Nutrition and Wound Healing

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EVERY STUDENT of biology has been fascinated by the regeneration of the severed limb seen in many of the lower organisms. Wound healing is a similar epimorphic process. The chemistry of the process in man is comparatively unknown. At the present time it is necessary to proceed on the premises that what is good for growth is also good for repair, and that experimental data compiled on the dog, the rat, the salamander, and even the axolotyl are pertinent in man.

THE HEALING PROCESS

The ideally coapted wound contains a minimum of devitalized tissue to be autolyzed. The wound surfaces are separated by a homogeneous mass of fibrin which rapidly develops into strands. At this time the wound has practically no strength save that inherent in the sutures utilized to close it. After a lag period, fibroblasts derived from the wandering connective tissue cells start their amoeboid motion along the fibrin strands, elongating as they grow out. They are followed by the endothelial buds. The stimulus to this process is not known. Oxygen lack and local nutritional deficiency are possibilities to be considered. Others have suggested that specific chemical substances such as glutathione[1] or its sulfhydryl radical[2] might be responsible. As the process proceeds with the migration and proliferation of fibroblasts and capillaries, the formation of collagen is evident as the intercellular matrix matures. At this time the strength of the wound increases. Epithelization is a quite different problem, though an analogous one.

In man, normal wound repair is dependent upon numerous *local factors*. Since even the sharpest scalpel kills some cells, the amount of devitalized tissue between the coapted edges is important. The amount and character of foreign bodies such as ligatures and bacteria must be considered. The vascularity of the tissues to be repaired and the accuracy of the coaptation of the wound edges without undue separation by blood clots are important factors. It was shown in 1922 by Ebeling[3] that a 10 per cent rise in the temperature of a cold-blooded animal would double the rate of wound healing. This indicates that wound healing is a chemical reaction. Thus, if the local factors discussed previously are kept at an optimum, the most important variable is the supply of the components for the chemical reaction. To accomplish this in the human being nutrition must be adequate.

The catabolic effect of trauma and surgical operations have been pointed out elsewhere in this symposium. So far as these effects apply to wound healing we are able to assess only a few of them at this time.

HYPOPROTEINEMIA

The experiments of Clark[4] in 1919 showed that animals on a high protein diet had a reduced lag period in the healing of surface wounds, compared to those on a high fat, low protein diet. Mecray, Barden, and Ravdin[5] in 1935 reported that during the course of experiments on hypoproteinemia, the wounds in dogs' abdomens healed poorly while the animals were in the hypoproteinemic state. This Thompson, Ravdin, and Frank[6] showed to be due to delayed fibroplasia and to the separation of wounds by edema fluid. When the proteins were restored, the wound healed promptly. From this experiment it may be assumed that the delay in fibroplasia was due to edema separating the wound edges or to a lack of available amino acids for repair, or both. There have been numerous other experiments that tend to show that the lag

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period in wound healing is lengthened by hypoproteinemia.[7-9] Yet which is the more significant: the edema or the lack of amino acid building blocks? Any surgeon who has operated upon the edematous postmastectomy arm of a patient in good nutritional balance will feel that edema is the more important. Yet it would seem that other local factors are also involved. No satisfactory experiment to clarify this important clinical point has been recorded.[10]

The fact that protein synthesis cannot occur if the requisite amino acids are not present at the same time has been well demonstrated.[11,12] Localio and co-workers[13] showed in their experiment and in two clinical cases that the addition of *dl*-methionine increased the rate of wound healing. Other authors have felt that amino acids containing the —SH radical were important systemically.[14] The local application of compounds containing the —SH radical in granulating wounds has been discontinued, despite early favorable reports.[15]

In man there have been few studies of the pH of wounds such as have been done in the lower organisms, in which marked variations in pH from the regressive phase to the regenerative phase were noted. Such studies might have clinical importance, since animals on an acid diet have been shown to have a shortened course of wound healing.[16] Similarly, there have been no studies on the sulfur/nitrogen ratio which might give a clue to the amino acids locally involved in the lag period and in the healing process.

It is difficult to understand why, in a wide variety of experiments on animals from salamanders[17] to rats,[18] the fasted (but not starved) animal heals at a normal or even accelerated rate. In the early stages of wound regeneration both experimental animals and man seem to be without appetite. It has been suggested[19] that fasting increases the alkaline phosphatase which is known to be in high concentration in healing bone in man and in some healing wounds in lower animals.[20] However, few experiments on the alkaline phosphatase content of healing wounds in man have been reported.[21]

Clinical Importance of Hypoproteinemia in Wound Healing

In clinical practice so wide a variety of factors is involved in healing a wound such as an abdominal incision or an intestinal anastomosis that it is an insurmountable task to separate the importance of each factor. Surgeons have for years observed that their malnourished patients produce a great proportion of the wound complications. Yet, without apparent reason, an occasional cachectic patient on whom some emergency procedure is necessarily performed will heal his anastomosis and incision without incident.

One of the few clinical studies on this subject has been done by Localio.[22] He determined serum and tissue protein concentrations in patients judged clinically to be normal, to be debilitated, and in those with wound disruption. It appeared from this study that the protein concentration in fascia was of greater import than the concentration of protein in the serum. Examples were shown with normal serum protein concentration in the face of significant depletion of the tissue protein. Among the suggestions offered to account for this is the possibility that tissue protein stores are depleted in an attempt to maintain homeostasis of the serum protein.

