rate; but the rate of healing is variable even in different parts of the body and under different conditions in a single individual. Instead of counting days until sutures can be removed, the wound must be examined; sometimes one or two sutures must be removed to see if the skin edges are sufficiently adherent to permit removal of all sutures. In wounds where a narrow scar is important and were some tension is unavoidable, it is advisable to splint the immature scar with adhesive strops for 2 or 3 weeks or until new collagen has attained sufficient strength and reliability.

The appearance of a linear scar is frequently worse between the third and fifth weeks after wound closure than it is at the time sutures are removed. The irregular, raised, purplish appearance of immature scar tissue can be a cause of great concern to young patients. Resorption of excess collagen, development of pliability, and the fading of undesirable color are called *maturation* of the scar, and maturation occurs more rapidly in older people than in the young. Children and teen-age patients, particularly, may have a distressing amount of red color in scars for several years. This condition is temporary, however, and redness should not be an indication for secondary surgical revision.

Scars should be revised secondarily only after they have undergone maximum maturation. Beefy, red, hypertrophic, immature scars usually recur after excision, and it is often amazing how much natural improvement will occur if sufficient time is allowed. It is seldom wise to attempt surgical improvement of a scar in less than 6 months; often natural improvement will continue for as long as 12 months.

Secondary revision should not be performed with the idea of changing the color of a scar or with the idea that a scar can be eliminated completely. All that secondary revision can accomplish is to take out a scar which resulted from unskilled closure or closure under unsatisfactory conditions and to close the defect as skillfully as possible under optimal conditions. Leveling uneven edges, changing the direction sot that the scar does not cross lines of changing dimensions, and supporting a wide scar by the use of meticulously placed subcuticular sutures are the main improvements which can be accomplished. If scar tissue is elevated slightly above the level of surrounding skin, abrasion of that area with sandpaper or rotating brush will produce a smooth denuded surface over which new epithelium will spread in a more even sheet.

Wounds characterised by a loss of skin can be allowed to heal by contraction and epithelization if there is sufficient skin to be stretched across the defect. This is usually permitted only when infection prevents primary closure and when contraction does not

produce a contracture which would interfere with function or produce a cosmetically unacceptable scar. In all other wounds, a skin graft should be performed to replace the skin which has been lost.

At the moment, there is no known catalyst to speed up wound healing; about all that a physician can do to aid normal healing is to protect the wound from physical, chemical, or bacteriologic complications which retard or prevent healing. One useful exception to this statement is the utilization of topical vitamin A to correct inhibition of epithelization caused by cortisone therapy. Vitamin A does not accelerate epithelization over normal expectation, it only corrects inhibition of epithelization caused by a specific drug effect. Protection usually means the use of an artificial dressing unless a natural dressing material, such as an eschar or scab, can serve the same purpose. Once the scab or eschar deteriorates, however, it, like any other dressing material, must be changed (debrided), and either definitive coverage provided or an artificial dressing applied. As in the selection of suture materials, choosing dressing materials involves a clear understanding of the objectives of each component of the dressing and the fundamental biologic processes that the dressing is supposed to protect. The fist layer of a dressing is usually made of fine-mesh gauze, so that granulation tissue will not penetrate the interstices and cause hemorrhage when the dressing is removed. A long search for a pharmacologic substance to incorporate in the gauze to stimulate epithelial growth has been unsuccessful so far. Because certain by-products of the azo dye industry are carcinogenic, it was hoped that related dyes such as scarlet red might offer epithelial stimulation without being carcinogenic. All such substances have been disappointing, however, although most surgeons do use a gauze impregnated with some bland substance such as petroleum jelly or topical antibiotic in a water-soluble base. The main value of such medicated dressings is that there is less adherence of epithelium and vascular tissues to the dressing, hence less interference with wound healing when the dressing is changed. Dry gauze is a perfectly satisfactory dressing for most wound surfaces, however, and when carefully applied and removed, it can be as atraumatic as any other material. The usual coarse 4 x 4 hospital gauze sponge with its cotton-filled center is not a good material to place against open wounds; the interstices permit permeation by vascular tissue, and the cotton lint which is included becomes embedded in the wound. Sponges, mechanics' waste, cotton, and the like are used to give bulk to a dressing after the fine-mesh gauze has been applied to make the dressing conform to a desired shape and immobilize the wounded part. Nonstretchable, firm, roller gauze bandage and adhesive tape are used to complete the dressing in a typical occlusive (erroneously called "pressure") type of dressing. The nonstretchable gauze and adhesive tape provide a compact and stable immobilizing influence. A clean wound has very little drainage and no odor, and does not have to be dressed very often.

