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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 a subject with which every student of medicine is assumed to be familiar. Too often, in Reid's words, this subject has served as a "filler" for textbooks, and has been passed by with only a nod of recognition by the busy student and interne hastening into the arena of practice.

The most ancient of the healing arts has been the care of injuries, and the earliest medical observations of man have concerned themselves with the healing of wounds. Even animals, by instinct along, have learned something about the care of wounds. It is recorded that in its native state the monkey, after a flight through trees and bushes, cleans himself of thorns and twigs, and assists his neighbor in so doing, - a service reduced largely to a search for parasites in the case of the monkey in captivity. Livingstone has noted that the wounded gorilla withdraws the spear from his body and dresses the wound with leaves to allay hemorrhage. Primitive man carried over with his evolutionary progression not only a keen interest in wounds but also methods of dealing with them. Fractured bones have come to us from the stone age and the satisfactory healing, evidenced by many of them, indicates that even before recorded history began man had learned to apply splints to keep the part at rest and to maintain apposition. We can logically assume that even before the time of the Egyptian papyri three of the principles of would healing had been established: namely, the removal of foreign material, the control of hemorrhage, and the maintenance of rest. Many strange and fantastic conceptions of disease and treatment are recorded, but it is of interest to note how these three principles with increasing refinement appear, disappear, and reappear in surgical writings up to the present day.

In the pre-Listerian days the surgeon was handicapped by a lack of knowledge of bacteria, although he undoubtedly suspected their presence. Except for this fundamental lack, however, the ancient surgeons made many keen observations on the healing of wounds and recognized certain factors in the process which we would do well to reemphasize today. The Tulmud warns against touching wounds with the hands since the fingers cause inflammation. The ancient Hindus practiced would closure with linen and bowstring sutures. The Greek surgeons emphasized the need for cleanliness in the operating room, and prescribed careful cleansing of the hands and nails, and the wearing of clean clothing. Theodoric in the 13th century warned against the probing of wounds and taught the need for cleanliness. He maintained that wounds may be closed and that they would heal without suppuration if properly cared for, a phenomenon that was not seriously considered possible, except in rare isolated instances, until the late 19th century. Henry de Mondeville advised the washing of wounds to remove foreign matter and the avoidance of all things likely to cause pus. Larrey, surgeon to Napoleon, recognized the need for the immediate care of wounds and established the twenty-four-hour limit in the Napoleonic armies. He emphasized the necessity of rest and pointed out the harmful effects of too frequent changes of dressings. Many of the wounded in the ill-fated Russian campaign were transported from Russia into France before their original dressings were removed. Diefenbach, as early as 1856, advised would excision so as to convert irregular crushed would edges into clean regular ones which could be closed primarily. Pirogof went to great trouble to obtain clean water for the cleansing of wounds and by the introduction of the use of plaster of Paris in war, surgery showed that he recognized the great value of rest in would repair.

One further conception of wound healing emerges from the great mass of superstition and black magic of ancient and medieval medicine. It was early expressed by Celsus, who noted that the natural reactions of nature were often beneficial and that such a phenomenon as fever might be helpful in promoting cure. The idea that the tissues possess the power of healing in themselves may be inferred from the teachings of Theodoric, but it reaches its first unequivocal expression in the writings of Paracelsus. Out of his tremendous amount of confusing rhetorical and bombastic argumentative writings, some so obscure and mingled with alchemistic and mystical references as to be almost unintelligible, there develops a conception of the treatment of injuries entirely new and different from anything which had gone before. It can be expressed no better than in his own words: "For you should know that by their nature the tissues contain within themselves an inborn balsam which heals wounds. So should every surgeon know that it is not he but nature that heals wounds. But that the surgeon should know in what manner he may serve to further nature's healing, let him protect the wound from ever present external enemies, that they do not interfere with or poison nature's balsam, but that it may be allowed to work with all its natural forces under the surgeon's protection. Under protection and rest and skillful dressings, nature heals the wound edges together and makes the flesh grow. For what makes flesh and blood and marrow? not man, not food but nature which possesses in itself the power to grow and multiply. Food and drink only support this power; the rain and earth do not make wood, only the tree itself can do so, but without rain and earth the tree dies." (68) Paracelsus, however, did not busy himself greatly with operative surgery, although it is probable that he had experience in the handling of war wounds, and it remained for a more practical and less evangelistic surgeon, Pare', to recognize the validity of Paracelsus' teachings and bring them before the profession of his day. Pare's observation on the harmful effect of severe traumatizing agents was accidental, but his teachings of the value of bland dressings and his dictum, "I dressed him - God cured him", have come down to us as epochal contributions to surgery.

Samuel Gross in the middle of the 19th century expressed again the conception of would healing and care which Paracelsus and Pare' had so brilliantly defended. It remained, however, for William S. Halstead to develop the rational care of wounds based upon a study of the process of repair. He tried at all times to evaluate and apply the various principles of wound healing in his work. His work has left as its greatest heritage an appreciation of the natural healing powers of the tissues and the necessity for not handicapping these powers with chemical or mechanical trauma, hemorrhage, foreign bodies, and infection.

The literature for the past twenty years is replete with reports of studies of wound healing. The gross and microscopic changes during wound repair have become well known, as have the factors which influence it. As to the actual nature of the healing process, however, how and why these growth-promoting substances act, we know very little. Healing appears to be a natural property of living organisms, which under certain optimal conditions proceeds at a definite and measurable pace.

The healing of wounds is a complex phenomenon and cannot be described in terms of a few specific governing factors. The regulation and control of growth of tissue presents problems not understood, and since the healing of wounds is dependent on the growth of tissue the problem of healing is not easy. However, there is certain information available regarding deterrents to healing in surgical wounds in patients. Deterring factors may be classified as (1) general or (2) local.

