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Factors influencing wound healing

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INTRODUCTION

I offer no apology for what might seem to be undue emphasis upon subjects with which every surgeon is assumed to be familiar. No doubt the surgeon is well aware of the older, more fundamental principles of wound healing, but his interest in the perfection of some technique, the most effective use of a particular suture, the efficient sterilization of the air in the operating room, and similar items, often results in his neglect of these underlying principles. Leonardo da Vinci said: "He is a poor master whose work surpasses his judgment; he alone is advancing toward the perfection of his art whose judgment surpasses his work."

The ambition of every surgeon is to see all wounds which he has treated, whether surgical or traumatic, heal cleanly, rapidly, and with minimum discomfort to the patient. There are many factors which may influence the course of tissue repair, most of which are under the control of the surgeon, if he but recognizes them and understands the manner in which their influence is exerted.

For purposes of discussion, these factors have been arranged in groups--those dependent upon surgical technique, antiseptics, suture materials and suture

technique, plasma proteins, vitamins, and associated miscellaneous factors, and will be discussed in that order.

The mass of literature now available is too great to warrant a review of all of the complications. Methods of treatment of wound infections complicating healing will be avoided except those methods which seem to illustrate the application of a factor or of factors directly influencing the process of healing.

The term "clean wound", as used in this paper, indicates wounds made by a sterile instrument or an object considered clean, and which are treated immediately. "Contaminated wounds" are those in which organisms are known to be present, and are treated within six to eight hours after injury. Wounds not treated until eight hours or longer after injury are considered either infected or clean, depending upon the subsequent course. Healing by "Primary Intention" indicates healing a wound without delay and without infection. Healing by "Secondary Intention" is used to indicate healing following an infection and drainage which has been overcome, while a wound which is left open for a few days and then sutured is said to heal by "Third Intention."

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NORMAL WOUND HEALING

The normal repair process has been better understood in all of its phases since the exhaustive review presented by Arey in 1936. The meticulous work of Carrel (25) furnished the impetous which resulted in research and the modern conception of the process of wound healing.

The process of regeneration or healing is apparently initiated by some external as well as internal factors. This was postulated by Carrel in 1921 (23) after he had shown that wounds protected by non-irritant dressings such as connective tissue, showed no signs of granulation tissue or contraction for as long as 25 days, while irritants such as turpentine, staphylococcus and acids reduced the latent period to as short a time as 2 days or less. Burrows (21) suggests that the reaction of growth in the wound is not for the purpose of healing, but merely the result of crowding of the cells and stagnation of the environment because of the damage to blood vessels and the inflammatory slowing of circulation locally.

Later investigators, McJunkin and Matsui (86) seem to corroborate Carrel's work, but are even more specific. In their experiments with macerated fetal tissues

applied to wounds, they found that homologous macerated fetal epidermis stimulated epidermal regeneration in the wound, while other fetal tissues had no effect. This, they believed, indicated the presence of a growth-promoting substance specific for epidermoid cells.

Carrel (25) divided the process of wound repair into four periods or stages: the quiescent period, the period of granulous retraction, the period of epidermization, and the cicatricial period.

During the quiescent period, when the dimensions of the wound do not change (25), there is in reality great activity which is not evident superficially. This period lasts from the time of resection until the beginning of granulous retraction. Immediately after the wound is produced there can be noted three zones relative to tissue injury. The first zone includes the region in which the tissue is destroyed directly by the wounding agent. The second zone is that next remote layer whose tissues are subject to traumatic necrosis, the extent depending upon the type of trauma inflicted. In the third zone, seen in severe tearing wounds, the tissues are subjected to molecular violence and the constituent cells experience injury of a sort that may lead to necrobiosis, although many of the cells of this region are

able to recover and participate in regeneration. The fact that the first zone is not surrounded with a zone of tissue of full vigor is of importance in the process of repair.

Signs of inflammation become apparent, with localized redness, local edema with thickening of the edges, cellular infiltration and an outpouring of exudate. This inflammatory process is a protective one, as well as a necessary step in the reparative process. Lymph and blood cover the surface of the wound and fill the interstices of the traumatized tissue, leucocytes migrate into the exuded blood and devitalized tissue and soon a framework of fibrin is laid down, (54, 5, 55, 32).

Due to tissue enzymes and the action of leucocytes, blood and devitalized tissues are digested or removed by a process of phagocytosis (5). If the amount of devitalized tissue is great, it will be separated from the living tissue by this process of traumatic inflammation and cast off much in the same fashion as a gangrenous toe is separated by the formation of a line of demarcation.

The constructive phase of wound healing begins before the destructive one ceases. In 1910, Hertzler (54)

and later Crossen (32) after studying wounds in the peritoneum came to the conclusion that the chief process in wound healing is the formation of fibrous tissue, while the formation of the higher types of tissues is less important.

Coincident with the digestion and separation of dead tissue, new cells make their appearance in the reparative region. These new cells are of the connective tissue type and may be classified as the mesenchymal, ameboid, fixed macrophages and fibroblasts (5). Maximow (91) has studied these cells and offers some interesting observations. He believes that the mesenchymal cells are embryonal and undifferentiated, resembling fibroblasts. They are usually distributed along the blood vessel walls, especially the capillary walls, and will form new cell types when they are stimulated. The ameboid cells are in the main derived from the blood stream, but some may originate in the mesenchymal tissue of the region (5). These cells are identical with the lymphocyte. The plasma cell, granular leucocyte and mast cells are modifications of ameboid cells. The fixed macrophages are reticuloendothelial cells and have characteristic staining properties in that they take an acid aniline dye. The fibroblasts

are differentiated from the mesenchymal tissue and are supposed to produce white connective tissue fibers in the vicinity of the wound. Baitsell (5), however, believes that the fibers are not different tissue, and are not formed intracellularly. He found the staining reaction to be the same as that of fibrous connective tissue--in other words, the fibers are merely a transformation of the original fibrin network, as suggested by Hertzler (54).

Accompanying this fibroblastic proliferation, the capillary endothelium is likewise stimulated to proliferate. New endothelial buds may be identified growing out from the vessel walls, and accompanying the connective tissue cells, forming a new blood supply to the inflammatory zone.

When the devitalized tissue has been extruded, the base and edges of the wound appear pink and have a finely granular appearance, which is the granulation tissue. Each granule consists of a capillary loop or vascular tree covered with new cells of the type described. The sheet of granulation tissue thus provides a cellular protective membrane to the injured body surface which has hitherto been covered by a fibrinous layer produced through the coagulation of the wound secretion. It has

been shown that this is a real protective layer by Bilroth (28) and DuMortier (35). Arey further states: "In short, granulation tissue presents the ideal condition for defense against infection; this includes marked hyperemia, active exudation, local leucocytosis, and young vigorous component cells which lie snugly together and have not yet elaborated paraplastic products."

It is by this process of granulation tissue formation that the wound defects are bridged, the process varying upon factors such as the size of the defect to be bridged, the presence of infection and extrinsic elements to be discussed later. The whole process requires two to three days. Carrel (25) says that the contractions draw the edges of the wound in, rapidly at first, then more slowly until the wound is 10 to 15 mm. across. The contractions are greater and more rapid in larger wounds. The rate of reparation of the contraction period is directly proportional to the size of the wound. This period ends with the beginning of epidermization.