Infected wounds have considerable drainage and odor and, therefore, must be dressed often to provide suitable drainage and tolerable appearance. It is common practice to use a wet dressing on infected wounds, which means that the inside layers of the dressing are intentionally moistened with saline solution or some other substance. The realization that there is no catalytic effect upon healing or any control of infection from water and that maceration of skin or eschar produces favorable conditions for bacterial or fungus growth throws doubt upon the beneficial effects to be obtained by applying a wet dressing. The usual answer is that drainage is increased by capillary action or that debridement is accomplished as detritus sticks to the dressing. Such reasoning has never seemed logical to the author; a dry dressing will absorb more wound drainage than a saturated one, any debridement can usually be

accomplished more efficiently by mechanical means. It often appears that wounds become cleaner more quickly with the use of wet dressings, but in the author's experience this is partly because wet dressings are changed more often. Of course, less pain may be associated with wet-dressing changes than with dry-dressing changes. However, when dry dressings are changed frequently and skillfully, surface detritus may be removed more effectively by dry dressings than by wet ones. One sound reason for using a wet dressing, however, is that wet heat is more penetrating than dry heat, and when additional warmth is desirable to increase the local inflammatory response, a warm moist dressing is effective. Failure to keep a moist dressing warm by the addition of external heat, however, results in a cold soggy dressing which has not particular virtue and which is definitely inferior to a frequently changed dry one.

Skin Grafts

Skin grafts are classified as free grafts (meaning that they are separated completely from their donor sites before being transferred to recipient areas) and pedicle grafts (which maintain a vascular connection with the general circulation). Free grafts are full-thickness (which means that the entire thickness of the skin, including epidermis and dermis, is transferred) and split-thickness (which means that the entire epidermis and only a portion of the dermis are transferred). The remainder of the dermis after split-thickness skin grafting remains at the donor site.

The "take" of a free graft refers to the pink appearance of a graft which occurs between the third and fifth days after transfer, signifying that vascular connections have developed between the recipient bed and the transplant. Before this time, free grafts are white, unless microvascular surgery has provided instantaneous restoration of circulation, and do not show any change in color when pressed upon and released. It is a matter of considerable conjecture whether there is diffusion of gases and nutrients between cells of the graft and underlying capillaries prior to development of actual vascular connections, and it has been assumed in the past that diffusion was necessary to keep cells nourished during the first few days. When grafts which include more than full thickness of the skin do not survive as free transplants, or when split-thickness grafts with pus or blood interposed between graft and capillary bed do not survive, it has been considered that diffusion could not occur through fat, pus, blood, etc. It seems more likely now, however, that diffusion is not important in the take of a graft and that mechanical barriers such as pus, blood, or fat prevent the take of a free graft by preventing vascular connections from occurring. Whatever the reason, the thicker the graft, the more likely will be the failure of take if mechanical or inflammatory conditions at the graft-wound interface are less than optimal. For this reason, thin grafts are used to cover less than ideally prepared wounds; full-thickness grafts are reserved for surgically produced wounds under optimal conditions.

In taking a full-thickness skin graft the surgeon will produce a wound which will have to be closed by suturing the edges together or by applying a split-thickness skin graft from another donor site. If this is not done, closing of the wound in one area with the graft will leave a wound of the same size and shape at the donor site. Full-thickness grafts are usually small grafts which can be taken from a place where there is an excess of thin skin, such as the inframammary fold or the groin. where the donor site can be closed by suturing the skin edges together.