In order that a wound may heal it must be at sufficient rest for the parts to adhere, but many mechanical factors found in surgical patients cause motion of the approzimating edges. Imperfect suturing, activity on the part of the patient, coughing, straining, or rough handling on the part of attendants disturb the quietness of the wound. Locally, excessive trauma, infection, strangulation of tissue, presence of foreign bodies, and excessive tension are factors which predispose to poor wound healing. (39)(41) Other factors, especially in clean and otherwise uncomplicated cases, are usually less apparent and must be considered as due to general disturbances in the patient, since no local or mechanical cause is known. Concurrent disease and malnutrition probably are the most important of the general causes of poor would healing.

It is well recognized that the patients general health plays an important part in the process of healing. In persons who are poorly nourished, those with hypoproteinemia, with jaundice, and with certain systemic diseases there may be a disturbance in wound healing. This type of patient deserves, and usually gets, special consideration in preoperative and postoperative care, in order to restore to as near normal as possible his rate of healing. Attention to such special problems is admittedly important. Attention to many small details in the handling of wounds of all patients, regardless of their general health, is also important. The type of incision, the care and gentleness in handling tissue, strict attention to asepsis and hemostasis, the choice of type and size of suture material, and the care in approximation of wounds without strangulation of tissue all will influence the rate and security of healing of an incision.(73)

The first five or six days following wound repair are the critical days. During this time, the lag period or exudative phase of wound repair, the stage is being set for the abrupt onset of fibroplasia. Necrotic tissue is being liquefied and removed, bacterial contaminants are being dealt with, and an increasing local resistance to bacterial invaders is developing. The tensile strength of the wound during this period depends almost entirely upon the sutures and the relaxation obtained by rest and splinting. Rest and avoidance of unnecessary manipulation are therefore particularly essential to proper healing during the exudative phase. That the wound is more susceptible to infection during this phase of wound healing and that for this reason alone cressings should be avoided for at least five or six days has been shown by experiments.

Many of the large and small details associated with the care and treatment of wounds may be ignored, and still have satisfactory would healing occur in most cases. However, by constantly striving to perfect surgical technique the surgeon will invariably secure better end results.

The literature now available is too extensive to warrant a review of all the numerous factors and complications which influence would healing. I have limited this paper to the more important and recent factors which influence would healing. I have divided these into general factors, local factors, and miscellaneous factors.

HISTOLOGY

From a metaphysical standpoint, it would be interesting to discover why a wound heals; but from a scientific standpoint, it is infinitely more important to know how it heals, because it would then be possible to find what stimuli start the complex mechanisms of the regeneration of the tissues.

The mechanisms involved in the cicatrization of a wound are familiar to all surgeons. Summarized briefly, granulations appear on the open surface and by their contraction the edges of the epidermis are brought closer together. Then the epithelial cells wander on the granulous tissue and a new epidermis is formed. These phenomena can be divided into four periods: quiescent period, period of granulous retraction, period of epidermization, and the cicatricial period.(18)

The quiescent period extends from the time of the resection or injury to the time of the beginning of the granulous retraction. During the first days the dimensions of the wound do not vary. Often the immobility of the edges of the wound during the quiescent period ceases rather suddenly; there is no period of transition and the active period of reparation starts immediately. The main characteristic of the quiescent period is the great variability of its duration. In some cases it lasts only one or two days, while in others it lasts four or five days.

At the end of the quiescent period the edges of the wound begin to advance toward each other. The reduction in the size of the wound is very active during the first days of the period of granulous retraction. Then it becomes progressively slower until it comes to a standstill. The activity of the granulations depends on the dimensions of the wound or in other words the rate of reparation of the granulous period is directly proportional to the size of the wound. The period of granulous retraction plays a very important role in the healing of middle sized and large wounds and is less important for small wounds.

The function of the granulous period is to prepare the surface of the wound for the wandering of the epithelial cells. But it seems probable that its main role is to bring the edges of the wound fairly close together.

Following the period of granulous retraction we come to the period of epidermization. The epithelium spreads at first very slowly. This epidermis is exceedingly delicate and a great many external factors interfere with its growth. The best medium for its growth is certainly coagulated fibrin. The time of the beginning of epidermization does not depend on the age of the wound but on its dimensions. If the wound is large, the epidermization is tardy and vice versa.

Therefore, it appears that the law of reparation by epidermization is absolutely different from the law of separation by granulous retraction. The rate of the epidermization is inversely proportional to the dimensions of the wound. The maximal activity of the epidermization seems to take place when the cicatrization is nearly complete, and when the edges of the new epithelium are very close to each other.

After the period of epidermization comes the cicatricial period. The evolution of the scar is very slow and the cicatricial period of a wound very long. The mechanisms which are instrumental in the cicatrization of a wound are coordinated in such a way that the reparation is continuous and progressive. Nevertheless, the reparation presents phases of maximum and minimum activity during which the rate is higher or lower. During the quiescent period, the end of the period of granulous retraction and the beginning of the period of epidermization the rate of the reparation is slow. It is maximum at the beginning of the period of granulous retraction and at the end of the period of epidermization.

Certain characteristics of the healing of the simple wound are familiar to the surgeon. The edges of the wound become adherent to each other through the clotting of the blood. There is a direct transformation of the fibrin clot into a new fibrous tissue without any intracellular action. This newly formed fibrous tissue which fills the wound space is apparently identical in appearance, structure, function, and staining reactions with regularly formed permanent connective tissue.

It was generally believed in the past that this new fibrous tissue was only a temporary tissue and that it would be replaced in time by a permanent connective tissue formed through an intracellular action of the fibroblasts. It was believed that the fibrin, in wounds healing by first intention, formed a temporary tissue which held the wound surfaces in place and stopped up the wound, thus preventing infection. Later the fibrin disappeared not by liquefaction, but through actual consumption by the new tissue cells which showed a positive chemotropism to the fibrin mass and were thus attracted into the fibrin clot in large numbers. The permanent tissues which go to fill the wound space were then formed by these cells through an intracellular action.(4)

The present view is that this new fibrous tissue remains in the wound as a permanent connective tissue. The fibroblast cells which wander into the new fibrous tissue apparently do not digest the fibers which have previously been formed. Their only apparent action is to break up the larger bundles of fibers by their movements among them.