Epidermization begins as soon as a base for the support of the epithelial tissue is available. This is the chief factor in determining the time and place of

the union of the epithelium of the two sides, according to Hartwell (49). Carrel (25) believes that epidermization begins only when contraction has drawn the edges down to within a distance of 10 to 15 mm. apart, and that the rate of epidermization is inversely proportional to the dimensions of the wound. He has shown that the process begins at the point where the wound edges are closest together. Living cells of normal epithelium are potentially amoeboid, and cover the healing wound by extension of a thin membrane of cells derived from the prickle cells of the two sides, which ultimately unite(49). According to Hartwell (49), mitosis occurs secondarily and late in the process, indicating a rearrangement and multiplication of the cells of the membrane after the wound is covered. The new basement membrane is formed from the lower cells, and is not an extension from the old basal layer.

The scar tissue is early rich in cells and blood vessels and comparatively poor in fibrils, during the time the scar is pink and elevated. As the process ages, the structure becomes poor in cellular elements and rich in fibrils. As a result of the mechanical constriction of the blood vessels, it becomes pale in color. This is the cicatricial period of Carrel (25) which begins as soon as epidermization is complete. Carrel found that the scar of a large wound is comparatively smaller

than that of a small wound, because the contraction is greater and epidermization begins later, (25).

SURGICAL TECHNIQUE

After analyzing the healing of wounds of some 3,000 cases reported in the literature, Goff (45) stated that "the important predisposing causes of non-union are absorbable suture, trauma and poor technique, while the principle exciting cause is infection." The former is yet a debatable question, and is discussed more fully in another part of this paper. The remainder of his statement may be logically and correctly considered as poor technique. However, these and other items will be discussed individually, though somewhat briefly.

The importance of the location of the incision has been considered and understood by surgeons since the anatomy of the blood and nerve supply to the tissues was first discovered. It is such a simple matter and its importance so easily understood, that it is just as easily forgotten in the press of other important considerations arising at the time of operation. Recently, the anatomic incision has been studied more fully by Singleton and Blocker (117), Mason (90) and Howes (62). They believe that consideration of the direction of tension upon the tissues is of equal importance. Cutting across fascial fibers makes suturing difficult, the sutures tear out more easily, and healing of the wound is delayed. This, they believe, is especially true in abdominal incisions involving the posterior sheath of the rectus muscle.

Gentleness in the handling of tissues was advocated by Pare (97) and is still emphasized by modern authors (90, 34, 38). Trauma to the subcutaneous tissue at operation, from rough handling of the tissues and blunt dissection, careless ligation of superficial vessels, rough use of retractors or undue tension exerted by stay or tension sutures, is considered to be the cause of serum collections in clean wounds. There will be greater sloughing and serum collection following the use of strong antiseptics, according to Reid (106) and Whipple (139). A late observation on the use of sulphanilamide locally indicates that it seemingly results in greater serum outflow from the wound, (Bricker and Graham, 17).

The problem of infection is as old as surgery itself. The many sources of contamination of the surgical wound from the time of incision to complete healing have been repeatedly enumerated by the various authors in their discussions of imperfectly healed wounds. Eliason and McLaughlin (38) state that in the vast majority of cases pathogenic organisms gain access to the wound by implantation, either from the outside at the time of operation, from septic material at the time of operation or from faulty technique during the postoperative care of the wound. Mason (90) believes that the

problem of infection is considered at the expense of other equally important factors, and emphasizes the fact that prevention is not synonymous with antiseptics, which is a mistake commonly made. He states also that every wound is contaminated, and that infection will depend upon disturbances in wound healing, and is not the cause.

It is rarely possible to trace an infection to the drapes, instruments, suture material and gloves since their sterilization has approached perfection. The preparation of the operative field has been practically standardized to the extent that a thorough cleansing with soap and water prior to operation, followed by the single application of an antiseptic is accepted as adequate. Ives and Hirshfeld (70) cultured a series of wounds during operations and found that all were contaminated, and showed that postoperative infections were largely caused by the same organism found in the wound at operation. Most of these organisms could be found on the skin of the patient and in the operating room air. In this respect, Cox (31) and Van Alstyne (133) have shown that a scalpel may carry organisms from the skin into the deeper tissues of the wound.

Meleney and Stevens (92) have called attention to the role played by streptococcic carriers in the

production of wound infections. These authors found that one-third of the operating personnel were harboring the hemolytic streptococcus in their throats. They suggest that both the nose and mouth of all of the operating team be adequately covered to protect against this source of wound contaminations. It is common in some hospitals to see the surgeon and his assistants masked and gowned completely, while the unmasked anesthetist peers and talks over the screen into the wound. It has been suggested that the patient be masked, especially in such operations as a thyroidectomy.

Mass ligation and excessive use of suture, both in size and in number of stitches, are pointed out by Mason (90), Howes (62) and Carstens (26) as causes of infection and faulty healing. The latter author recommended the use of flamed adhesive tape in closing abdominal wounds to avoid the use of subcutaneous and skin sutures. Eliason and McLaughlin (38) report that a special effort was made on their service at University of Pennsylvania Hospital to reduce the amount of catgut used in subcutaneous tissues. All small bleeding vessels have been ligated with a single tie of No. o plain catgut, using flat knots only on larger vessels. The use of a subcutaneous stitch for

approximation of this layer has been largely obviated by employing a deeply placed vertical mattress suture of silk for the closure of the skin and subcutaneous tissues. The results have been more than satisfactory.

In a discussion of surgical knots and sutures, Taylor (128) states that "regardless of the type of suture, the knot is the weakest point". He demonstrated the swelling and loosening of knots tied in catgut suture and placed in moisture. He also showed that knots tied in treated silk suture will slip when tension is applied. Both Taylor (128) and Howes (63) believe that the triple-throw knot, with all of the throws tied square is the best all-purpose knot.

DuMortier (35) has shown that the surgical wound is most susceptible to postoperative infection during the first six hours after closure. After this period the wound is progressively less susceptible to infection. He was unable to demonstrate any decrease in the resistance of the wound to infection on the fifth or sixth day when the skin sutures were removed.

The technique which was developed by Koch for the treatment of contaminated wounds (74) revolutionized this particular phase of surgical procedure. Briefly, his directions are: first, cover the wound

with sterile gauze, then with cleansed hands or wearing sterile gloves, and using sterile sponges, wash a wide area around the wound gently but thoroughly with soap and water; finally, remove the gauze and wash the wound itself thoroughly with soap and water. If the wound is irregular and has deep pockets, this part is cleansed after the sterile linen is about the field, with the wound held open by means of sterile retractors. The excess soap is washed away with sterile water, and no antiseptics are used. He believes, and his results show, that this is all that is necessary to convert a contaminated wound to a clean wound.

The removal of foreign bodies, devitalized tissue such as skin flaps separated from the underlying tissue, avascular muscle, and shredded fascia, and hemostasis may be considered as one problem, since their presence or the presence of a blood clot within the wound forms an excellent culture medium. This was pointed out by Pare (97) in his teaching concerning necrosis and debris. In fact, surgeons before the time of Pare had found the removal of this material necessary. In an article entitled "Clean Wounds, Ancient and Modern", Professor G. E. Gask (43) tells of a book of surgery written by Henri de Mondeville (1260), in which the

methods and procedures sound startlingly modern. Of contemporary methods, de Mondeville said, "By this method more patients die than recover, and of those who survive, the treatment is prolonged by three months". His own instructions were: "Do not probe wounds. Remove all foreign bodies. Approximate the lips of the wound as much as possible and suture them if necessary. Foment afterwards with wine."

