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PREFACE

The 1970 Surgery Annual is the second Surgery Annual being published by Appleton-Century-Crofts. The format and purposes of the Annual, established in 1969, remain unchanged. The Annual presents surgical subjects of considerable current interest; comments on the major developments in the basic sciences and in the clinical practice of surgery. It also includes chapters on subject matter which is not readily available or critically presented in other publications. Each chapter is an original contribution prepared specifically for the Annual. The subjects are selected after extensive review of papers given at major medical meetings, from articles and journals, from reports of investigative studies, and after discussion and exchange of views with many outstanding surgeons and investigators.

The authors are invited to participate in the Annual not only because of their professional competence but also because of their ability to communicate well. They are encouraged to present their material as a discourse, and to include their personal views and comments. The interpretation of "recent advances" was to a great extent left to the individual authors.

Further issues in the series will each have several short chapters devoted to brief but adequately detailed comments on changes or advances on material included in previous issues of the Annual. That approach will allow us to increase the number of subjects discussed in the overall series, and to broaden our coverage of surgical material.

The table of contents reveals the breadth of the subject matter being presented. The coverage of a number of subjects was requested by many surgeons, and other physicians.

Starting with this issue, Dr. Lloyd Nyhus joins me as co-editor. He will share the many details and the challenges involved in the preparation of a yearly book in surgery. I would like to express my appreciation to the Editorial Advisory Board for their advice and help; to the authors who prepared and contributed, chapters to the 1970 Annual; to Mr. David Stires, Editor-in-Chief of Medical Books, Miss Joan E. Donovan, and Mrs. Karen S. Katz, of Appleton-Century-Crofts who assisted in production of this issue.

PHILIP COOPER, M.D.

CONTENTS

RECENT ADVANCES IN WOUND HEALING

THOMAS K. HUNT

Experimental study of wound healing was largely a surgeon's domain until approximately 10 years ago when technologic advances in protein chemistry made the detailed study of collagen possible. Collagen soon became one of the most intimately known proteins. The science of wound healing for a while became lost in the growth of collagen biochemistry. Now, because of these advances in collagen chemistry, wound healing research can be applied to clinical situations in a very exciting way. Six recent advances are of major conceptual importance and of practical value to the surgeon.

1. Advances in knowledge of protein synthesis and the discovery of protocollagen hydroxylase are of central importance to our understanding of the healing process and have opened a large field of clinical investigation into the importance of oxygen and blood flow to healing.
2. The discovery of the collagenolytic enzyme has major conceptual value to all surgeons.
3. The effects of cortisone on wound healing and particularly the antagonistic actions of vitamin A on the cortisone effect have practical value and potential future use in control of healing.
4. The discovery that zinc deficiency impairs healing is of major practical importance.
5. Improved techniques of closing wounds have led to decreased infection rates.
6. In a rather nebulous but important way an earnest quest for biologic control over the healing process has begun.

PROTOCOLLAGEN HYDROXYLASE

Among the many advances in collagen chemistry was the discovery several years ago by Udenfriend and Prockop, and their groups, of the enzyme proline-collagen hydroxylase, also called protocollagen hydroxylase.

Hydroxyproline is present only in collagen and has become the label for the collagen molecule. However, hydroxyproline is not synthesized into the collagen molecule. Proline instead is incorporated into collagen and becomes hydroxylated only after the peptide chain is separated from the ribosomal complex. A similar mechanism exists for the incorporation of lysine into collagen and its subsequent hydroxylation to hydroxylysine. These two hydroxylation steps are important in the synthesis of collagen. Without them final assembly of the collagen molecule cannot occur, since hydroxyproline and hydroxylysine play an important part in the cross-linking of peptide chains into the triple helix of collagen. The biologic requirements for the hydroxylation reaction are ferrous iron, alpha-ketoglutarate, molecular (atmospheric) oxygen, and ascorbic acid.[1] Protocollagen hydroxylase cannot perform its function in the absence of atmospheric oxygen.[2]

We have known for some time that epithelial cell replication increases with increasing Po_2, and that the rate of epithelization at high altitude is slower than that at sea level.[3,4] Recently it was found that better healing occurred in skin grafts if the patient was exposed to hyperbaric oxygen.[5] With the discovery of protocollagen hydroxylase, the possible reason for oxygen effect became more obvious, and the demonstration in our laboratory that the oxygen tension is low at the surface of granulation tissue led to the hypothesis that the rate of healing is possibly governed by oxygen supply even in the normal wound[6,7] (Fig. 1).