The strength of this early adhesion is not sufficiently great for the first two or three days but that a minimum strain will separate the edges. If such is likely to occur, it is necessary to reinforce the adherence of the wound edges with sutures. In from five to eight days it has become solidified. After this the reinforcing action of the sutures is no longer necessary. In from eight to twelve days, the strength of the wound is such that it meets the ordinary exigencies of daily life, and toward the end of this period it has become a scar.

When microscopic methods of study became available, this phenomenon was studied and visualized in terms of the behavior of cells. It became known that certain groups capable of phagocytosis serve to clear up the debris of dead matter, while others multiply in the fibrin network of the clot forming connective tissue, and still others have to do with the growth of new blood vessels thus completing the process of organization. This phenomenon as a whole will be divided into two phases; that in which the exudative reaction is most marked and that in which the proliferative reaction is predominant. Furthermore, when the amount of necrotic tissue is the least, then the exudative reaction is minimal, leaving the fibroplastic process to bridge the gap between the healing surfaces, the vascularization of the new tissue going hand in hand with its formation.(51) The continuity of the injured part is reestablished, and the laying down by the fibrocytes of collagenous material in fibrils results in the cicatrix of adult connective tissue. This additional knowledge enables one to understand better the processes which are involved in the healing of a wound, and to speak of these in terms of cytology rather than in those of gross morphology.

It is apparent that the master reaction in this process, to which the clearing up of the debris and the bringing in of nutrient material by the new blood vessels are subsidiary, is that of the multiplication of the fibroblast.(43) Cells of other types may be involved but they are transitory and relatively ephemeral, while the fibroblasts originate, divide and achieve maturity in direct continuity with the wound.

In order to further understand the way of wound healing, it is necessary to attempt to explain why it is that the various component processes proceed as they do. To consider adequately all the phenomena involved would transcend any reasonable limitations of space. A consideration of certain of the more obvious features will be reviewed.

The building of a provisional granulation tissue, when it occurs, is essentially a filling process of embryonal material followed by gradual conversion into permanent connective tissue. Some of the activities of these cells are interpretable on the basis of theories to be discussed. Retraction and contraction of the wound probably represent, for the most part, secondary features however important they may become from the practical, surgical point of view. Retraction is purely a mechanical phenomenon while contraction is due in considerable measure to the production and subsequent shortening of connective tissue fibrils. This latter is a more or less secondary concomitant of connective tissue reparation. Contraction, however, may transcend somewhat such a subordinate role if Burrow's(50) contention be true that under certain conditions the epithelium actively drags the edges of the wound together. In this instance it would become a function of epithelial activity whose main phenomena are amebism and mitotic proliferation.

Turning, therefore, to these two most dramatic expressions of healing, it is necessary to inquire further into the conduct of a differentiated tissue, epithelium, which by a process of lateral spreading is able to repair its defects.(81)

One important factor of ameboid movement is the utilization of a stereotropic response by which cells (epithelial and others) move always in contact with solid or semisolid bodies. In the case under consideration the substrate is chiefly fibrin fibers. This sterotropic response explains the movement of epidermis along the floor of the wound, between scab and floor, or even along the fibers of the coagulum itself. But there is apparently another agency at work which directs the cells away from their own tissue into the neighboring foreign material and especially into the wound defect. This activity finds expression in a centrifugal growth, which takes place in a solid media in the absence of distinct directive fibers. This induces the various kinds of cells to move into clots and especially fibroblasts to organize blood clots; this likewise induces epidermis to fill the defect, and muscle and nerve to regenerate in a centrifugal direction.

Much useful information on the problems at hand may be gained through observations on naturally free ameboid cells. When these cells leave the blood channels and come in contact with solid material their granular cytoplasm separates into a hyalin cytoplasm and granular endoplasm. The hyalin portion spreads outward in the form of pseudopodia while at the same time the cell surface becomes sticky so that agglutination takes place between neighboring cells and between cells and the adjacent foreign body. Contact with solid substances or other surface changes produced through chemical action, brings about alterations in the cell periphery which in turn leads to changes (physical and chemical) in the cell as a whole. It seems probable that these alterations of surface tension are preceded by metabolic changes, perhaps consisting of processes of ionization which extend progressively inward. Such cell ionization leads to water intake, increased viscosity, liquefaction and surface stickiness. Within physiological limits these changes may well be reversible. The ultimate factors underlying this process, the extent to which surface tension alone operates, and the degree to which the latter are mere accompaniments of more fundamental physical and chemical changes. All such desirable details must for the present remain unknown.

Unlike free amebocytes, the cells involved in wound healing, clot organization and growth in tissue culture are rather definitely polarized to the effect of the foreign environment. The latter affects chiefly the side of the cell presented to it. As is well known, such polarized stimulation is accompanied by differences in electric potential on the stimulated side. This increase in potential may be deeply involved in the alterations in surface tension, and the accompanying physical and chemical changes, which characterize this side of the cell. Such potential differences will continue as long as a cell faces the foreign body in one direction and remains in contact with other cells of its kind in the opposite direction. Thus the conditions are set up which serve to direct a centrifugal movement toward the foreign body. Oxygen is a further requirement for this activity, and successful organization in vivo is dependent on the proximity of blood vessels. In any event, by the production of lateral pseudopodia directed toward the foreign body the growth is brought about.

At the same time the changes in stickiness at the cell surface lead to the characteristic stereotropic response. This reaction modifies the tendency toward strict centrifugal growth, and it is the stronger force so long as growth occurs where it may successfully operate. In this way deviation from a pure centrifugal growth is brought about. Nevertheless, in wound healing, stereotropism on the whole merely strengthens centrifugal growth. Thus it is that growth continues until the effect of the foreign body is removed; that is to way, until the wound is closed and the clot organized.(1)(2)

Of the responses induced in the regenerating epithelium there is left the important topic of augmented cell division. How this comes to pass cannot be explained with satisfaction at the present time. The internal structure and activities of the cell appear relatively more important in this reaction than the external influence, yet the presence of a foreign body seems to be able to induce cell division.