Strict adherence to the principle of hemostasis has led many a surgeon to sacrifice Pare's fundamental idea of the value of eliminating necrosis. Reid (106) states that carrying out hemostasis by means of ligation or cautery is a matter of individual judgment, in order to avoid excessive tissue damage.

Ellis in 1931 (39) reported that only 60 percent of electric knife skin wounds healed by primary intention, while 97.5 percent of scalpel wounds healed successfully. Spelman (123) found that wound healing was retarded in direct proportion to the efficacy of the electric knife in producing hemostasis. The layer of coagulum covering the wound surfaces prevents the appearance of the exudate and fibrin formation in the wound, which is so necessary for the first stage of healing.

Speed (121), out of his experience during the World War, pleads for prompt removal of foreign bodies to avoid long drainage, secondary sinus formation, secondary hemorrhages, and the psychologic reaction. Hertzler (55), Mason (90), Howes (67), Koch (74) and others are strongly in support of this statement.

The use of the drain has been a boon to the surgeon, but it is frequently over-used. Pare knew nothing of its use: his method of closing a "fistulous ulcer" was to "press out the filth contained in it, and begin binding at the bottom and gradually closing to the top" (97). Hertzler (55) asserts that a gauze drain is better because it produces more fibrosis, while a rubber drain results in a greater secretion, prevents healing, and of even greater importance, it keeps the vessels open with resultant secondary hemorrhage. Crossan (32) believes that the frequent removal and replacement of a drain is more injurious than its mere presence in the wound. The drain promotes the appearance of more lymph and leucocytes (hence fibrin) which is destroyed upon disturbance of the drain. In addition there is the danger of infecting the wound with new organisms, and of pressure necrosis. Howes and Harvey (67) denounce unnecessary use of drains, but they recommend them for

the release of tension and the protection of the sutures in infected wounds.

The question of dressings to be applied to the wound has been a major problem since the beginning of surgery. Various methods have been used, including lint, tents, balsams, coctions, salves--in short, anything to keep it draining (for suppuration was considered necessary to healing) and to heal the wound away from the air, (89, 37, 97). Theodoric instructed that the wound be cleansed with warm wine, and a bandage soaked in wine wrung out and applied, (43).

Pare's primary interest in bandages seems to have been to maintain the position of the wound edges, as suggested by his instructions for the use of sutures in "regions difficult to bind or bandage, such as the throat and belly", (97).

Nearly 75 years ago Bilroth showed the necessity of preserving intact the granulation tissue, as cited by Christopher (28). He demonstrated that pus-soaked dressings applied to intact granulation tissue had no effect, while a mere scratch in the granulations before applying the pus dressing resulted in infection, fever and drainage. This has been confirmed by DuMortier (35) in recent years. But despite this, the use of dry

gauze dressings frequently changed, which adhere to the granulation tissue and result in damage to the tissue when dressings are changed, is still common. The advent of non-adherent dressings, such as vaseline gauze applied to the wound, and in the wound as recommended by Orr (95), has been very beneficial. Sollman (120) and Beiter (8) proposed the application of liquid petrolatum directly to the wound, a thin film of cotton over this, and cover the whole with melted paraffin. The wound is then covered with a pad of cotton and a bandage applied. Their reasons for using this dressing were decreased pain at dressing changes, and a minimum destruction of granulation tissue. This method was recommended especially for large burns.

The pressure exerted on the wound by the dressing is another major item for consideration. Blair (14) states that the maintenance of a definite external surface pressure is essential to life, and to the proper functioning of the organs. Normal pressure, as maintained by muscle and fascial sheathes, influences the movements of the alimentary canal, the movement of blood through the tissues and similar functions. In a wound, this normal pressure relationship is disturbed, and artificial replacement should be provided. Gatch (44) shows that in addition to eliminating dead spaces and serving

as a harmless form of hemostasis, the pressure dressing reduces localized edema. His explanation is based on Starling's theory: the pressure in the tissue spaces is equalized with that of the pressure of the blood in the vessels, which then allows the osmotic pressure of the blood to withdraw fluid from the tissues into the blood stream.

In a paper published in 1934, Speidel (122) reported amazing results, which have not as yet been confirmed, with the use of a peptone broth preparation in non-healing, draining wounds. Sodium chloride and sodium hydroxide were added until the reaction was pH-7, which was non-irritating. The broth is applied in a saturated compress, by infiltration into the margins and base of the wound, or by irrigation. He had used this method in a number of cases, with no failures; one example cited was that of a non-healing wound of some four weeks' duration, which was healing in two days following treatment with the broth. He believed that the proteins act as antigens, stimulating the development of antibodies and the appearance of phagocytes both locally and generally.

Eliason and McLaughlin (38), after observing that herniorrhaphy incisions are particularly prone to become infected, suggested that possibly local anesthesia,

which is so commonly used in these cases, may serve as a predisposing factor by lowering the resistance of the tissues about the operative site. Burt and Gius (22) studied and reported their results on the use of prolonged local anesthetic in oil in abdominal wounds. They made abdominal incisions in cats, with and without infiltration. For infiltration they used plain almond oil and anesthetic in oil. There was no evidence to indicate that the injection of either plain or anesthetic oil increased the discharge with either silk or catgut suture, or that wound healing was delayed in any way.

They suggested the use of such an anesthetic to reduce the incisional pain and prevent abdominal wall and diaphragmatic splinting, thus lowering the incidence of pulmonary complications because of freer respiratory movements.

ANTISEPTICS

Antiseptics, as we know them today, are a product of the more modern world of science. Their need, naturally, was not recognized until the historic works of Leeuwenhoek, Pasteur, Koch and Lister. From that time until the present the "discovery" and development of solutions designed to kill bacteria on instruments and in the wounds has been one of the major activities in the field of medicine.

Reference to the use of substances to promote healing, or to promote suppuration, however innocently it was used or regardless of the purpose of the user, can be found in some of the earliest medical literature. It is interesting to note, however, that there have been periods of popularity followed by periods of rejection, just as has occurred in other medical fields.

The Edwin Smith Surgical Papyrus (37), estimated to have been written during the time of the pyramid builders, outlines the treatment of wounds in a manner remarkably similar to modern methods, but no mention is made of the use of any healing coction whatsoever. During the "Dark Ages", little is known of the Medical procedures. The dogmatism of Galen, 150 A.D., required suppuration for healing. Then in Salerno, Italy, in

1100 B.C., appeared the first medical school of modern history. This school taught the necessity of suppuration for the proper healing of wounds. During this whole period, then, the use of tents, balsams, probes, and ointments, and the sealing of wounds against the air, was the accepted procedure. The aim of the surgeon was to promote suppuration, poultice the abscess, and drain it. If the patient survived this, he might, with good fortune, recover and the wound would heal. In the eleventh century Theodoric and Henri de Mondeville recommended more moderate treatment, and advised against probing except for foreign bodies (43). But despite this, little change was seen. Even Ambroise Pare (1510-1590) poured boiling oil into wounds until he was forced, from lack of oil, to use a cold dressing consisting of raw egg-white with such improved results that he abandoned the hot oil. Parecelsus (1493-1541) decried the promotion of suppuration. He spoke of a healing balsam within the body which cured the wound, and implied that the surgeon should not do too much (43).