If we concentrate on the subcutaneous space or fascia where normally metabolism is slow, we realize that the healing process requires far more meta-

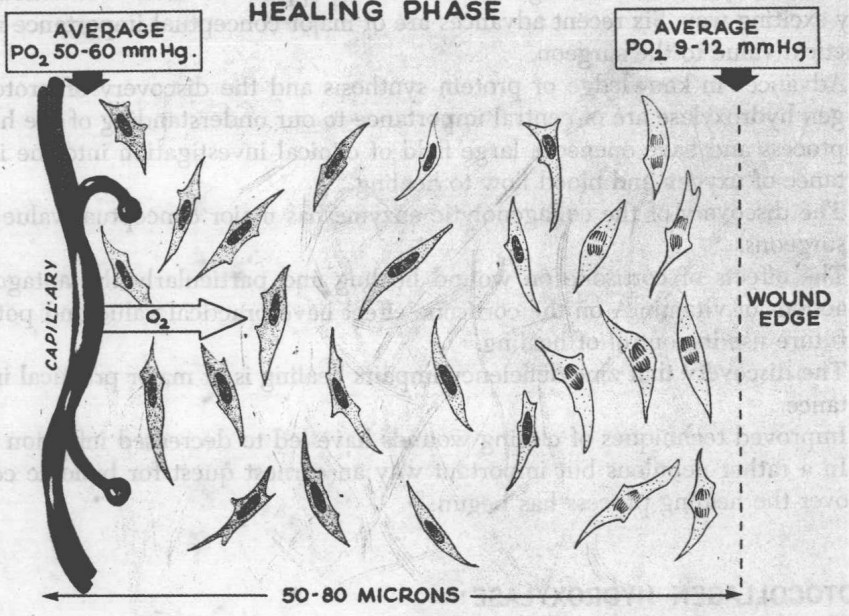

Fig. 1. During the early healing phase, while the nutrient capillaries are budding and trying to establish new circulation in the area of regeneration, oxygen gradients are extreme as illustrated in the schematic diagram.

bolic activity than this tissue has ever or will ever again require. At the same time, however, the blood supply to the injured area is diminished. A paradoxical situation then arises in which the blood supply is at its least when need is greatest. Gradients of oxygen from approximately 50 to 60 mm Hg at the capillary level to 5 to 10 mm. Hg Po_2 at the wound edge in closed wounds dramatize the hypoxic character of even normal wounds. In ideal healing, where a cleanly incised wound is precisely approximated without aid of clamps, sutures, or cautery, cut vessels would probably regain continuity as in a skin graft by the third or fourth day. Such wounds might not be hypoxic for more than a few days and might not need extra oxygen. Few wounds are so ideal.

Kulonen et al. showed that the tensile strength of skin wounds was increased in animals breathing 40 to 60 percent oxygen as compared to those kept at 20 perent oxygen. They also demonstrated that collagen production at seven days was increased in subcutaneously implanted sponges in oxygen treated animals.[8]

Recent work in our laboratory confirms the findings of Kulonen and his group, although we used different methods. We have also shown that the response of wound oxygen tension to added atmospheric oxygen is slow and incomplete, indicating that the added oxygen is used in the wound. Moreover, wound Pco_2 rises when oxygen is added, suggesting that the metabolic rate is greater with the added oxygen. Open wounds close slightly faster in higher oxygen tensions and more slowly in below-normal oxygen tensions. Whether both contraction and epithelization are involved is not known at this time.

Yablon and Cruess have shown that intermittent hyperbaric oxygen increases the healing rate of bone, and Ketchum and his co-workers have shown that burn wounds heal somewhat more rapidly with the use of intermittent hyperbaric oxygen.[9,10]

In all, the evidence seems to be overwhelming that the normal wound is often hypoxic, and that healing in most circumstances, particularly in closed wounds, will be more rapid when the oxygen supply is increased.

The converse, that wound healing will be diminished by decreased oxygen supply, also seems to be true. Using various models, we demonstrated that hypovolemia is the most potent cause of wound hypoxia[11] (Fig. 2). Increased blood viscosity also appears to be a cause. Normovolemic anemia causes only a mild decrease of wound Po_2. This adds more information for the resolution of the old clinical question of whether anemia is detrimental to wound healing. Hypovolemia is detrimental, but normovolemic anemia must probably be very severe before it interferes materially with wound healing.

The discovery that ascorbic acid is essential to the protocollagen hydroxylase reaction now show at least one place where this vital substance acts and relates oxygen deficiency to scurvy.