GENERAL FACTORS

Only within recent years have surgeons begun to appreciate the fact that the rate of efficacy of wound healing is dependent in no small measure upon several important biochemical factors. These are: (1) the protein concentration of the serum, (2) the carbohydrate metabolism, (3) the ascorbic acid content of the tissues, and to a limited extent (4) calcium and phosphorus metabolism in the healing of fractures.

As far as is known at present these four factors affect wound healing specifically, although it has been stated that the over-all picture may be modified by the general status of body nutrition and by vitamins other than ascorbic acid.(16) There is little evidence, however, that such is actually the case.(46) Poor body nutrition will be reflected in depleted serum proteins and not infrequently in a decreased concentration of ascorbic acid in the tissues as well, thus influencing the processes of tissue repair.

It is obvious that imperfect suturing, coughing, straining, or rough handling disturb the adherence of the wound edges. Also excessive trauma, infection, strangulation of tissue, foreign bodies, and excessive tension are important local factors predisposing to poor wound healing.(39)

PROTEIN METABOLISM

Clark,(50) was the first to study the effect of diet on the healing course. The sole influence he observed was upon the latent period, whereas the periods of contraction and epithelization remained unchanged.(1)(42) Hence the type of diet used influenced the total period of healing proportionately as it affected the latent period. High protein diet eliminated the latent period completely, whereas high fat diet prolonged it to six days. High carbohydrate and mixed diets were intermediate in effect. The fact that proteins stimulate cellular proliferation while fat acts as an inhibitor has been demonstrated in various other ways.

Somewhat different are the results of Howes and Harvey(49) who studied the progress of wound healing from another standpoint, by testing the tensile strength of the regenerating connective tissue. In this instance the duration of the latent period was not affected, but once growth was started the velocity of fibroblastic repair increased distinctly under high protein diet.

It is universally appreciated that protein is necessary for the growth and repair of tissues since, fundamentally, tissues are protein in structure. Unlike fat, the reserve store of protein in the body is relatively small (two kilograms), the energy equivalent of which could supply the basal caloric requirements of the average adult for only five days.(10) Protein deficiency in blood and tissues will rise rather early, therefore, in conditions of protein starvation or inanition.

Tissue and plasma protein deficiency may occur even in the presence of adequate protein intake. The enzymatic hydrolysis of protein and the absorption of the amino acid end products may be interfered with in patients with achylia gastrica, gastrectomy, jejunostomy, ileostomy, jejunocolic fistula, and diarrhea. In diseases of the liver this organ may fail to synthesize protein from the amino acids brought to it by the portal vein (cirrhosis of the liver, hepatitis, chloroform poisoning, thyrotoxicosis, liver abscess, and acute yellow atrophy of the liver.) Again, protein may be lost in excessive amounts from the body (suppuration, burns, chronic loss of blood, nephorosis, and chronic bile peritonitis.) The surgeon should remember that the amount of protein lost in pus may range from eight to twenty one grams per cent.(55) It is obvious from what has been stated above, therefore, that hypoproteinemia may result from prehepatic, hepatic, or posthepatic causes.(25) Since plasma protein is in dynamic equilibrium with tissue protein, a deficiency of the former reflects a depletion of the latter. The total serum or plasma proteins vary normally from six to eight grams per cent of which the albumen component ranges from four to five grams and the globulin from two to three grams per cent. The albumen is the important component, since its relatively smaller molecular size compared to the globulin is attended by greater osmotic pressure. This is important, since edema, which interferes appreciably with wound healing, is dependent in no small measure on the osmotic pressure exerted by the serum albumin. In fact, when the total serum protein falls to approximately five grams per cent or the serum albumin reaches two and one half grams per cent, edema is imminent.

In patients with hypoproteinemia, wound healing is slow and the tensile strength of the wound is decreased. It was shown twenty five years ago that the latent period in wound healing, that is, the time from the injury to the time of fibroblast proliferation, may be shortened almost to the point of elimination by a high protein diet.(19)

more recently it was demonstrated that the rate and degree of growth of fibroblasts in wounds may be increased by an augmented protein intake.(42) Still more recently, severe hypoproteinemia has been shown to retard the formation of bony callus in experimental fractures.(85)

Hypoproteinemia not only causes delayed and inadequate wound healing but may be attended by sudden disruption of wounds.(40)(95)(60)(74) Recent studies have confirmed these observations, although it must be conceded that decreased serum protein by itself is neither a necessary nor sufficient cause for wound disruption in all cases.(59) Obviously, poor surgical technique and excessive intra abdominal pressure from any cause would favor wound disruption even in the presence of normal serum proteins.

Diminished serum proteins further result in delayed gastrointestinal motility and may cause failure of function of surgical gastrointestinal stomata.(14) Moreover, the accumulation of edema fluid in the walls of the gut which commonly occurs in nutritional deficiency states interferes with the "take" of the stoma.

Hypoproteinemia is best combated by a high protein diet (two to three grams of protein per kilogram of body weight, provided, of course, such diets can be administered and utilized. It has been calculated that three hundred and seventy five grams of protein are required each day for a period of ten days to elevate the serum protein level from five to seven grams per cent.(28) Whenever possible, surgical patients should be prepared for operation by several days of optimum nutrition, including a well balanced diet of high protein intake, of high caloric value, and of high vitamin content. It has been stressed that this period of preparation should begin at home ten to fourteen days before the operation.(47)

When the administration of a high protein diet is impossible for any reason or when emergency surgery must be performed in a hypoproteinemic patient, other means of protein administration must be resorted to. For this purpose, whole blood, plasma, or casein digests may be used. The most efficiently utilized protein in the treatment of hypoproteinemia is plasma,(100) since homologous plasma protein apparently furnishes all the body needs for protein.(48) Two units of plasma contain approximately thirty five grams. It is obvious that if the total body needs for protein were to be derived from plasma, whole blood, or serum, the cost of such therapy would be prohibitive. Moreover, there is some recent evidence that the injected plasma protein, especially when administered in large amounts may not be retained permanently in the blood and tissues of the recipient;(29) this is a rather important finding and certainly requires confirmation.