With the advent of Pasteur and Lister, and the era of carbolic acid, the search for germicidal substances began in earnest. And again, as with Theodoric and de Mondeville, in the midst of all the extolled virtues of various antiseptic and germicidal solutions,

Zeidler, Zeichel, Senger and Schimmelbusch (134) as early as 1893 to 1895 questioned the use and value of such agents in wounds. But such men and ideas were too much in the minority to exert enough influence to make themselves heard. Lister's study of carbolic acid and its germicidal properties naturally resulted in its use topically in the wounds themselves, in varying strengths. And, since hands, instruments were not sterilized, infections still occurred.

Then came Dakin's solution, and later the Daufresne modification of Dakin's solution, which was hailed as the ultimate in the treatment of infected wounds. It is still used in modern surgery, not with the idea of a germicidal action so much as to wash out the wound.

The World War furnished new impetous to research in the field of antiseptics. Wright (146) said that an antiseptic, to be rendered harmless to the tissues, must be deluted, and thereby reduce the antiseptic power, which at best are effective only on the surface. Also, the use of Iodine around the wound blistered the skin and opened the way for spread of the infection. Therefore, he proposed the use of hypertonic saline (5% solution) which he believed attracted water and albuminous

substances from the blood and deeper tissues to the surface of the wound. Also, he said, the leucocytes likewise attracted to the wound site disintegrated, releasing trypsin which digested the injured and infected tissue, and the remains were easily washed away by the incoming fluids.

This new development immediately aroused comment. It caused secession of many of the adherents of the old antiseptic school, partly because of the disappointing results of the antiseptics, and their failure to sterilize the wounds. However, there was little evidence, theoretical or experimental, indicating the use of hypertonic saline except Wright's work.

Soon after the appearance of Wright's articles, another Englishman, Taylor (129), refuted the hypertonic saline theory, on the following points: With the use of this solution, water would, he agreed, leave the cells. Also, the salt would enter the cell, according to the laws of osmosis, which, he conceded, would be removed by the blood and its effect therefore minimized. However, Wright had neglected to consider the effect of the protein content of the tissue cells, which would cause the cells to absorb water in proportion to the difference in the amounts of protein in the cells and

in the solution. This would, then, result in local edema; likewise, if the concentration of the solution were suddenly reduced, further inrush of water would occur and greater edema would result because of the high salt content of the cells. Then he added, with a final thrust, "trypsin will not act in a 5% saline solution."

Fraser and Bates (41) reported highly satisfactory results using Hypochlorous acid (Eusol) in irrigating wounds, both infected and wounds contaminated during actual surgery. He used a .5 percent solution, and alternated it with a hypotonic salt solution after the wound was granulated. O'Connor (94) in the next year, reported that Eusol caused eruptions in the surrounding skin. He recommended the use of a peroxide-carbolic acid solution in a strength insufficient to kill organisms instantly, since this would also damage the tissue cells. With this applied in four-hourly irrigations, he recommended also free drainage, hot fomentations, absolute rest on a splint, and a glass or two of stout beer or good wine with meals.

The use of salt tablets, wrapped in gauze, and packed into a wound which had been opened up and cleaned was recommended by Roberts and Stratham (109). The packs

were to be untouched for four to five days, when the wound was cleaned and redressed with a similar pack. After the second dressing, the wound was usually granulated and clean. No antiseptic was used. The salt pack was rejected by Wright (146) on the grounds that the concentration of the salt was quickly lost by dilution in the wound secretions. The rationale of this method could, of course, be confronted and disproved by Taylor's argument.

Carrel (24), with characteristic thoroughness, would seem to have ended the argument concerning hypertonic solutions when, after careful study, he stated that flushing of an aseptic wound with hypertonic saline or with distilled water resulted in immediate reinfection, and that neither modified to a measurable extent the rate of healing of an aseptic wound. However, a revival of the question in more recent times is the report of Taylor (127) in 1935. He made bilaterally symmetrical wounds in the superficial fascia of the abdomen of rabbits, and applied to them various solutions by means of a rubber cover fastened to the skin with rubber cement. He measured the amount of fluid withdrawn from the cover, and the amount of protein and salt in the fluid after contact with the wound for varying lengths of time. He concluded that the

protein content equaled only that which would normally diffuse from the wound, and that the wounds absorbed enough salt to maintain an edematous condition; that the increase of phagocytes at the wound site as a result of the inflow of water to the surface was still not definitely known; that the solution reached only the superficial and not the deeper infected tissues; and that isotonic and hypotonic solutions gave the same beneficial effects as hypertonic solutions. Hence, the results must be due to a poultice effect, rather than to the concentration of the solution.

Concerning the use of known antiseptic solutions in the wounds, little has been said. Reported studies of this phase of the question are surprisingly few. An ingenious experiment devised and reported by Bond (16) in 1916 is one of the earliest actual attempts to evaluate various substances with respect to their effect and influence on wound healing. Strings imbedded with indigo particles were buried in wounds, with and without the use of antiseptics. He also, by means of phagocytized indigo particles, studied the emigration of phagocytes from the blood vessels, the phagocytosis, and the immigration to the vessels. He concluded that antiseptics in moderate concentrations have less effect on the emigration and phagocytosis than many have

failed to effect significantly the processes of repair, and he stated as his conclusion that factors other than the local dressing appeared to play the dominant role in determining the rate of wound healing. The antiseptics failed to sterilize or to alter the cultural characteristics of any of the wounds.

Sager, Vedder and Rosenberg, (112) after making bilaterally symmetrical wounds down to the peritoneum in a series of dogs, contaminated both with a virulent broth culture of Staph. aureus. One wound in each dog was then held open, and an antiseptic was allowed to stand in the wound for 20 to 25 minutes, after which both wounds were closed and covered with collodion. They found that they were unable to improve the condition of the infected wounds, and that the antiseptic injured tissue, causing more drainage in those wounds. The experiment was done with tincture of metaphen, tincture of merthiolate, 2 percent aqueous gentian violet, and azochloramide.

There is apparently general agreement that strong antiseptics will result in greater inflammation and sloughing in wounds treated with them than will occur in those not so treated. Reid (106) and Koch (74) state that antiseptics have a definite value on the skin, but are not to be used in lieu of soap and water and

careful cleansing. He believes that upon fresh wounds they do more harm than good. Both Reid and Whipple (139) state that debridement is more important than any chemotherapeutic agent such as Carrel-Dakin solution and other antiseptic solutions. Reid (106) recommended washing the wound with normal salt solution before and after debridement, using soap and water when dirt and grease have been ground into the wound, while Koch (74) and Bisgard (13) use soap and water, and no antiseptics, in all contaminated wounds.

An unusual article published by Albee in 1932 introduced another question into the subject of bacteriocidal substances and wound healing. Albee had, for some time after the introduction of the Orr vaseline gauze treatment of osteomyelitis (95), felt that some unknown or unrecognized factor was responsible for the success of the treatment. The work of D'Herelle (33) on the bacteriophage was responsible for his study of the problem, (1). He found that 94 percent of the cases he treated with the Orr method developed a bacteriophage spontaneously. However, his laboratory determines the predominant organism in the wound, and the strain of phage required is introduced into the wound before dressing it, with remarkable results. It is entirely possible that bacteriophage will develop into a very valuable aid in

the treatment of infections although Orr (96) discourages the idea that it is such an important factor in the success of the method--if bacteriophage is present, it is so much to the good. He sums up the question thus: "We attempt to provide adequate drainage, rest for the wound and for the patient, protect it against secondary infection, and prevent deformity--we ask no more".

