SOME PATHOLOGIC ASPECTS OF CUTANEOUS WOUND HEALING

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THE important aspects of proper wound healing should be of decided interest to every scientifically minded surgeon. The author wrote on this subject in 1943.[1] Since that time some new concepts have come to our attention on this topic which for our purpose can be divided into the normal and the abnormal phases. Let us review the highlights which have to do with the normal components of wound healing, for the abnormal aspects might be better understood if we consider the factors which are involved in the normal phases.

Indeed, the healing of a skin wound is an amazing phenomenon. Carrel has shown that a wound will not heal within three weeks if all debris and blood clots are removed and the wound is protected from outside irritation; yet if irritation or infection occur, cicatrization will begin in less than two days.[2] Hence tissue injury probably inaugurates a hormonal response by the fibroblasts which migrate to the site of injury and where they then begin to proliferate. This hormonal concept of wound healing can be traced to Virchow (1858). In 1892 Weisner wrote that this traumatic effect was an indirect one since the injured cells released wound hormones which caused the normal cells to proliferate. Naswitis (1924) demonstrated the actual existence of growth-stimulating substances.[3]

The fibroblast is the main unit of repair. Ham[4] states that fibroblasts are the most numerous type of cell in most sections of areolar tissue. These cells form both the collagenic and the elastic fibers of areolar tissue, and they form also the amorphous intercellular substance in which the elastic and collagenous fibers are embedded. Ham[5] has given the following description on the healing of a wound: "It has been explained previously that the blood that flows into the space between the lips of a cut on the skin soon clots. This results in the cut edges, if they are not too far apart, becoming glued together with a fibrin mesh. In a skin wound, such a fibrin mesh is rapidly invaded by fibroblasts and capillaries; the tissue resulting from the growth of these two elements is termed granulation tissue. And, in such a site, it is to be observed that, in a short time, the fibrin disappears and collagen fibers are deposited between the new fibroblasts. The new tissue, rich in collagen, is said to constitute a scar. It is of interest that fibroblasts seem to be essential for the formation of both mucopolysaccharide amorphous intercellular substances and collagenic fibers. Meyer has suggested that in forming intercellular substance the young fibroblast may secrete a non-fibrillar precursor of collagen together with hyaluronic acid and a chondroitin sulfate. The acid amorphous intercellular substance may then denature the precursor of collagen, causing it to become fibrillar, with each fibril having an investment of amorphous substance."

The primary requisites for proper wound healing are well known to most surgeons. Healing by "first intention" requires a clean, accurately approximated surgical wound.[6] Other factors which assist in adequate wound healing are proper asepsis, perfect hemostasis[7] and the careful handling of all viable tissue as advocated by Professor Michael Mason.[8] Conversely, a known factor of importance which has to do with improper wound healing is the relation of hypoproteinemia to wound disruption which was first demonstrated in the dog by Thompson, Ravdin and Frank, who showed that the hypoproteinemic dog is frequently incapable of normal fibroplasia. Also, avitaminosis C is a systemic factor which interferes with proper wound healing,[9] as does lack of rest and good general health, for albuminuria and diabetes particularly obstruct repair[10] and the fibroplastic response to leukotaxine, according to Menkin.[11] Christopher[12] has stated that the effects of vitamins A and D on wound healing are not yet sufficiently established. However, in passing, I have found very recently the concomitant conditions of hypovitaminosis D and the presence of keloids in several patients. Hence I am not too certain that these

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two conditions are not interrelated intimately.[13] This topic is now being investigated by the author.

The ultimate end result of a wound can be noted by the presence of a scar which is composed mainly of connective tissue whose fibers are denser and less elastic than those which are found in normal skin. From a cosmetic viewpoint scars are important to the patient, as every clinician knows so well. A fine linear scar is preferred to the irregular, thick and unsightly type; and when the latter is prominent, it may have developed into a hypertrophic scar or a keloid which can be defined in pathologic terms as non-inflammatory fibroma.[14] Lever[15] writes that there are two types of keloids, (1) the primary or spontaneous and (2) the secondary or post-traumatic. He claims that the two types do not differ clinically or histologically. Lever states that "primary keloid, which represents a true tumor, presents the same histological appearance as a dermatofibroma. The cells of the tumor show no phagocytosis. Secondary keloid is not a tumor but represents a reactive fibrosis. Nevertheless, it cannot be differentiated from a dermatofibroma on a histological basis. In an early keloid one finds a moderate number of fibroblasts. An old keloid may show practically no cellular elements."