Casein digests offer a convenient and relatively inexpensive method of administering parenteral proteins. Such hydrolysates have been shown to maintain nitrogen equilibrium when injected intravenously or subcutaneously. Ascorbic acid should be given simultaneously, since it has been shown that this vitamin is essential for the proper metabolism of certain amino acids, namely, phenylalamine and tyrosine.(66)

The parenteral administration of protein food by means of amino acids represents as great an advance in therapy as the injection of glucose as a means of supplying calories or of water and electrolytes in maintaining water balance and in correcting dehydration, or as the injection of crystalline vitamins in combating vitamin deficiencies. Indeed, the addition of amino acids to the usual parenteral fluids makes possible the administration of an almost complete diet without recourse to the usual digestive processes.(21) Thus starvation can be avoided almost completely even though the patient is unable to take anything by mouth. Complete rest of the gastrointestinal tract, which heretofore inevitably resulted in protein starvation, can now be achieved with an almost full dietary intake.(30) Thus both food and rest can be utilized; both factors are obviously very important in the healing of many types of lesions. To limit the parenteral diet to water, electrolyte, glucose and vitamins is no longer justified; the addition of amino acids makes the mixture more nearly complete.

The administration of one hundred cubic centimeters of amino acids will yield fifteen grams of protein to the body provided, of course, that the amino acids are completely synthesized to protein by the liver. When parenteral feeding is the only means of sustenance, adequate amounts of carbohydrate must be given simultaneously for its protein sparing action.

In order to offset possible reactions such as flushing, nausea, vomiting, chills and fever, amino acids should not be administered intravenously too rapidly. Most postoperative patients are able to tolerate from seven and one half to fifteen grams per hour without difficulty. In the average postoperative patient (without liver dystrophy or undue protein loss) nitrogen equilibrium can be attained by the administration of one to one and one half grams of protein per kilogram of body weight.

CARBOHYDRATE METABOLISM

McQueeney(70) reported in 1916 that he believed the feeding of a high carbohydrate diet in surgical patients resulted in better healing of wounds than did a regular diet. 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 decomposition products of protein metabolism, he stated, were responsible for the difficulties and faulty wound healing which occurred.

It is generally appreciated that surgical wounds tend to heal slowly, inadequately, or not at all in patients with uncontrolled diabetes mellitus. The healing of abdominal incisions in dogs rendered diabetic by pancreatectomy has been studied. The repair of these wounds is abnormal compared to the behavior of identical wounds in healthy animals used as controls. Edema of the tissues, delayed and decreased deposits of fibrin, excessive cellular reaction, slow formation of new blood vessels, and frequent thromboses in preformed vessels were noted in the diabetic animals. Healing proceeded normally, however, when the diabetes was well controlled.(11)

The view has long been held that the hyperglycemia in the uncontrolled diabetic renders the individual more susceptible to infection. Bacteriologic studies have shown, however, that blood to which varying concentrations of sugar had been added proved to be no better culture medium for staphylococci than blood without added sugar.(9) Hyperglycemia per se probably does not retard wound healing nor predispose to infection provided that (1) insulin is acting and the metabolism of the tissue cells is not disturbed; (2) the peripheral circulation is adequate; and (3) the resulting glycosuria and concomitant polyuria do not produce excessive dehydration.

VITAMINS

The effect of vitamins on wound healing goes back several hundreds of years. As early as 1747, James Lind showed that orange or lemon juice was a specific cure for a failure of wound healing due to a lack of vitamin C.(67) Twenty five years ago, it was observed that in scurvy the main deficiency was a lack of intercellular cement substance. Since then, it has been demonstrated frequently that an adequate concentration of vitamin C in the tissues is a necessary prerequisite for normal wound healing. This vitamin is essential for the maturation of precollagen to the collagen of fibrous tissue.(62) Histologically speaking, there is a failure of wounds to heal in the presence of a vitamin C deficiency because of the inability of the supporting tissues to produce and maintain intercellular cement substance.(101) Apparently this vitamin is also essential in the healing of fractures, since the production of osteoblasts appears to be dependent upon the vitamin C content of the tissues.

In guinea pigs, wound healing is retarded when the animals are kept on a subscurvy diet. The tensile strength of wounds is about one half of normal on the sixth post operative day and about one quarter of normal from the eighth through the fourteenth days. The addition of high vitamin C dosage to the diet of such animals postoperatively permits the wounds to reach the same tensile strength by the eighth postoperative day.(39) In human subjects, it has been found that a sufficient depletion of vitamin C produces a decreased ascorbic acid content and tensile strength in healing wounds in the skin and fascia. A fasting plasma ascorbic acid level below two tenths per cent must be reached before these changes occur.(7) Wound disruption is more often seen in northern people in the winter. This may be attributed to lack of vitamin C in the diets of these people.(31)

Many chemical and biophysical procedures have been devised in order to evaluate vitamin C deficiency; these have been reviewed critically.(61) Three methods will be described briefly here: (1) the fasting vitamin C content of the plasma, (2) the vitamin C saturation test, and (3) the tourniquet test.

The normal fasting vitamin C is stated to range from seven tenths to one and four tenths milligrams per cent of plasma. A deficiency in plasma vitamin C usually reflects an inadequate concentration of this vitamin in the tissues in spite of the fact that the dietary history may indicate an adequate consumption of citrus fruits. For reasons that are not as yet too clear, some persons either fail to absorb this vitamin from the gastrointestinal tract or are unable to store it in the tissues.