In 1936, Robinson (110) suggested the use of Urea and allantoin in the treatment of chronic purulent wounds on the assumption that it stimulated healing. Immediately, then, Holder and McKay (58) disagreed with him, stating that its benefit arose rather from its solvent action upon the dead tissues and from its bacteriocidal action. Bogart agreed with Robinson in his report on the use of Urea in the next year (15). Obviously, more study is necessary to determine whether it <u>is</u> beneficial, as well as whether it is, or is not, bacteriocidal. Holder used crystals or a saturated solution, while Robinson used a 2 percent solution, so satisfactory correlation of their reports is impossible.

SUTURE MATERIALS AND TECHNIQUE

The discussion of the suture and the ligature must begin with meagre historical references to its use centuries ago. The story of the catgut suture is also the story of the evolution of the musical string. Made from linen, animal skins, sinews and intestines, they were used for tying, mending, and for musical instruments. Strings from the harp and violin, which were made from the twisted intestines of sheep and of other animals, appear in the records of surgery throughout the ages.

Some 5,000 years ago, the unknown author of the famous Edwin Smith Surgical Papyrus (37) laboriously inscribed in hieroglyphics his treatment of wounds, which has been translated as follows:

> "Draw together the edges with stitching, bind with fresh meat the first day; if it is then loose, draw it together with plaster, treat with lint, grease and honey until healed."

Celsus, in the first century A.D., described the ligature as of ancient origin, and is said to have recommended its use in an attempt to control bleeding, prevent pus formation and to secure primary healing (99), (118), and it is believed that he used catgut, flax and

hemp for a similar reason, (105). The Arabian Rhazes (900 A.D.) describes the stitching of wounds with a thread made from the intestines of sheep (82). Roger of Parma (1210), Henri de Mondeville (1260), Parecelsus (1493) had, down through the years, been exponents of the use of ligatures and sutures (105). Ambroise Pare, father of modern surgery, and the one most responsible for the revival of the use of the ligature, had apparently studied the problem more thoroughly than was customary. In his writings (97) he discusses wounds, giving a classification of the various types, as well as sutures and their types. In general, he recommends that the surgeon "unite the divided parts, remove foreign bodies, keep the lips of the wound close together, and preserve the temper of the wounded part". His ligatures and sutures were to be of linen, "not too old, but new; not too coarse, but fine", and he stressed the importance of applying sutures in the recesses of deep wounds, that they might heal from the depths outward.

It must b e remembered, however, that during all these years, the teachings of Galen were still the basis of most medical practice and were instrumental in preventing the advance of medical science for so many centuries. His dictum that suppuration or "coction" was

necessary for the healing of wounds is a notable example, and was greatly responsible for the slow acceptance of the suture principle.

The researches of Physic (82) in 1816 demonstrated the absorbability of catgut and the non-absorbability of silk and flax. Actual research in this field really began with Lister (82), who in 1869 first referred to the use of antiseptic catgut. This initiated tremendous interest in surgical suture material which has extended to the present time.

In the days before asepsos, when all wounds, unless by fortunate chance, became infected, heavy silk and linen sutures undoubtedly caused persistent infection and chronic sinus formation, and finally had to be removed. At that time the ideal suture was one which would be absorbed and allow the wound to heal, eliminating to a large extent these persistent sinuses and the necessity of removing the sutures later. Catgut was such a suture, and has become almost universally accepted as the ideal suture.

Halsted in America and Kocher in Europe were not satisfied with the high percentage of wound infection in so-called "clean" cases, and experimented anew with silk. Finally, in 1913, after many years of careful observation and experiment, Halsted published his

classical paper on the uses and advantages of silk as a suture material, stating at that time, "the relatively high cost of catgut, its bulkiness, the inconvenience attending its use and sterilization, its inadequacy, the uncertainty as to the time required for its absorption, and the reaction it excites in the wound induced me to discard it completely in clean wounds in the surgery of the human subject and of the animal", (48).

The appearance of this article, with his striking results and presented to a profession so vitally interested in anything with which the incidence of wound complications might possibly be reduced, together with the influence of his standing in the medical world, naturally resulted in a widespread adoption of silk. However, the use of the silk suture without strict adherence to the principles laid down by Halsted resulted, in the next few years, in an astonishing outbreak of poor results. Frequent occurrences of infections, with accompanying chronic draining sinuses, soon resulted in a reversion to the use of catgut.

The controversy over the types of suture and their effect upon the course of wound healing has been oscillating from silk to catgut to silk for years, and

is one of the more prominent questions for research today. In 1925 Goff (45) analyzed wound healing in 3,000 abdominal wounds, and found a marked advantage of silk over catgut. He reported an incidence of 12.1 percent faulty healing in wounds closed with absorbable suture, with only 4.3 percent in wounds in which nonabsorbable suture was used. Actual infection occurred in 10 percent of wounds with catgut, and only 4 percent closed with silk. In 245 wounds thought to be contaminated at the time of operation, 83.5 percent of those closed with catgut showed faulty union, while only 70 percent of those closed with silk were so affected.

Howes and Harvey (67) in 1930 recommended 20-day catgut No. o used as interrupted suture because it was small enough to minimize tissue damage, yet strong enough to satisfy the physical aspects of suturing. They believed that it will maintain half of its strength until the wound is half healed, and will be completely absorbed when the wound has reached its maximum strength. They acknowledged the fact that silk was perhaps stronger, but the results when the wound became infected were too disastrous to warrant the risk of its use.

Then, only three years later, Howes alone (64) in reporting the results of his experiments on the strength

of wounds in rat stomachs sutured with silk and catgut, showed that fibroplasia began earlier when silk was used and that the exudative phase was shorter. He also found there was no advantage in the use of large sutures, adding no greater strength to the wound immediately or later in the stage of repair. He concluded with the remark that silk must be used with a definite technique, which would undoubtedly give better results if applied in the use of catgut.

Whipple (140) in 1933, and Shambaugh (115, 116) in 1937, reported equally satisfactory results in the use of silk. Whipple found that wounds closed with silk exhibited a greater tensile strength from the first day on than those closed with catgut. Shambaugh reports suppuration occurring twice as frequently with catgut sutures as with silk, and a discharge occurring eight times as often. In addition he makes the unusual statement that the presence of silk does not delay healing in suppurating wounds.

As the mass of evidence against catgut accumulated, and the questions of tissue damage, imperfections in the suture material, infections, and rapid digestion were investigated by first one author and then another, a new question appeared in the literature--that of

hypersensitivity to catgut. European investigators, Reid (107), Frugon (42), and Gratia and Gilson (46) reported that catgut cannot be antigenic because it is absorbed, and therefore any reaction produced with catgut after so-called sensitization is non-specific.

Jenkins (76) reported a suture test in which he found that 20-day chromic catgut was digested in six to ten days in some brands, and in fifteen to twenty days in others, and 40-day chromic catgut usually lasted a few days longer. The plain catgut became untied and could be lifted out in two or three days.

Further investigation of the sensitivity theory led Kraissl, Kesten and Cimiotti (77) to study wound healing, following sensitization of guinea pigs by injections of solutions of plain catgut, chromic catgut, and chromic acid. There resulted abnormal or non-healing in the majority of the wounds, while the wounds in all of the guinea pigs not sensitized healed normally. They then tested 332 patients for sensitivity to the same three substances. They reported 14.15 percent were sensitive to one or more; 15 percent with a history of allergy and a previous operation were sensitive; 9.5 percent with a history of an operation alone were sensitive, and 17.3 percent with a history of allergy alone gave a positive test. All five whose wounds disrupted had a positive response.

