ANNALS OF SURGERY

VOL. 112 OCTOBER, 1940 No. 4

TRANSACTIONS

OF THE

AMERICAN SURGICAL ASSOCIATION

MEETING HELD IN ST. LOUIS, MO.

MAY 1, 2, 3, 1940

ADDRESS OF THE PRESIDENT

THE CRITICAL LATENT OR LAG PERIOD IN THE HEALING OF WOUNDS*

ALLEN O. WHIPPLE, M.D.

NEW YORK, N. Y.

THIS GREAT HONOR of election to the presidency of the American Surgical Association is deeply appreciated, especially when I consider the character and ability of my predecessors and the standing and attainment of you, my colleagues, who have conferred upon me this durable distinction.

It seems strange that in the more than half century of the life of this Association, 50 years of the greatest advances in the history of surgery, none of the Presidential Addresses have dealt with the subject of wound healing. Was it because it was considered an old, commonplace subject of insufficient interest to surgeons? Rather, I believe, it was because the subject presented many poorly understood biologic factors and controversial points of technic which made those, who had been chosen by their associates to preside over their meetings, hesitate to present such an everyday topic. This makes my temerity the greater in attempting to present a certain phase of the subject before such an experienced and critical group of surgeons.

I have chosen this topic—the lag period or phase of adjustment in wound healing—because it is the critical period of repair in which is initiated the sequence of definite processes leading to the fibroplastic fusion of the wound surfaces, and because this sequence may be helped or hindered by the surgeon in his management of the patient and of the wound.

* Delivered before the American Surgical Association, May 1, 1940, St. Louis, Mo.

Wound repair is preeminently a surgical problem. As surgeons, we treat accidental wounds—and we make wounds. We should, therefore, be particularly interested in their optimum repair and the part we may take in accelerating or retarding the reparative process. As teachers in medical schools, and as senior surgeons in leading hospitals, our example and our interest in wound repair play a major part in the sound basic training and apprenticeship of the younger attending surgeons and residents who will follow us in handing on the fine traditions of American surgery.

Wound healing is a composite biologic phenomenon which conforms, in general, to the laws of growth. The processes involved interact with one another, but each shows quantitative variations, depending upon the tissue involved in relation to the conditions present in the wound. The three most important processes involved in wound repair are: (1) The ameboid movement; (2) the mitotic proliferation; and (3) the maturation of the cells engaged in the fusion of the wound surfaces. But before ameboid movement and mitotic proliferation can progress, certain activities in the wound space and the bordering tissues of the wound surfaces must first be completed. These activities take place during the latent or lag period. Their extent and relative interaction are determined by both local and systemic conditions.

The local factors are: (1) The amount of killed or damaged tissue in the wound surfaces; (2) the vascularity of the tissues involved. The more abundant the capillary bed the more rapid the repair; (3) the integrity of the blood flow to the damaged tissue. This determines the nutrition and viability or the necrosis of the tissues bordering on the wound surfaces; (4) the amount and character of the exudate in the wound space and in the tissues bordering the wound; (5) the number and character of infectious organisms in the wound space and the bordering tissues; (6) the number and character of foreign bodies to be extruded or encapsulated.

The systemic conditions which determine the duration of the lag period and which have a profound influence on one or more of the local factors are: (1) The age of the tissues, whether they are adolescent, normal adult or senescent and degenerated; (2) the state of normal hydration. Dehydration or overhydration of the tissues is determined by the water, electrolyte and protein balance in the blood, and may profoundly alter the conditions in the wound surfaces and the wound space contents; (3) normal nutritional balance. Protein deficiency retards, high protein diet accelerates wound healing. Fat heals slowly. A high fat diet prolongs the repair of wounds; (4) vitamin balance. It has been definitely shown that both C avitaminosis and C vitamin deficiency prolong the lag period because of the essential rôle of vitamin C in the formation of intercellular substance and the maturation of the fibroblast and the transformation of fibrous to collagen fibers; (5) the state of the general circulation and blood picture. Poor circulation and severe anemia definitely alter or delay wound healing.

In the study of wound healing the least complicated sequence of reparative processes is seen in the cleanly incised wound made and closed with

the strictest aseptic, atraumatic and hemostatic technic. For this reason such a wound is of the greatest interest to both biologist and surgeon. In such a wound the lag period of four days is uniform provided there are none of the systemic deleterious factors present. The initial escape of blood and plasma is minimal, the formation of a fibrin mesh from the plasma is not unduly delayed by the necessity of elimination of much dead tissue by autolysis, heterolysis, and phagocytosis, and the excessive exudate of bacterial and foreign body reaction does not widely separate the wound surfaces. The quiescent period of agglutination of wound surfaces by a thin layer of fibrin in such a wound is short.