The vitamin C saturation test is a valid procedure, perhaps more so than the fasting ascorbic acid content of the blood. In this test, the patient voids and discards the urine, then one gram of ascorbic acid dissolved in ten cubic centimeters of saline is injected intravenously and the urine is collected for exactly five hours after the injection. If the tissues contain adequate amounts of this vitamin, more than four hundred and fifty milligrams of ascorbic acid are excreted in the five-hour urine. Obviously, in persons with deficient stores of vitamin C, the greater part of the injected vitamin is absorbed by the tissues and decidedly less than four hundred and fifty milligrams are excreted in five hours.

The tourniquet test, unlike the two procedures described above, requires no chemical analyses. The test has recently been modified. A circle the size of a twenty-five cent piece is drawn four centimeters below the elbow crease on the inner aspect of the forearm. The blood pressure manometer is then applied as usual upon the upperpart of the arm and inflated to a pressure midway between the diastolic and systolic pressure of the patient. This is maintained for fifteen minutes after which the pressure is released; at the end of five minutes the number of petechiae within the circle is counted with the naked eye. A normal count is rarely over ten petechiae. In the presence of vitamin C deficiency the associated increased capillary fragility is reflected in high petechial counts. It should be noted that the tourniquet test will give false positive reactions in the blood dyscrasias (leukemia, polycythemia, thrombocytopenic purpura, etc.). Again, negative results will be obtained in patients with vitamin C deficiency in the presence of moderate or severe anemia, primary or secondary.

Delayed or imperfect wound healing in the presence of ascorbic acid deficiency is best treated by the liberal use of crystalline vitamin C. This material may be administered intravenously in daily doses of one half of one gram gram dissolved in a small volume (ten cubic centimeters) of physiologic saline or distilled water or added to a glucose or glucose-saline infusion if such therapy is being used simultaneously. Vitamin C may be prescribed orally and, in most instances, this route is eminently satisfactory. Tablets of vitamin C containing twenty five, fifty or one hundred milligrams each of the crystalline material are obtainable. Three hundred to five hundred milligrams per day in divided doses may be ordered. Allergic reactions to ascorbic acid are rare; in fact, this vitamin has been used freely in the treatment of various types of hypersensitivity.

I have discussed 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. Vitamin D does not appear to improve the healing of wounds but vitamin A in moderate doses is reported to have a beneficial effect. Cod liver oil, which contains both vitamin A and vitamin D was first employed in 1934 as a dressing for wounds and has been widely used. Its action in wound healing was thoroughly examined along with that of other oils. It was found that cod liver oil, pure vitamin A, arachis oil, linoleic acid, cocoanut oil, and liquid paraffin all stimulated collagen regeneration to varying degrees, but that epithelial regeneration was promoted by lineoleic acid only. Vitamin B appears to play no part in wound healing.(39)

HORMONES

The effect of the various hormones on wound healing has been thoroughly investigated. Hypophysectomy does not seriously interfere with the proliferation of fibroblasts and epithelial cells in wound healing,(89) and the administration of extracts of the anterior lobe of the pituitary gland has been shown to exert no significant effect on the healing time.(23)

Thyroid administration has been reported to be of value clinically in wound healing. Barclay, Cuthbertson, and Isaacs,(5) investigating the healing of skin wounds in rats found a significant reduction of eleven per cent in the mean time required for healing when dried thyroid gland was fed during the period of healing. If the animals were, in addition, given thyroid in the diet before operation the time required for healing could be reduced by as much as twenty two per cent. The authors do not, however, advise the use of these metabolic stimulants to influence the rate of normally healing wounds in human patients.

It has been suggested by investigators that the adrenal cortex produces two hormones which are present in the urine in increased amounts in the first twenty four hours after injury.(20) One, the "N" hormone, is a testosterone-like substance which causes retention of nitrogen. The other is termed the "S" hormone and causes conversion of protein to sugar, and therefore a loss of nitrogen. After trauma, the adrenal cortex first puts out an excess of both "N" and "S" hormones, which appear in the urine, but later only the "S" hormone appears in excess. Subsequently the output of "N" hormone also diminishes. At this stage, administration of testosterone might perhaps be expected to be of some benefit. The effect of local applications of testosterone on the healing of wounds in man has been examined.(8) They found that it had no value in stimulating epithelial regeneration.

ENZYMES

The role of enzymes in wound healing is obscure. It has been shown by histological, histochemical, and chemical tests that a high concentration of phosphatase is present in the invading polymorphs around a wound, in the scab, and in the regenerating connective tissue, especially at about the fifth day.(32) The role of phosphatase might be expected to be of greatest importance in the healing of fractures and this is so. It has been shown that experimental fractures treated with phosphatase and with a suitable substrate such as calcium glycerophosphate, heal more quickly than controls.

PARENTERAL SALINE SOLUTION

Dr. McDougal(68)(69) calls attention to parenteral saline solution as a factor which may influence the security of healing of laparotomy wounds. In reviewing the cases of wound disruption, one thing seemed outstanding. Almost every case occurred in patients who had received large amounts of parenteral saline solutions. It is generally recognized that intravenous fluids are given rather haphazardly, and glucose in saline solutions seems to be more popular than glucose in distilled water. It seems reasonable to assume that excessive saline solution in the body tissues might do real harm to the process of repair in a wound. We know of the difficulty of healing a wound in an edematous ankle or leg. It is not uncommon to see a patient receive enough saline solution to cause grossly visible edema, and lesser amounts may reasonably cause subclinical edema.

In postoperative patients it can be shown that intravenous or subcutaneous saline administration neither causes elevation of blood chlorides nor does it increase the urinary excretion of chlorides. In fact, the postoperative excretion of chlorides in the urine is considerably diminished for a number of days. The administered saline must, then, be distributed throughout the body tissues and by osmosis, an increased amount of fluid will collect in the tissues. Chlorides collect readily in areas of inflammation, whether the inflammation is due to bacterial injury or to trauma from an incision. Therefore, it would seem reasonable to assume that a surgical incision collects a relatively large proportion of the administered saline solution, thus increasing the edema of the wound tissues.(94)(36) This added edema in the wound would naturally delay healing, make it a weaker wound, and could actually cause strangulation of tissue by the sutures.