COLLAGENOLYTIC ENZYME

The preceding section dealt largely with the synthesis of collagen. Improved techniques of measurement of protein synthesis have shown that degradation of

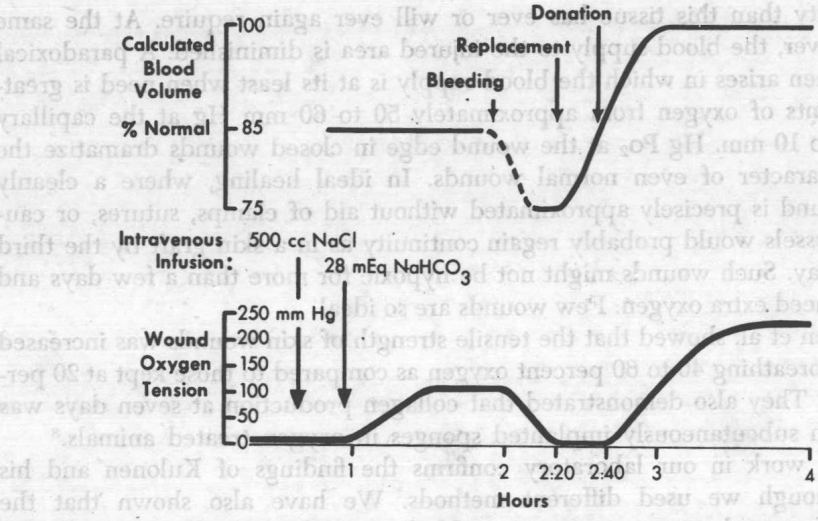

Fig. 2. Diagram of a single experiment in which a hypovolemic dog had a wound oxygen tension very close to 0 despite the administration of 100 percent oxygen by endotracheal tube. A saline infusion did not change the low Po_2 but subsequent correction of the metabolic acidosis finally achieved a small increase in wound oxygen. Bleeding at that time reduced oxygen once again to 0 despite the fact that the animal was only in "light shock" at the end of the bleeding period. Replacement with blood and a donation to restore blood volume to a calculated normal resulted in finally a relatively normal oxygen tension for a wound of this age.

collagen is also an extremely important phenomenon in wound healing. Gross et al. first demonstrated an enzyme which lysed collagen under physiologic conditions.[12] Shortly thereafter, Grillo and Gross demonstrated this enzyme in healing wounds.[13] Recently, Cronin, Jackson, and Dunphy have shown that surprisingly large amounts of collagen are destroyed and removed in the vicinity of colon wounds.[14]

Healing is a competition between lysis and synthesis of collagen. Anything which increases lysis or decreases synthesis is likely to be detrimental to healing.

Clinical factors known to decrease synthesis rates and thereby increase the risk of inadequate healing are scurvy, oxygen deficiency, protein depletion, and probably cortisone. Some infections can inhibit collagen synthesis. Collagen lysis is stimulated by starvation, cortisone, infections, inflammation, and trauma (either within the wound or distant from it).

The concept of collagen lysis is also important in the process of remodeling of wounds. It has long been apparent that wounds remodel themselves. As time passes, the healing ridge disappears, the wound becomes more flexible, the incision line sometimes tends to spread, and other clinical signs of atrophy or remodeling occur. The process of remodeling has been dramatically demonstrated by Forrester and his colleagues, who demonstrated that wounds gain in tensile strength for as long as six months after injury. Forrester showed that although there is some weakening adjacent to the wound at 10 days, probably because of collagen lysis, there is increased rigidity thereafter. Despite the increasing rigi-

dity of the healing wound, strength rises during the next six months. However, the wound remains brittle. Forrester correlated this set of observations, done with complex mechanical techniques, with scanning electron microscopy of collagen patterns in the healing wound. He found that the collagen pattern at 100 days is vastly different from that at 10 days, indicating an extensive degradation and replacement of collagen.[15]

The appreciation of the magnitude of collagen lysis in both the early and late phases of wound healing should lead to improved surgical management of wounds. The surgeon now has a better way of assessing the risk of inadequate healing and has the potential to control the end results of healing if collagen synthesis and collagen lysis can be manipulated one against the other.