Beluffi (9) in the following year reported the results of an extensive investigation on catgut allergy: "Catgut does not possess antigenic properties; previous introduction and absorption do not produce a sensitization toward it or toward other proteins; reactions are interpreted not as allergic, but as foreign-body reactions). Pickerell (99) coroborated these findings.

Howes (62), not entirely satisfied, reported his investigation to determine the immediate strength of the wound with relation to the suture used. He concluded that sutures are necessary only in fascia, and then in the smallest bite to avoid mass ligation and necrosis. His results showed that larger suture merely increased the foreign body reaction, adding nothing to the strength, and increased the probability of faulty healing. He again recommended No. o multiple sutures, placed 0.5 cm. apart for maximum strength.

In this modern age of synthetic materials, it is quite probable that some new suture will be developed eliminating many of the present difficulties and objections attendant upon the use of silk and catgut. A report on experimental studies of the use of Nylon as buried suture was made by Aries (4) early in 1941. He believes that it has all of the good qualities of silk,

but is stronger, less irritating, and does not allow as much invasion of its interstices by leucocytes as does silk. Since it is more elastic, it does not cut through tissues as much as silk.

Without doubt, more study will be made before Nylon will be generally accepted, but we may reasonably expect the development of new, more nearly "ideal" sutures, or some other solution of the suture problem.

PLASMA PROTEINS

Until recent years, the problem of diet in surgical cases, though prominent in the minds of surgeons the world over, has been relegated to the limbo of the stylists and fadists of the medical profession. Any changes made preoperatively or postoperatively were directed toward reduction or elimination of the dreaded "gas pains" which have been so common a part of the postsurgical recuperation. As long ago as the sixteenth century, Pare (97) recommended that the diet be "small, cold, moist; abstain from salt, spices and wine", during the healing of a wound.

Actual study and research in the problem of diet in relation to the healing process was neglected until the early part of the present century. McQueeney (88) had reported in 1916 that he believed the feeding of carbohydrates in surgical cases resulted in better healing of the wounds. He ran a series of studies, about half of the cases treated as usual, and the others with special attention to their diet with very marked benefit. The acetone and other decomposition products of protein metabolism, he stated, were responsible for the difficulties and faulty wound healing which occurred.

Only two years later, Clark (29) reported his results from the first experiment on the effects of diet on wound healing. Using dogs as subjects, he found that a high protein diet practically eliminated the quiescent period while fat diets somewhat lengthened it. As a consequence, the date of final healing was about five days later when fat diet was used.

Sauerbruch (114) found that there was less secretion and fewer organisms in the wounds when he used a diet high in protein, fat and with the addition of phosphoric acid. An alkalin diet, on the other hand, resulted in edematous wounds, formation of pseudomembranes, and an increase in organisms.

Then in 1930 appeared the well-known work of Howes and Harvey (52), in which they reported the relation of the velocity of fibroplasia to variations in diet. Using albino rats, they made small wounds in the stomach and recorded the pressure necessary to rupture the wound at varying intervals postoperatively, with a standard diet as control, compared to the other group fed on a high protein diet. They reported that the proteins had no effect on the latent period, but the rate of fibroplasia was increased from the fifth to the ninth days with a resultant earlier healing.

Following this flurry of interest in the plasma proteins and wound healing, the question naturally arose in the minds of various investigators as to the underlying reason for any effect upon the wound. As already mentioned, the effect of proteins on the process of fibroplasia, so important in healing, had been studied. As early as 1895, Starling (124) discovered that blood proteins--fibrinogen, serum albumin and serum globulin--exert an osmotic pressure.

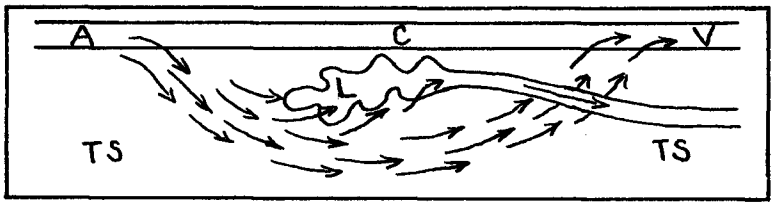

Diagram Illustrating Starling's Theory

TS- tissue spaces C- blood capillary
A- artery L- lymph capillary
V- vein
Edema may result from: 1. venous obstruction with increased pressure in C; 2. damage to endothelial wall in C resulting in increased permeability; or 3. obstruction of lymphatics so L does not remove protein matter from the tissue spaces.--Gatch (44).

In 1932, Krogh, Landis, and Turner (78) studied the movement of fluid through the capillary wall. Although they were interested in the problem from the standpoint of venous pressure, they also found that a rise in colloid pressure decreased the rate of filtration into

the tissues. Korfmacher (75) believes the edema is due partially to trauma, at the site of operation, but mostly to a lowered protein level.

Weech and his collaborators (135, 136) have shown that hypoproteinemia can be induced by dietary means, and that edema subsequently developed and was easily overcome by a return to a general diet. Bruckman, D'Esopo and Peters (19) showed that hypoproteinemia is directly caused by starvation, and hence could be caused by diseases. This was pointed out more definitely and corroborated by Jones and Eaton (72) in a survey of 34 surgical patients, who developed nutritional edema.

It was then logical for Howes and Harvey, with Briggs and Shea, to investigate starvation and its effect upon the rate of fibroplasia (65). Adult and young rats were used, the controls fed on a regulated diet, one-half this amount for the partially starved rats, and only water given to the last group. Wounds were made in the stomach, and fibroplasia judged according to the strength of the wound. Surprisingly enough, partial and complete starvation had no effect on the healing in the adult rats. They explained this on the basis of an increased protein metabolism in starvation and on an increased acid condition, as suggested by Sauerbruch (114).

However, in the young rats, partial starvation markedly retarded healing. The starved rats died too soon to allow study of the wounds, but the only strength at the time of death was that of the sutures used in closing. Gatch (44) states that the nutritional edema resulting from hypoproteinemia delays wound healing by preventing an orderly interchange of nutrient material and waste products between the blood and the tissue cells. Thompson, Ravdin and Frank and others believe that this edema is intensified by the addition of large amounts of sodium chloride, as is often done in the use of intravenous saline postoperatively, (130, 124, 44).

Thompson et al., (130), in a series of 11 dogs fed on low protein diets until they showed hypoproteinemia, attempted to correlate wound disruptions with this condition. Abdominal wounds were made, closed and biopsied on the seventh and fourteenth days. Both sections showed a failure to heal, although the silk sutures held the edges together. The tissues appeared unhealthy, and fluid could be expressed from the surfaces of the wound. Fibroblastic proliferation was found only occasionally in the 7-day sections, which showed marked delay. The 14-day sections showed fibroblasts, but they were in greatly decreased numbers as compared to the normal. In another article (131), published at the same

time, they reported a similar experiment in which they used only three dogs, but followed the operative procedure with the injection of lyophilized plasma at the rate of 300 cc. per day for the first 6 days, then 150 cc. per day for 4 days. The wounds appeared to heal normally.

Feeling that the absence of data on the actual concentration of serum protein and its fractions in this experiment made it difficult to evaluate Thompson's results, and believing also that the dogs suffered from more than hypoproteinemia because they were subjected to restricted diet, Koster and Shapiro attempted to enlarge upon and verify this work in 1940 (76). They determined and reported the total protein, albumin, globulin, and the oncotic pressure of the serum of 58 patients whose wounds were carefully observed. In general, the patients with deep infection or disruption showed a lower total protein concentration and a lower oncotic pressure of the serum than those whose wounds healed normally, all of whom showed normal values as reported in the literature. (See chart on next page).