Whether there is a definite initiation of the ameboid movement of new connective tissue cells by growth stimulating substance elaborated by freshly damaged cells is not yet proven. Some 20 such activating factors have been described. Certainly, in tissue cultures it has been shown by Carrel and his associates[1] that embryonic tissue juice stimulates cell growth. Products of cell destruction are considered by many workers to have a stimulating effect on the reparative process. Baker[2] considers glutathione and hemoglobin to be the stimulating substances in fibroblastic proliferation. Hammett[3] claims the sulphydryl radical as the essential effective stimulus to cell proliferation in wound repair. Von Gaza[4] believes that the inadequacy of oxygen supply and other nutritive substances in the ischemic border or plane in wounds leads to a tissue hunger which initiates cell division and ameboid activity of fibroblasts and endothelial buds.

The destructive or lytic phase by which dead tissue is removed is succeeded by ameboid movement into the fibrinous zone of fibroblasts, derived not from the adjacent fixed tissues but from the wandering connective tissue cells, fibroblasts, polyblasts and histocytes. At this time mitotic proliferation of these mesenchymal connective tissue cells is accelerated.

Leo Loeb[5] has emphasized the importance of two processes in this stage of the lag period connected with the ameboid movement and proliferation of the invading fibroblasts. The first is the phenomenon of stereotropic response of growing cells to surfaces. Fibroblasts in contact with fibrin strands or fibrils have a strong tendency to elongate and grow along the fibrils, just as epithelial cells show ameboid movement along plane surfaces of granulation tissue or beneath the scab. The second reaction is a centrifugal force which directs the cells away from their own tissue and into the plasma mass in the wound space. This induces various kinds of cells, including fibroblasts, to move into blood clot in a fan-like manner to take part in the organization of the clot. Similarly, endothelial buds show a centrifugal growth into the organizing fibrin with a spread of the vascular bed and thus enter into the formation of granulation tissue.

These reactions may be considered essentially the reactions of cells to foreign bodies. Surface changes in cells lead to agglutination and occur in response to the stimuli which may well be due to differences in electric poten-

tial. Ameboid movements, phagocytosis and giant cell formation represent different manifestations and degrees of the same reactions.

With the maturation of the fibroblasts and their elongation along the fibrin fibrils uniting the wound surfaces, and the development of collagen fibers from the elongated fibroblasts, there takes place the change from the lag period of no appreciable tensile strength in the wound to the second phase of wound healing, the period of fibroplasia, characterized by a sudden and rapid increase in tensile strength. Harvey and Howes,[6] in their many contributions to the study of the tensile strength of wound repair, have established wound healing on a firm physiologic basis and have given surgery the soundest and the simplest rationale for the management and technic of wound repair. For the tensile strength of the wound is what really matters, both in the rapidity and permanency of its accomplishment.

From the practical surgical standpoint the lag period is the interval between the receipt of the wound and the beginning of tensile strength, during which time the wound surfaces have to be held together by mechanical means, by sutures, by splinting, or by constantly maintained pressure. These measures must be carried out with the least damage to the wound surfaces and bordering tissues, maintenance of maximum nutrition, adequate blood supply, minimum foreign body reaction, and maintenance of rest by immobilization of the damaged tissues. This is the period of wound repair where the surgeon can contribute constructively or destructively by the intelligent employment of his art.

It is in his efforts to insure and maintain wound repair that the thoughtless surgeon makes his most common mistake by suturing the wound edges and individual layers too tightly—and with suture material out of all proportion to the holding strength of the tissues. Anyone who has studied the vascular bed of the peritoneum or of muscle by micromanipulation technic is aware of the minute amount of pressure necessary to obstruct or obliterate the blood flow in the capillaries and the arteriovenous channels. Undue tension in the sutures will cause wide zones of anemic, even ischemic tissue, thus prolonging the lag period, by increasing the lytic process in the wound.

In no field of surgery is this factor of tension ischemia better illustrated than in intestinal anastomosis. Fortunately the peritoneal layer, because of its very rich capillary bed, is the surgeons', as well as the patients', best friend. The recent introduction of the Miller-Abbott tube as a preoperative measure in resections of the small intestine and in right-sided colectomies, has reduced the mortality following these major procedures 50 per cent—all due to the fact that the bowel is deflated before and after the anastomosis, thus removing that ominous factor of tension.

It is in the understanding of the systemic factors of wound healing that the most recent advances have been made. In this field the science of surgery adds immeasurably to the art of wound repair. Attention is called to these factors outside of the wound in the management of repair.

(1) *Age Influence.*—Clinically, it has always been known that wounds

heal more rapidly and firmly in the young than in the old. DuNoüy[7] demonstrated a faster rate of wound healing in young animals, and Howes and Harvey[8] found in young rats an earlier onset of fibroplasia, a lessened retardation, and an earlier termination of the process. It becomes the more important to maintain tissue nutrition and avoid the local deleterious factors of infection and foreign body reaction in repairing wounds in the old patient and in senescent, poorly nourished tissue.