A keloid differs from a hypertrophic scar since it involves skin areas beyond the limits of injury.[16] Furthermore, hypertrophic scars contain small collagen fibrils while keloids are composed of large collagen fibrils.[17]

When a wound heals normally, there is a cessation of the formation of fibrous tissue as soon as continuity has become established. However, this is not the case with the formation of keloids, for here the proliferation of fibroblasts continues with a piling-up, as it were, of fibroblasts. The trigger mechanism, which may be responsible for this reaction, may be the leukotaxine of Menkin, as has been mentioned heretofore. This results in the formation of the new growth which is called a keloid. This mass is forced upward from its stromal bed by two major forces, (1) the concomitant edematous states and (2) the ever enlarging neoplasmal growth, so that, at length, this mass pushes through the integument as a herniation of that structure in a manner similar to that of a uterine fibroid and polyp.[18]

Why do keloids develop in certain individuals and races while in others they do not? Obviously many factors are responsible. I shall discuss briefly a few of those etiologic agents which may be involved.

Tissue injury is of prime importance in most pathologic inquiries. Wertheimer and Ward[19] have confirmed Hardy, Goodell and Wolff's hypothesis that a very close relationship exists between tissue damage and pain. Their very recently reported studies support the concept that the adequate stimulus for pain is tissue injury.

In our current consideration as to the trigger mechanism for the growth of keloids I believe that the release of leukotaxine from tissue damage might be the stimulus for the infiltration and the growth of fibroblasts. The leukotaxine is released through the presence of inspissated blood in the tissue stroma. In support of this thesis is the series of experiments which I performed upon myself some years ago. Repeated blood serum injections were administered to the right thigh areas. The thighs were employed to allow for auto-injections. These areas were extirpated after such repeated injections produced experimental localized edema.[20] Upon the extirpation of these tissue areas the experimental skin areas, which received the intracutaneous injections of blood serum, hemorrhaged much more freely than did the tissues from the opposite left thigh, which had received similar repeated intracutaneous injections of physiologic saline solution as the control. Furthermore, the skin areas which received the blood serum exhibited marked fibromatous changes which were totally absent in the skin control areas.

Hence from these interesting observations it appeared that experimental edema, produced by the inspissated blood serum injections in these skin areas, apparently attracted fibroblasts which began laying down connective tissue. The overproduction of the fibrous mass plus the pressure of the edema exerted upward pressure, so that these neoplasms could herniate through the integument if allowed to remain intact for a longer period of time. Upon careful histologic examinations these new tumor masses appeared to be very similar to early keloids. We also found the presence of dilated blood vessels in these keloidal areas. This accounted for the excessive bleeding upon extirpation which was not experienced when the skin areas, which received the saline solution, were removed. From these observations

it was believed that there is a direct relationship between the presence of tissue edema or hemorrhage and the later formation of fibrous (scar) tissue. Furthermore, Schadeberg and I have recorded the presence of a reversed albumin-globulin ratio in a very severe case of keloidosis.[21] The latter condition can produce tissue edema through increased capillary permeability which may lead to severe tissue edema and finally to the piling-up of fibroblasts to produce the so-called spontaneous keloids. Vitamin D deficiency may also cause increased capillary permeability, as has been mentioned heretofore.

Treatment of keloids will not be considered. However, I can state that the new vasoconstrictor substance, kutapressin,* isolated from liver by the author, has given highly satisfactory results to many colleagues who have treated keloids with this material. This apparently can reverse at least partially the blood fluid extravasations which lead to the early formation of keloids and hypertrophic scars.

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* Kutapressin is manufactured by the Kremers-Urban Company of Milwaukee, Wis.

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