However, they found also that some of the patients with normal concentrations and oncotic pressure had infections and disruptions, so they concluded that

hyperproteinemia must not be a necessary or sufficient condition to be the only cause of disruption.

	Average Protein	Average Albumin	Average Globulin
Moore and Van Slyke (9 patients)	7.1	4.3	2.8
Linder and Van Slyke (8 patients)	6.73	4.11	2.61
Salvesen (32 Patients)	7.0	....	....
Korfmacher (6 patients)	6.80	4.40	2.40

Korfmacher (75)

Ravdin (104), in 1940, stated that he at first attributed the delay in fibroplasia to the presence of the edema, but decided that the edema is merely an indication of a protein deficiency, which is in itself the important factor. Casten (27) agreed with him, and suggested that the next step would be to produce edema with excessive salt administration while maintaining the plasma proteins at a normal level, and study wound healing under these conditions.

Brown and McCray (18) in a review of the literature on serum protein studies in hyperthyroidism found it both incomplete and confusing. A study of twenty-four patients with hyperthyroidism before and after operation revealed no significant findings. Deusch

(13), quoted by the same authors, believed that the decrease in serum protein paralleled the severity of the disease and the weight loss. Improvement following surgical therapy resulted in a rise in the serum proteins.

Bartels (6) found a definite relationship to exist between the level of total proteins and the severity of hyperthyroidism. He attributed changes in serum proteins to disturbances in the function of the liver, a rough correlation being found in the level of total proteins and the excretion of hippuric acid used as a test of hepatic function. The findings in Korfmacher's small series seem to confirm these observations. These reports would appear to confirm the suggestion of Bruckman and others (19, 72) of ten years ago.

VITAMINS

The beginning of the story of vitamins dates back several centuries when scurvy lurked menacingly in the hold of all seafaring craft, only to have it miraculously disappear when land was reached, and fresh food was again available. But the first mention of this disease with the faintest hint of surgical importance occurred in the account of Lord Anson's voyage around the world in 1740-44, written by Richard Walter, the chaplain. Only one ship of the four original and a handful of men ever reached home. The chaplain wrote of an attack of scurvy on shipboard, and mentioned that old wounds broke open; one which had been received fifty years before in the battle of Boyne broke open and bled as though it had been recently made. One man had fractured an arm a year before, and had been completely healed, when the callous dissolved and the arm appeared recently fractured (132). As early as 1747, James Lind showed by controlled experiments that orange or lemon juice was a specific cure (80).

Based on the long-held conviction of physicians in the tropics that beriberi was a disturbance of nutrition, Eijkman in 1896 (cited by Holman - 60), presented the first scientific evidence of the important accessory

food factors by producing experimental polyneuritis in in pigeons fed on polished rice. Fraser and Stanton (40) took 300 Javanese laborers into the jungle, divided them into two groups, feeding one group a ration containing polished rice and the other the same food except for the substitution of less refined rice. Beriberi developed in the first group after three months, and when the diets were reversed, the second group developed the disease. The clinical significance of vitamins in surgery is just beginning to be appreciated.

Since the isolation and chemical synthesis of vitamins, controlled scientific experimentation has been made possible and has advanced in great strides. In 1933 Howes et. al. (65) studied the effects of starvation on the healing of wounds in rats (discussed more fully in relation to Plasma proteins in another portion of this paper) and suggested rather timerously that the retarded healing in young rats might be due to a deficiency in vitamins.

Archer and Graham (2) reported observations in 1936 on definitely scorbutic patients whose wounds became hemorrhagic, the edges became bluish, livid and showed no tendency to heal. Even scars and ulcers broke out afresh. They, and Platt (100) in the same year, also reported the development of scurvy, or subscurvy in cases

such as gastric ulcers, carcinoma, neurotics and others in which restricted diets were necessary or unavoidable. Archer and Graham based their findings on comparison of the low ascorbic acid excretion in the urine following a high intake, indicating a low tissue content.

It is well established now that the intercellular substances in general, and the collagen of all fibrous tissue structures in particular, require ascorbic acid for their production and maintenance. The original observations of Hojer (57), later corroborated by Wolbach and his collaborators (142, 143, 144), showed that ascorbic acid is intimately concerned with the synthesis and maintenance of intercellular supporting materials.

Since the repair and tensile strength of soft tissue wounds are direct functions of fibroblastic proliferation and collagen formation, it is at once apparent that Vitamin C may play a prominent role in the phenomenon of wound healing. Lanman and Ingalls (79) noted imperfect healing of operative incisions in guinea pigs maintained on a low intake of ascorbic acid. The tensile strength of wounds of the stomach and the abdominal wall of such animals, measured 10, 20, and 30 days postoperatively, was greatly inferior to that observed in normal control animals.

Taffel and Harvey (126) carried out a series of absolute and partial Vitamin C deficiency on the healing of stomach wounds during the first 14 days after operation. The tensile strength of the wound was used as an index of healing. Young guinea pigs were divided into a normal control group, absolutely scorbutic groups, and partially scorbutic groups.

In the control group, the curve of healing of stomach wounds, as measured by their tensile strengths, was parallel with that noted in soft tissue wounds of other experimental animals. After the fourth postoperative day there was an abrupt rise in the curve which continued until about the tenth day, when the velocity progressively decreased. During the latter phase of healing some of the wounds became stronger than the surrounding uninjured stomach wall.

In absolute scurvy, there was observed on the fourth day an increase in the strength of the wounds, a fact which has not been explained, but by the sixth day the strength was markedly inferior to that of the normal animal. This can be attributed to the inadequate collagen formation known to occur in Vitamin C deficiency.

In the partially scorbutic group, there was no deviation from the normal until the eighth day, with a return to normal strength again at the twelfth day. However,

significantly, there was a greater incidence of rupture in the uninjured tissue surrounding the wound site.

The inferior strength of the wound at eight to ten days is interesting when it is remembered that clinically the great majority of wound disruptions occur during this same interval (119, 130, 38, 50).

Advanced cases of scurvy are relatively rarely seen and offer warning enough in themselves when they do appear. It is the incipient, symptomless, subscurvy cases which are important to surgery. As mentioned before, the relationship of scurvy to wounds has long been known, but the recognition of the importance of Vitamin C is new to the medical profession.

In 1939, Wolfer and Hoebel (145), feeling that there were definite possibilities of Vitamin C deficiencies arising from 1- deficient diet--volume or otherwise; 2- obstructive gastro-intestinal lesions, especially at the phdorus and above; 3- long period of vomiting; and 4- syphilitics and alcoholics, began an investigation of a series of patients with such histories and complaints. The blood and urine ascorbic acid levels were checked in all patients, and the blood levels were found to be low (below .6 mgm percent.). All of these patients were treated with 1.0 gm Cebione (Cevitamic acid) and 0.5 gm

sodium bicarbonate in 30 cc. of distilled water administered intravenously every day until the tissues were saturated--that is, until the blood and urine levels were elevated, and little change would occur in either following the administration of the solution. The wounds in all of the cases healed rapidly and normally.