In order to investigate the effect of parenteral saline solution on the rate of healing of abdominal incisions, the following methods were used: Adult white rabbits were separated into three groups. Under general anesthesia the abdomens were carefully shaved and prepared with ether and alcohol. Vertical incisions, five centimeters long, were made just to the right of the midline. The incisions were made as nearly identical as possible and sutured in identical manners. One group was given twenty two cubic centimeters of glucose in saline solution per pound of body weight per twenty four hours. Another group was given the same amount of glucose in distilled water. The fluids were administered partly by vein and partly subcutaneously, and the animals were allowed nothing by mouth. The third group was given a regular diet by mouth without any parenteral fluids. The animals were sacrificed on the seventh postoperative day at which time the strength of their abdominal incision was determined as follows: Under anesthesia a number seventeen gauge needle was inserted into the abdominal cavity and connected to a mercury manometer. Air was gradually introduced into the abdomen through a smaller needle in the opposite side until the intraabdominal pressure became great enough to cause separation of the wounds. The highest reading on the mercury manometer obtained before wound disruption occurred was recorded as the wound disruption pressure. The average pressure which was necessary to disrupt those animals that had received glucose in saline was sixty seven millimeters of mercury, while those animals receiving glucose in water were able to withstand an average intraabdominal pressure of one hundred and one millimeters of mercury before wound disruption occurred. The results in this group of animals that received a regular diet postoperatively, originally separated as a control group, did not differ significantly from animals receiving glucose in water, as far as strength of their wounds was concerned. It will be noted that the wounds of animals receiving glucose in saline solution were, on the average, thirty two per cent weaker than the wounds of animals receiving glucose in water. Sections of tissue from the wounds and samples from other areas of the abdominal wall were taken for tissue chloride analysis. It was found that wound tissue is richer in chlorides than in normal tissue, and the wound tissues and normal tissues of animals receiving glucose in saline solution have a higher chloride content than do those receiving glucose in water.

The usual so-called isotonic saline solutions contain nine grams of sodium chloride per liter. A person certainly does not require this much salt each day for normal metabolic processes. A healthy, ambulatory person can excrete excess chlorides through the kidneys. Postoperatively, however, the patient's kidneys do not seem able to excrete an excess amount of sodium chloride. It would seem that most patients receive parenteral saline solutions when they do not require it and cannot handle it. Therefore, it may, if given in sufficient amounts, collect in the tissues and so weaken the wound, or delay its healing that disruption may occur.

Saline solution given postoperatively may cause disruption of the wound by acting in two different ways: Not only by delaying the healing of the wound, but it may also be a cause of distention of the intestines, thereby increasing tension on the wound.

Obviously, if a patient is losing chlorides through gastric suction, fecal fistula, or a diarrhea, he should receive saline solution as replacement. It is probable that one or two liters of saline solution given postoperatively as a routine will do no significant harm, but in those cases that require parenteral fluid therapy for a period of several days, saline solution should be used cautiously and only as replacement for that lost by the patient. Fluid therapy can be carried on in the form of glucose in distilled water for weeks without significant alteration in blood chloride levels provided the patient is not losing chlorides by one of the routes mentioned above. It is strongly urged that fluids in the postoperative period be primarily glucose in water and not glucose in saline solution.

LOCAL FACTORS

LOCAL CHEMOTHERAPEUTIC AGENTS

The sulfonamides are frequently placed in surgical and accidental wounds. The objectives of local therapy with the sulfonamide drugs are to prevent infection where infection is minimal or potentially present; to prevent the spread of infection already present; to eliminate infection already present; to avoid local damage to tissue cells; to avoid absorption of amounts of drug which might be toxic; to reduce the number of organisms present in the local area of infection before application of the drug to a number which can be controlled by the concentration of the drug which can be attained; to maintain an adequate concentration of the most effective and least toxic drug for an adequate period of time to eradicate completely the infection; to apply the drug in such a way that an adequate concentration is attained immediately and the drug is in contact with all organisms; and to avoid introduction locally of any substance which would inhibit the action of the drug.

Because of their widespread use it is important to know whether or not they damage tissues or influence wound healing. When sulfanilamide and sulfathiazole are added to tissue cultures in concentrations above one to one hundred and fifty, they are mildly toxic for chick embryo fibroblasts, macrophages, and epithelial cells.(52)

A number of investigators have placed sulfanilamide in experimental wounds in dogs, rabbits, and guinea pigs. Although some of the workers have reported that the drugs cause bleeding and the formation of gelatinous clots,(57) expecially if used in excessive amounts, others have concluded that in general sulfonamides do not damage tissue or interfere significantly with wound healing.

In contrast, other workers have presented evidence based on animal experiments suggesting that the sulfonamides may interfere with normal healing processes. Hawking,(38) working with guinea pigs, found a diffuse infiltration of polymorphonuclear leucocytes and monocytes in the tissues about wounds that had been treated with sulfanilamide, sulfapyridine, and sulfathiazole. This reaction he concluded was no greater than a foreign body would cause. Taylor reports that an inflammatory reaction in the form of edema and accumulation of polymorphonuclear leucocytes and monocytes occurs when sulfanilamide, sulfapyridine, sulfaguanidine, sulfathiazole, or sulfadiazine are placed under the anterior rectus sheath in dogs. After three days, crystals of sulfathiazole and sulfadiazine are still present, and minute abscesses form around some of the crystals. Glynn used sulfanilamide, sulfathiazole, and sulfapyridine locally in rabbits. He found considerable edema and polymorphonuclear leucocytic infiltration during the first three days. Phagocytic activity actually appeared to be decreased in wounds that had been treated with the sulfonamides. Definite muscle injury occurred in all of the wounds treated with sulfanilamide. Sulfathiazole produced slight inhibition of fibroblast proliferation while sulfanilamide did not. He concluded, however, that the evidence of irritation is not sufficient to warrant discontinuing the use of these drugs locally.(79)