It was once thought that split-thickness skin grafts must be taken through the level of the dermal-epidermal undulating interface so that small islands of stratum germinativum cells would remain to reepithelialize the denuded surface. Because of this notion, surgeons were careful to take grafts as thin as possible, and the taking of a split-thickness skin graft was relegated to only a few highly skilled individuals. It seems obvious now that if it were possible to take a graft through only the epithelium, a satisfactory take wound be unlikely. Most of the cells would be dead, and the covered wound would be resurfaced by cells which would provide no better coverage than that which would have occurred from normal epithelization. The qualities of skin other than water-proofing (strength, flexibility, appearance, etc) which are desired in a graft are qualities provided by the dermis. The final appearance of both the recipient and donor sites, therefore, reflects the amount of dermis which has been transferred and the amount of dermis which is left behind. Epithelial cells migrate out of deeply located glands and hair follicles, and donor sites which do no extend through the entire depth of the dermis will be reepithelialized from these sources. Dermis, being a complex organ and not a simple tissue, does not regenerate, however, and if all the properties of normal dermis are desired in the recipient area, full-thickness dermis must be transferred; if less than the full thickness is transferred, the resulting graft will be abnormal in appearance and function.

In choosing the thickness of a free skin graft, qualities which are desired in the recipient area must be balanced against cost incurred in the donor site. How such factors influence selection of graft thickness can be illustrated by comparing two extremes in wound and donor-site conditions. In a large thermal burn, the recipient area is not optimal in that it is usually infected and edematous and involves a large area. The take of a graft is therefore uncertain, and revascularization is problematic. From the standpoint of the donor site, it may be necessary to procure severe grafts from the same area to obtain enough skin for the entire wound; thus rapid healing, with a remaining dermis thick enough for subsequent grafts to be taken, is mandatory. In this case, both donor-site and recipient conditions require thin grafts. In contrast, a 2-cm-diameter wound caused by loss of skin from the cheek of a young person presents an entirely different set of requirements for an optimal graft. The recipient bed should be optimal if excised immediately or prepared later in the operating room. The need for full-thickness dermis is mandatory so that normal texture, color, and thickness will produce the most cosmetically acceptable result. The graft is small, and so a variety of areas with a 2-cm redundancy of skin can be found for a donor site. Thus all factors point to the selection of a full-thickness graft. In other wounds the choice may not be quite so clear, but the principles involves in these two cases are the factors which must be considered in selection of any free graft.

Split-thickness skin grafts have a tendency to develop deep pigmentation after transfer. The thinner the graft, the more pronounced is postoperative pigmentation for 6 to 9 months following transfer. It is important to warn patients who have recently had split-thickness skin grafts placed on exposed areas of the body that protection from solar radiation is mandatory for at least 6 months. Thick grafts have less tendency to develop undesirable pigment, and they will usually blend into their new surroundings more quickly than thin ones.

Finally, a word should be said about the concept of the "dressing graft". Split-thickness skin is the best possible dressing material for an open wound, and failure of many surgeons to take advantage of this fact in treating complicated wounds is usually based on the mistaken

notion that placing a split-thickness skin graft on a wound is tantamount to closing the wound. Although the possibility that some portion or all of the graft may take and thus close the wound is the main advantage in using split-thickness skin grafts as a dressing material, placing the graft on a wound of questionable suitability for closure does not in itself produce a closed wound in the same manner as suturing two full-thickness skin edges together. Actually, a skin dressing does not close the wound any more than a petroleum jelly gauze dressing. If the wound has been inadequately debrided or infection is not yet controlled, the graft will slough in a few days and may disappear by the time of the first dressing. In such instances nothing will have been lost except a few square centimeters of split-thickness skin from the donor area. Dressing a questionable wound of relatively small size with split-thickness skin, therefore, is a sort of biologic test to determine suitability for closure, as well as providing some benefit if even a part of the graft survives. Xenografts of porcine skin, human allografts of split-thickness skin, and human amnion also are used as biologic dressings to test the suitability of the wound for definitive closure and to prevent metabolic and infectious complications of large wounds remaining open for protracted periods. Such grafts should be removed before take occurs and often are changed several times before optimum conditions for autograft application are obtained. In the judgment of the author, a porcine xenograft is a poor choice for a biologic dressing. Availability through a commercial source makes it easy for a surgeon to obtain porcine grafts, but expense to the patient and theoretical considerations of crossing major histocompatibility loci auger strongly for using human skin obtained from autopsy specimens or amnion obtained from the delivery room.