(2) *Normal Fluid Electrolyte and Protein Balance.*—The symposium that is to follow this address is evidence of the interest of the surgeon of to-day in this exceedingly important factor in tissue metabolism and tissue repair. Overhydration may cause as serious disturbance in wound healing and prolongation of the lag period as dehydration, for edema definitely delays the onset of fibroplasia. Extreme degrees of dehydration, as seen in prolonged or severe fluid and electrolyte loss, deplete intercellular fluid and may disturb the intracellular salt and fluid balance, which will threaten not only local wound healing but the individual himself. Methods, now perfected, for determining fluid and salt balance are essential in following the course of patients operated upon after, or with severe fluid loss from hemorrhage, fistulae or prolonged increased temperature. These same determinations of hematocrit and plasma specific gravity and acid-base ratio should be determined in order to avoid overhydration.

Protein deficiency, seen in hypoproteinemia, may be caused by prolonged protein starvation, or protein loss following hemorrhage, inflammatory exudate or fistula drainage. Hypoproteinemia, because of the reduced large molecular content of the blood, results in fluid loss from the capillary bed into the intercellular spaces and intercellular edema. Ravdin[9] and his associates have demonstrated abdominal wound disruption in over 70 per cent of dogs operated upon in the presence of hypoproteinemia. The wound edges in periods after wound closure were soggy with edema and, in some instances, showed no evidence of fibroplasia at the seventh and fourteenth days. The wound surfaces were held together only by the silk sutures employed in the closure. In wounds sutured with catgut only the knots were left; in others no remnants of catgut could be found. Unfortunately, we have all noted this same picture in disrupted abdominal wounds in depleted patients. It is essential to determine the blood protein level in the cachectic or depleted individual before operation and to precede surgery with measures directed toward raising the protein content to normal. Plasma transfusions and, whenever possible, because more effective, the Miller-Abbott tube should be employed for administering split-protein products which the patient cannot take by mouth.

(3) *Normal Nutritional Balance.*—Protein maintenance, aside from its effect on intercellular fluid, is necessary to provide cellular nutrition. The manner in which tissues obtain their nitrogen and build up their new protoplasm still remains a mystery, but the fact is that tissues in the wound require protein as well as the tissues elsewhere. Clark[10] was the first to study the

effect of diet on the healing wound. It is interesting that the type of diet employed influenced the total period of healing proportionately as it affected the latent period—a high protein diet eliminated the lag period, whereas a high fat diet prolonged it to six days.

Herrmannsdorfer[11] claimed that an acid diet exerted a marked effect in hastening wound healing, on the ground that bacterial growth is inhibited; whereas on an alkaline diet the wound swarmed with bacteria, and was accompanied with a foul exudate. Reimers and Winkler[12] produced an acidosis in dogs, through the administration of ammonium chloride, and found a definite shortening of the period of wound healing.

(4) *Vitamin Balance.*—Of the enormous amount of research undertaken to establish the rôle of the many vitamins in tissue metabolism, two vitamins have emerged as being of special significance in relation to wound healing.

Vitamin C.—It is now well-established that intercellular substance in general, and especially in the capillary bed, and the collagen of all fibrous tissue require ascorbic acid for their production and maintenance. Höjer[13] found an atrophy of connective tissue in scorbutic guinea-pigs, and was the first to call attention to a general deficiency in collagen formation. Wolbach,[14] in this country, has confirmed these findings and has shown that ascorbic acid is intimately concerned with the synthesis and maintenance of intercellular supporting substance. This is of special significance in the capillary bed where lack of or deficient intercellular cement substance results in hemorrhage into the wound space and in the bordering tissues prolonging the lag period. Lanman and Ingalls,[15] and Taffel and Harvey[16] have shown by animal experiments that not only C avitaminosis but partial vitamin C deficiency causes a prolongation of the lag period and delays the return of tensile strength because of insufficient collagen fiber formation.

Methods of determining vitamin C in the blood are still inaccurate and are being refined. This accounts for the conflicting reports by workers in this field. There is still some uncertainty as to the length of time man can remain C-vitamin depleted before showing signs of scurvy, but the rôle of vitamin C in the formation of intercellular substance and collagen seems definitely established.

It is the partially deficient vitamin C state that is seldom suspected or anticipated. Holman[17] found that 44 per cent of the "run of the mill" patients in the Stanford-Lane Surgical Clinic wards were deficient in vitamin C—and this in the land of the Sunkist orange. Of 34 patients admitted to a London hospital,[18] 14 showed evidence of vitamin C deficiency. All those above 70 years of age showed relative deficiency. It was also found that patients admitted for peptic ulcer therapy showed no vitamin C deficiency, but four days of a strict ulcer dietary regimen resulted in a deficiency of vitamin C. This is a most important consideration in the preparation of patients, with ulcer or carcinoma, who have been on rigid diets, such as the Sippy regimen. They should regularly be tested for blood vitamin C content and not operated upon until the deficiency is corrected.