The next year, Holman (60) likewise studied a series of 70 patients who came to the Stanford-Lane clinic for surgery, and found that 44 percent showed a low Vitamin C blood level (.15-.3mgm.percent). Nine patients were below .15mgm. percent, in the scorbutic level. As a consequence, he routinely prepares his patients for several days before surgery on a high-protein, high-caloric, high-vitamin diet, including vitamin concentrates for five to seven days preoperatively. In emergencies, vitamins A, B, C and K are given parenterally.

In an attempt to reach some definite conclusion regarding the relation of Vitamin C deficiency and wound healing, Lund and Crandon (85) performed an experiment using one of the authors as the subject. A vitamin-free diet produced early signs of scurvy at the end of five months, and severe symptoms at six months. The ascorbic acid plasma level, however, was down to zero in 42 days. After three months, a wound was made in the

lumbar region through the skin, fascia, and aponeurosis, and closed in layers as usual. This wound healed well, but a similar wound made after six months offered difficulties. The sutures were made to hold in the tissues with difficulty and the wound made no progress in healing. Biopsy revealed a firm dry clot filling the wound, and no evidence of fibroplasia could be found. 1 gm. of ascorbic acid intravenously daily for ten days resulted in a perfectly healed wound. They reviewed four case histories of gastro-intestinal disorders, all of whom had low plasma levels of Vitamin C and failure to heal properly until ascorbic acid was given intravenously, observations which are in agreement with those of Archer and Graham (2) and Ingalls and Warren (68).

Hartzell and collaborators (50) in the course of some 200 determinations during the past year (1940), found that persons suffering from carcinoma of the gastrointestinal tract or gastric or duodenal ulcers almost invariably show low Vitamin C levels as a result of a decreased or restricted diet.

Recently it has been shown by several investigators (84, 145, 7, 50) that there is a decrease in the concentration of the plasma ascorbic acid following operations. Hartzell et. al. found that the average postoperative drop in eleven controls with normal preoperative

values was about 0.05 mgm percent. Lund (84) states that in cases in which the preoperative value is low, the postoperative decrease is proportionately greater. He believes that this postoperative drop may be explained by the decreased intake and also by an increased metabolism resulting from the usual postoperative fever. He also believes that the demand of the newly formed tissues which are produced in the healing process may use the vitamins at a rate faster than that for normal tissue growth.

In the final analysis, then, it must yet be proved that Vitamin C is responsible for abnormal healing, or failure of wounds to heal; but it seems quite logical to conclude that it is one of the more vital factors in determining the regenerative results in wounded tissues.

I have discussed only Vitamin C in relation to wound healing thus far. The literature concerning the other vitamins in this question is not over-abundant, and such as is available is rather indefinite. American investigators have not become markedly interested, but the reports of various European authors has been quoted to some extent.

Reports of the successful use of Cod Liver Oil in the local treatment of burns by Steel (125), Zolton (148),

and Hayashi (53) have led Iost and Kochergin (69) to study its effects and the results in traumatic and surgical wounds. They believe the beneficial effects to be due to the abundant Vitamin A and D content of the oil. It was first suggested by Loehr (83) in 1934 that Vitamin D stimulated epithelial growth, and Iost and Kochergin feel that their results verify this. They consider it possible that there is a lack of vitamins in the traumatized tissue as a result of an interrupted supply or to an increased demand. They demonstrated that Cod Liver Oil lowered the vitality of the pyogenic organisms in the wound.

Sandor (113) states that a deficiency of Vitamin A reduces the resistance of mesenchymal and epidermal cells to infection. He sought a means of applying Vitamin A locally, and was very successful with pure paraffin oil containing 2,000 I.U. of Vitamin A per cc. As a control, he used pure paraffin oil alone, with good results, but was convinced that the vitamin content was obviously beneficial.

The use of Vitamin A in the treatment of wounds acquires greater significance in view of the report of Holman (60) in which it was found that 26 percent of a series of patients showed a marked avitiminosis A.

MISCELLANEOUS FACTORS

The importance of various diseases in surgical patients in relation to wound healing cannot be minimized. It is common knowledge that diabetic patients frequently offer difficulties following surgical procedures, since many an unfortunate surgeon has discovered too late that a minor surgical case is a diabetic and has become a major problem in wound healing. McKittrick (87), Paullin (98) and Priestly (101) believe that such complications are due to the fact that, surgically, the diabetic is primarily a case of circulatory deficiency. They emphasize the importance of preoperative care with glucose, insulin, and sufficient fluids, and of immediate postoperative care in the same manner. Rabinowitch (103) and Gurd (47) have adopted the use of insulin in hyperglycemic patients who do not show glycosuria, since they have found that these cases also have disturbances in wound healing.

Hyperthyroidism, mentioned in the discussion of plasma proteins, seemingly influences wound healing indirectly through resultant changes in the plasma protein level of the blood. Cohen (30) and Puckett (102) reported increased healing of indolent wounds following the oral administration of thyroid extract. Brown and

McCray (18) and Bartels (16) have correlated these results with the subnormal plasma protein levels which they have demonstrated in a high percentage of their hyperthyroid patients. Both found an increase in plasma proteins following the operation.

Meninger (93) believes that patients with syphilis are an operative risk always, although their recovery may be without incident. He reports that infection is quite common in these patients, as well as the development of gummas in the wound. His studies give no indication that preoperative treatment is of any benefit, except possibly for the protection of the surgeon.

An apparent relationship between ovarian disfunction and wound healing is discussed in a case review by Wheeler and Adams (138). An abdominal wound in a seventeen-year-old girl, after a two-year period of alternate progression followed by regression at the menstrual period, healed completely in 21 days following an oophorectomy. They attempted no explanation, but they did state that no endometriosis was demonstrable at the time of operation.

Efforts to determine the stimulating factor in the tissue repair process have resulted in a variegated

array of suggestions. Bentley (10) has shown that epithelial growth in tissue cultures in vitro has a profound effect upon the connective tissue arrangement and growth. Brunschwig and collaborators (20, 73), in an attempt to find a relationship between the growth of neoplasms and wound healing, found that wounds in or near experimental papillomas and carcinomas healed apparently uninfluenced by the carcinogenic agent, 1-2 benzpyrene. However, when wounds were made through experimental sarcomas, the contour of the healing portion of the sarcoma conformed to the contour of the tumor mass.

Stimulating substances also have their place in medical literature. Reimann (108) and Birnbaum (12) report excellent results with thiocresol applied topically. Robinson (110) found that urea and allantoin had a stimulating effect upon fibroplasia. This was later confirmed by Bogart (15), Hooker (61) and Holder and McKay (58).

Evidence sufficient for general acceptance of all of these factors must yet be obtained, but one must admit that there seems to be a sound basis for many or all of them.

CONCLUSIONS

The surgeon who strives for perfection of his technique in handling tissues, in the use of ligatures and sutures, of asepsis, and in the care and dressing of wounds will be confronted with fewer wound complications.

The use of antiseptics in wounds at any stage of healing is of no benefit, and is often a factor responsible for delayed healing. Substitution of antiseptics for ordinary cleansing with soap and water should be definitely discouraged.

The fine silk suture is again becoming popular, but it must be used with a definite, very strict aseptic technique. Despite the discouraging reports on the use of catgut, there are situations in which it cannot yet be replaced. The use of the "silk technique" with catgut might very well improve the results with that suture material.

The importance of both preoperative and postoperative dietary care of surgical patients cannot be overemphasized, especially in those cases in which the diet has been restricted for one reason or another. While proof of a definite effect of low plasma protein levels and vitamin deficiencies upon wound healing is lacking, the frequency of their close relationship to

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