When more than the skin has been lost, and the skin plus some other tissue such as fat, tendon, muscle, or nerve must be replaced to restore function and appearance, transfer of skin by pedicle flap or direct vascular anastomosis is required. As the name implies, pedicle transfers maintain vascular connection with the host, so that interruption of the capillary circulation never occurs. The vessels which are most important during transfer of tissue are the vessels in the subdermal plexus. These vessels are relatively large, frequently longitudinally oriented, and are located on the undersurface of the dermis between it and the subcutaneous fat. One frequently hears that a pedicle flap has been made thicker than actually needed for cosmetic or functional purposes in order to provide a safe blood supply. Fat on the undersurface of a flap does not add any appreciable blood supply, and it may be removed safely to produce as thin a pedicle as needed, provided that surgical manipulation does not injure the important vessels lying on the undersurface of the dermis. The problem in transplanting tissue by the pedicle method is to design a pedicle so that the base is as narrow as possible in relation to the length needed to cover the deficient area. It becomes a matter of considerable judgment, therefore, to gauge the shape and dimensions of a flap so that blood supply through the intact pedicle will be adequate to nourish the distal end of the flap. A great deal depends upon the natural profuseness of vascular beds; thus it is possible to move a pedicle flap on the face or cervical region which is three times as long as it is wide, while it may not be possible (without performing preliminary procedures to increase the blood supply) to transfer a flap on the leg which is no longer than it is wide. The blood supply in the base of a contemplated flap can be improved by performing a procedure commonly referred to as delay of the flap. The principle of delay is to gradually reduce blood supply to small segments of the circumference of the flap and thus improve the remaining blood supply to the point where a pedicle which was of insufficient width before the flap was delayed becomes adequate to nourish the flap. The mechanism by which delay (gradual interruption of a portion of the blood supply to a flap) improves the circulation in the base is not

completely clear. It seems doubtful that new blood actually grow into the area, although casual observation of changes in the vessels at the base suggests that this is what may happen. The rapidity with which delay improves the circulation strongly suggests, however, that the release of various amines, probably in response to changes in pH secondary to increased anaerobic metabolism, causes a closure of normally open shunts that prevent perfusion of the entire capillary network. The effect is a substantial hyperaemia at the base of the flap; over a period of several weeks and after several delaying procedures, the vessels in the pedicle base become racemose in appearance, and the amount of blood flow is increased to the extent that a relatively long flap can be transferred on a narrow pedicle. Following transfer of a flap, circulation must be observed carefully for the first 48 hours, as signs of impending circulatory embarrassment occur before irreversible thrombosis and cell death. It is not unusual for the distal end of a flap to be dusky following transfer; venous spasm secondary to the trauma of rotation may be all that is involved. Improvement usually occurs in a few hours, but during this time the danger of a venous thrombosis is increased; if there is any progression of cyanosis and edema, the possibility that tension on veins is interfering with return circulation must be investigated by removing a few sutures. Perhaps the most serious, but still reversible, sign of impending venous thrombosis is the development of a sharp line of color differentiation. A gradual change from normal pink to slight cyanosis is not so significant as a clear-cut line demarcating the area of circulatory deficiency from normal circulation. Even if all the sutures have to be removed and the flap returned to its original bed, the sign must be attended to, or an irreversible demarcation will soon develop, signifying complete thrombosis and certain distal necrosis. In sensibly planned and adequately prepared flaps, one does not have to be particularly concerned about arterial insufficiency; venous drainage is the function in which complications develop. Complications usually are the result of too much tension, poor dressing, hematoma, or infection. The use of heparin and low-molecular-weight dextran have seemed to be beneficial in dangerously compromised circulation. Hyperbaric oxygenation has been reported instrumental in saving flaps of laboratory animals, but is not practical for managing human flaps.