The healing of decubitus ulcers with high protein therapy administered to hypoproteinemic patients has remained a clinical landmark.[23] Yet Co Tui points out that decubiti are not commonly found in association with nephrosis.[24] Other writers[25] have observed depleted serum protein in cases of abdominal wound disruption, yet this cannot be accepted other than as a possible cause of disruption. The degree of the patient's hydration is a factor that can produce wide variation in this determination. This may account for the normal findings in many cases in the reported series. The writer has been impressed with the frequency of the association of wound infection in wound disruption. Cannon[26] stresses that the hypoproteinemic animal is also more susceptible to infection.

Levenson and associates[10] have presented numerous cases of healing burns in humans

with a marked delay in healing being manifested in the hypoproteinemic patient. They report some skin graft "takes" actually breaking down as the patients became deficient in protein. Yet every surgeon has had the experience of having skin grafts take perfectly in his patients with huge oozing areas from which protein is being lost more rapidly than it can be replaced by any route; while later, when the patient is in good nutritional balance, the last few grafts necessary to complete the repair may fail.

Vitamin Deficiency

The fat-soluble vitamins have not been given any assigned role in wound healing in man. It must be presumed that they have a role in the healing of bone wounds, much as they do in bone growth.[27] In general, it appears that large doses of either vitamins A or D inhibit the healing of soft wounds in experimental animals. There is conflict as to whether small dosages are helpful. Bush and Lam[28] feel that vitamin A will hasten the healing in vitamin A-deficient animals.

The use of vitamin A and D ointments in the clinical care of surface wounds was formerly felt by many workers to promote healing.[29] These substances, however, are rarely used today.

The B-complex group of vitamins must be essential to wound healing, according to Needam.[30] He points out that they are coenzymes in the transfer of most of the biochemically important simple organic radicals. Bosse and Axelrod[31] have shown that pyridoxine- and riboflavin-deficient rats show impairment in the rate and quality of wound healing. Biotin deficiency produced less marked changes. Findley[32] presents suggestive evidence that vitamin B_{12} helps increase the strength of wounds in rats during the early healing period.

Vitamin C, ascorbic acid, has been the subject of considerable work in both animals and clinical experiments. Needam quotes a Russian writer (D. D. Ryvkina) as showing that the vitamin C content of a regenerating axolotyl limb is higher than normal throughout the repair phase. Other writers likewise have shown that ascorbic acid is increased at the site of wounding.[33] There seems to be agreement among investigators that vitamin C is necessary for the maturation of collagen and adequate capillary invasion of healing wounds.[34,35] From a clinical point of view, however, the mode of action is not clear.[36]

There have been clinical reports of low ascorbic acid levels almost routinely found in patients with wound disruption.[37] A considerable number of writers have reported very low serum ascorbic acid levels in patients admitted to general hospitals for surgical operations.[38] After a period of hospitalization and preparation for operation, the serum levels of some patients drop even lower. In a careful experiment Wolfer and co-workers[39] showed that in human subjects with prolonged ascorbic acid depletion one might expect a 50 per cent diminution in the tensile strength of the wound. The high incidence of wound infection suggested the need for ascorbic acid in the tissues for maximum resistance to infection. Crandon, Lund, and Dill[40] performed an experiment in which in a man on an ascorbic acid-free diet the serum level dropped to zero in 41 days. Yet about this time an inflicted wound healed satisfactorily. After 82 days the ascorbic acid level of the packed leukocytes had dropped to zero. At 182 days an incision made in the obviously scorbutic individual failed to heal. These writers emphasize the fact that the serum ascorbic acid levels are of less value than those of the packed leukocytes. A similar interpretation might be made from the work of Carney,[41] who observed no difference in the healing of war wounds of soldiers in the Italian campaign on vitamin C-deficient diets and low serum levels, compared to those on adequate diets and high serum levels. On the other hand, most surgeons have the feeling that wound healing is impaired proportionately to the degree of ascorbic acid deficiency.[42] With the availability of excellent modern multivitamin preparations for oral and intravenous use, it is probable that deficiencies in the vitamin B and C group in postoperative patients are now uncommon. There are no clinical reports on wound healing and disruption in

patients alternately treated with large vitamin doses presently in vogue, compared to controls to whom no additional vitamins were administered.

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Our Forefathers' Blood

"The association of blood with life itself is among the primitive concepts of man. In the picturesque phraseology of the Old Testament, blood is a synonym for vitality, emotion and heritage. It constitutes the basis of one of the plagues described in Exodus when Moses caused all the rivers and streams of Egypt to run red. It is not surprising that both Pliny and Celsus describe the patricians rushing from their seats in the Coliseum down into the arena to drink the freshly flowing blood of dying gladiators.

"The thought that all these vital properties could be transmitted by the act of transfusion is of ancient origin. A rational approach to this act, however, necessarily awaited a clear understanding of the nature of the circulation."

—L. Blum and W. N. Nelson. *Bulletin of the New York Academy of Medicine* 31: 671, 1955.

Social Vomiting

"Long before the advent of any tube the simplest procedure by which to expel the gastric contents was to place a finger in back of the tongue to stimulate the vomiting reflex. Because such an act was crude the rulers of Rome who feasted for days introduced a vomiting feather. This feather was called a 'pinna' and was used in place of the finger. The Romans made use of the pinna in order to make room for further meals. This was all done without getting up from the table, since the servants would bring forth the vomiting pail when beckoned. Often the pinna alone was not effective; therefore, it was dipped into iris or cypress oil which not only made it more nauseating but also more efficacious."

—George J. D'Angelo. *Surgery, Gynecology & Obstetrics* 101: 247, 1955.