VITAMIN A AND CORTISONE

An unexpected but practical advance in wound healing occurred when Ehrlich discovered that vitamin A could overcome the antagonistic effects of cortisone on wound healing. Other investigators had shown that cortisone given within the first few days after injury decreases wound strength approximately 30 percent at seven days. Cleanly incised and primarily repaired wounds will usually heal even in the presence of cortisone. However, if any complication occurs and the wound is opened, it is extremely susceptible to the effects of cortisone. Almost all surgeons have seen indolent open wounds in patients taking cortisone. Ehrlich and his associates demonstrated in 1968 that vitamin A would restore wound strength to normal despite the use of healing-impairing doses of cortisone in rats.[16] The experiment was based on the hypothesis that cortisone's depressant effects on healing might be the result of the well-known tendency of this agent to stabilize lysosomal membranes, thereby inhibiting some lysosomal enzyme systems. Since vitamin A has the opposite effect on the lysosomal membrane, it was postulated that vitamin A might reverse the depressant actions of cortisone on healing. The findings demonstrated the antagonism but did not prove or disprove the lysosomal hypothesis. Both topical and systemic vitamin A have been used successfully in humans to accelerate the healing of cortisone-retarded open wounds. The investigators warned, however, that systemic vitamin A might antagonize the effects of cortisone elsewhere as well as in the wound and urged caution in the use of systemic vitamin A in patients who are using cortisone to suppress an inflammatory process. Despite the fact that the mechanism is not firmly established, this appears to be a practical advance in the management of nonhealing wounds (Fig. 3).

ZINC DEFICIENCY

Pories et al. demonstrated that zinc is an important element in healing[17] and found that zinc sulfate given by mouth accelerated healing in pilonidal wounds in humans. There is some disagreement as to whether this is an acceleration of

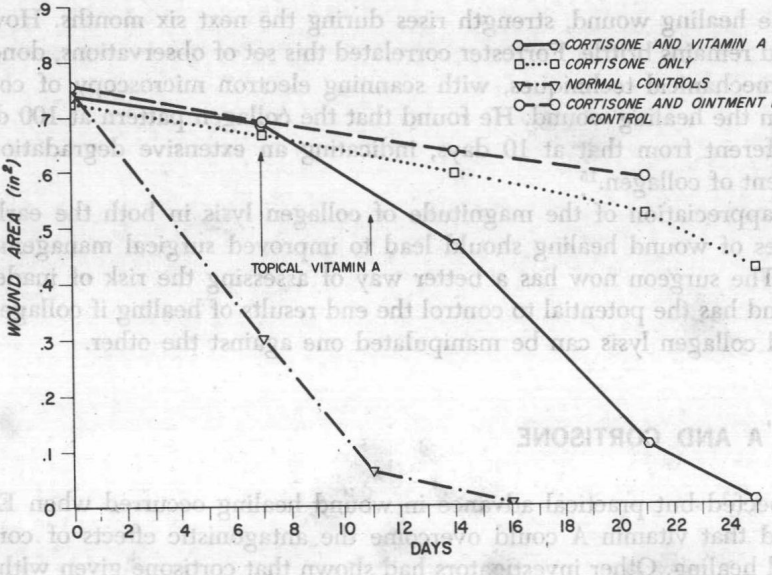

Fig. 3. After healing of open wounds was clearly retarded by systemic cortisone, topical vitamin A was applied to the wounds denoted by the solid line. They promptly started to heal normally despite the continued administration of cortisone. In this experiment, 4 wounds were made in each animal and only 2 were treated with vitamin A. Therefore, each animal served as his own control. The end result of topical vitamin A therapy in a cortisone retarded wound was an increased rate of epithelization with little change in contraction.

normal healing or the restoration to normal of healing depressed by zinc deficiency. Despite this disagreement, however, the recognition that zinc may be important in wound healing is important. Subsequently Pories has measured serum zinc levels in patients with indolent wounds.[18] He demonstrated that if the zinc level was below 100 μg percent and there was no other apparent reason for indolence, such as cortisone administration or ischemia, the wound eventually healed when zinc sulfate (220 mg) p.o. t.i.d. was given.[18]

CLOSURE TECHNIQUES

Most clinicians who have studied wound healing agree that the most secure closure, at least of the abdominal wound, is accomplished by placing wide, stout fascial sutures well back from the wound edge. This type of closure, of course, has been used by some surgeons for many years. This technique goes against the traditional Halstedian principle of many small sutures placed close to the wound edge. Perhaps the best demonstration of why the wider sutures are superior was given by Adamsons et al., 1966. They found that in normal wounds collagen is actively lysed for a distance of approximately 5 mm back from the wound edge.[19] This area then becomes weaker, and if collagen synthesis does not take place, sutures in this area are likely to pull through. The obvious disadvantage of wide suture closure is the tendency for an inexperienced surgeon to tie the