Advancement flaps and rotation flaps are the simplest pedicle transfers. These are dependent upon a redundancy of soft tissue adjacent to a defect so that the donor defect can be closed by approximating the skin edges or applying split-thickness skin grafts. More complicated flaps require the use of an arm as a carrier to provide circulation during the period that skin is detached from the original donor site, such as the lower leg. Because of similarity of tissue characteristics, safety in transfer, and expense and time involved, it is desirable to design flaps as close to the point where they are needed as possible.

One of the most sophisticated flaps is an island pedicle flap, which combines the pedicle principle of intact blood and nerve supply with some of the advantages of a free graft. The principle of the island pedicle is that careful dissection of the artery and vein (and sometimes the nerve) to a piece of skin can be performed so that the skin is detached from surrounding skin and remains attached to the body only by essentials for survival - an artery, a vein, and sometimes a nerve. Depending on the length of these structures, it is possible to move a full-thickness skin and fat graft, or an intact finger, or a portion of a finger or toe, a surprising distance. Transfer of hair-bearing portions of the scalp on a temporal artery-and-vein supported flap to the supraorbital region for eyebrow reconstruction and transfer of a finger to replace a missing thumb are examples of island pedicle transfers which are useful. The need to perform time-consuming and costly delay procedures has been reduced

significantly by the development of myocutaneous and free microvascular transfer flaps. Discovery that the muscle under skin supplies blood vessels sufficient to nourish skin is the basis for composite flaps that transfer intact the muscle, subcutaneous tissue, and overlying skin as a single unit rotated on the relatively narrow, sometimes even single artery and vein, vascular pedicle to the muscle. Pectoralis major, latissimus dorsi, gracilis, and tensor facia lata myocutaneous flaps are being used frequently to transfer soft tissue on a relatively narrow vascular pedicle without delay procedures. An example of a tensor fascia lata myocutaneous flap rotated 180° to a trochanteric defect on the single artery and vein nourishing the muscle is shown. Perhaps the most elegant such transfer is a free flap in which muscle, muscle and skin, or skin alone is transferred to a distant site. After transfer, the blood vessels are sutured by microvascular technique to vessels in the recipient area, thus reestablishing active circulation. Latissimus dorsi, gracilis, and groin skin flaps have been very successful in restoring surface defects in the lower leg and foot. Free jejunal and omental grafts have been utilized in the head and neck. Transfer of rib, subcutaneous tissue, and overlying skin by microvascular anastomosis of intercostal vessels to facial vessels has been useful in reconstructing composite defects of the face and lower jaw. An example of free-flap transfer of a latissimus dorsi and overlying back skin flap to the lower leg with anastomosis of the thoracodorsal vessels to the anterior tibial (end-to-side) artery and vein is shown.

Finally, it should be pointed out that, in the opinion of many, maturity in restorative surgery can be measured, in part, by how often one thinks of a pedicle flap as the only means of rebuilding a damaged area and then devises a way to make a free graft do as well. Pedicles are dramatic, particularly as used by military surgeons to rebuild enormous tissue defects caused by high-explosive wounds; fortunately, however, civilian injuries are not often so devastating, and the practical points of expense, length of time away from work, shortage of hospital facilities, and the like have to be considered in each case where a pedicle could be used. In addition, although areas such as the face may appear in photographs to have been superbly restored by massive flaps, yet it must be remembered that flaps have no dynamic function; they are expressionless, and often look better in photographs than they do as part of the constantly moving facial features. When a pedicle flap is needed, nothing else will suffice, and pedicles are an extremely valuable part of restorative surgery. The high cost of donor-site mutilation, length of time required for transfer, and adynamic features, however, make the pedicle flap definitely second choice to a free graft if a free graft can be used as well.