Vitamin K.—This more recently studied vitamin has a very essential rôle in the control of hemorrhage in relation to prothrombin deficiency. Of special significance, and life-saving, is the employment of vitamin K with bile salts in jaundiced or acholic patients. This is so well-known now that it is generally administered in all clinics. Jaundice is the warning signal to the surgeon for vitamin K therapy.

(5) *Circulatory Imbalance and Anemia.*—With present day methods for determining cardiac output and myocardial efficiency, the cardiovascular competence can be definitely determined before operation, and with direct donor transfusion or bank blood transfusion there is no excuse for operating upon markedly anemic patients. Hematocrit and blood plasma determinations have added tremendously to the scientific care of anemic and depleted patients before, during, and after operation.

The lag period is universal as a growth phenomenon. It is seen in plant, fungous and bacterial growth, as well as in the growth of cells in the repair of wounds. Because it is the interval during which the wound surfaces are held together by measures other than the natural body tissues and provided by surgical technics, this period is the surgeon's concern. Another most important rôle of the surgeon is in keeping the wound clean. When infection gains a footing the destructive stage of the lag period is prolonged or made to recur, with a corresponding delay in the fibroplastic phase. The destructive phase of the lag period due to infection is the dangerous period. In the presence of certain bacteria, such as the *Beta* hemolytic streptococcus or the colon group, the newer sulphonamide group of chemotherapeutic drugs prevent or shorten wound infection before the limiting pyogenic membrane prevents the diffusion of the drug by the blood stream. Local application of the crystals of these drugs promises real results in the control of bacteria in areas walled-off by pyogenic membrane or fibrinopurulent adhesions. These drugs *per se* do not hasten but rather seem to delay normal primary wound healing according to Bricker and Graham.[19]

Every true surgeon cannot help being interested in wound healing. The problems presented in the repair and management of the wound call for all the science as well as the art of surgery, especially in relation to the critical lag period of wound healing. The art of surgery, based upon the necessity for preventing tissue damage and foreign body reaction, consists of the aseptic and hemastatic use of sharp knife dissection, delicate instruments and fine suture and ligature material that is not more than twice as strong as the holding tissues. We can do this much at least in not making the lag period the dangerous period in wound healing.

REFERENCES

[1] Carrel, A.: Jour. Exper. Med., **15**, 516, 1912.
[2] Baker, L. E.: Jour. Exper. Med., **49**, 163, 1929.
[3] Hammett, F. S.: Proc. Am. Phil. Soc., **68**, 151, 1929.
[4] von Gaza, W.: Beitr. z. klin. Chir., **110**, 347, 1918.
[5] Loeb, L.: Jour. Med. Res., **41**, 247, 1920.

[6] Harvey, S. C., and Howes, E. L.: ANNALS OF SURGERY, **91**, 641, 1930.
Howes, E. L., and Harvey, S. C.: Yale Jour., Biol. and Med., **2**, 285, 1930.
[7] DuNoüy, P. L.: Compt.-rend. Soc. de biol., **109**, 1227, 1932.
[8] Howes, E. L., and Harvey, S. C.: Jour. Exper. Med., **55**, 577, 1932.
[9] Thompson, W. D., Ravdin, I. S., and Frank, I. L.: Arch. Surg., **36**, 500, 1938.
[10] Clark, A. H.: Johns Hopkins Hosp. Bull., **30**, 117, 1919.
[11] Herrmannsdorfer, A.: Deutsch. Ztschr. f. Chir., **200**, 534, 1927.
[12] Reimers, C., and Winkler, H.: Deutsch. Ztschr. f. Chir., **241**, 313, 1933.
[13] Höjer, J. A.: Acta Paediat., **3**, Supp. 8, 1924.
[14] Wolbach, S. B.: Am. Jour. Path., **9**, 689, 1933.
Idem: J.A.M.A., **108**, 7, 1937.
[15] Lanman, T. H., and Ingalls, F. H.: ANNALS OF SURGERY, **105**, 616, 1937.
[16] Taffel, M., and Harvey, S. C.: Proc. Soc. Exper. Biol. and Med., **38**, 515, 1938.
[17] Holman, E.: Surg., Gynec. and Obstet., **70**, 261, 1940.
[18] Holman, E.: *Loc. cit.*
[19] Bricker, E. M., and Graham, E. A.: J.A.M.A., **112**, 2593, 1939.

A most comprehensive and discriminating review of the subject "Wound Healing," including a very comprehensive bibliography, has been written by Leslie B. Arey, which is to be found in Physiol. Rev., **16**, 327–406, July, 1936.