The effect of sulfonamides on nerve and brain tissue has been studied by several workers. Holmes and Medawar found that sulfanilamide in high concentration causes degeneration of the axon and myelin sheath when applied to peripheral nerves of rabbits. The sulfonamides when applied to the sectioned and repaired nerves of the cat produces a foreign body reaction. The local use of the drugs, however, has no specific effect on the connective tissue sheaths or other nerve fiber sheaths.(38) One group of investigators obtained extensive fibroplasia in the dura, inflammation in the leptomeninges, vascular engorgement and hemorrhage, conspicuous microglial changes and gliosis in the wounds that were treated with the sulfa drugs.(71) They have also produced convulsions by placing sulfathiazole on the cerebral cortex.(77)

The reports describing the effect of the sulfonamides on the peritoneum are conflicting. Some authors(53)(57) state that sulfanilamide does not cause any gross or microscopic change in the peritoneum of dogs. Other workers state that there is no reaction with sulfanilamide or sulfathiazole, but that there is marked reaction with sodium sulfathiazole. On the other hand sulfathiazole, sulfanilamide, and sulfadiazine used in various forms produce adhesions in dogs, sulfadiazine producing a much greater local reaction than sulfanilamide or sulfathiazole.(15)

In human beings sulfanilamide and sulfathiazole have been used locally in clean operative wounds, in compound fractures, in traumatic wounds, and war wounds. The reporters observe reactions varying from no retardation of healing to delayed healing in fifty to seventy five per cent of the cases.(12) Delayed healing, which occurs when the drugs are used in large amounts and leads to the collection of serosanguineous fluid and to clot formation, could be avoided by not placing the drug between the skin edges and by reducing the amount of drug used.(58) One author in a clinical observation of over sixty cases states that in "muscle and fascial layers the sulfonamides appear to delay healing by their chemical effects on cell proliferation and by their presence as foreign material".(44)

Only a few microscopic studies have been performed on human subjects. Veal and Klepsen took biopsies from over seventy chronic ulcers. They noted that prolonged use of sulfanilamide may retard healing by inhibiting cellular growth and by retarding the vascularization of the granulation tissue. On the other hand, Rea, who studied tissue excised from the edge of neglected wounds, found no gross or microscopic evidence that sulfanilamide interfered with the normal physiology of healing.

The most recent work on the effects of the sulfonamides on human tissues was done by Posch and his associates. They obtained hospital volunteer patients. The skin of the back was cleansed and under anesthesia two identical incisions were made in the paravertebral resion. The incisions were approximately two centimeters in length and extended down to the paravertebral muscles. Two tenths of a gram of sterilized sulfanilamide or sulfathiazole power was placed in one of the wounds. The other wound was used as a control. Both wounds were closed with fine silk. At intervals varying from one to twenty eight days both wounds were completely exicsed.

Grossly the sulfonamide treated wounds had a broader scar than the controls. The deep portion of some of the sulfathiazole wounds that were excised during the first week was found to be separated by gelatinous clots not seen in the control wounds.

Microscopic examination of biopsy specimens taken within one week after the experimental wounds were prepared revealed a marked leucocytic exudate and focal areas of necrosis in the deep layers of the dermis and in the subcutis of the wounds in which sulfa had been placed. Fibroblastic proliferation appeared to be slightly delayed in the wounds that had been treated with sulfa. Since epithelial proliferation occurred promptly in both treated and control wounds, casual gross inspection led to the assumption that the wounds were healing with equal rapidity.

Examination of wounds excised seven to fifteen days following their preparation showed healing to be comparable in all wounds. In a few instances some evidence of infection and foreign body reaction was evident in the wounds in which the drugs had been placed. The fibrocyte proliferation appeared equal in all the wounds and collagen production was uniform.

From a study of the excised biopsy specimens, it is evident that sulfanilamide and sulfathiazole act as irritants to the dermis and the subcutis. In addition, they may produce focal areas of necrosis and marked leucocytic response in the adjacent tissues. However, the deleterious effects are short lived and are not evident in wounds seven to ten days old. Subsequent healing is prompt and within normal limits.

It is apparent that surgeons who employ the sulfonamides in wounds must be willing to accept an increased inflammatory reaction about the wound and an initial delay in healing. These undesirable effects can probably be minimized by the use of small amounts of the drug in the microcrystalline form. If excessive quantities of the sulfonamides, especially sulfathiazole, are placed in wounds, large aggregations tend to form that are absorbed very slowly.(76)

The tissue toxicity of some of the newer antibacterial substances has recently been compared with their speed of action and fate in the tissues. The substances tested were streptomycin, sulfamylon, calcium penicillin, parachlorophenol, tyrothricin, and zephiran.(50)

The average index obtained for the length of time required for the exudative phase and to produce two millimeters of new tissue was seven and one half days. Four hundred units of streptomycin combined with five per cent sulfamylon definitely slowed the rate of healing. Parachlorophenol gave only a fair rate and tyrothricin was just average and produced a slight exudate. Granulations remained thin with it. On the other hand, excellent healing rates were obtained with sulfamylon, five per cent and one per cent, and streptomycin, two hundred units per cubic centimeter, and with the combination of these. Calcium penicillin gave only an average healing rate while sodium penicillin definitely retarded the rate of healing.

For local chemotherapy sulfamylon, five per cent seems to be superior to the six previously mentioned antibacterial substances tested. It possesses the widest range of antibacterial activity and is relatively nontoxic. It is active in the presence of pus and blood and is not affected by changes in the acidity of the environment. It possesses rapid bactericidal activity. Sulfamylon in a concentration of less than three per cent should not be used. Neutralized sulfamylon should be used.

Streptomycin is next best. It failed to attack the streptococus in concentrations of two hundred units per cubic centimeter, and this antibiotic is destroyed by increasing the acidity of the environment. Like sulfamylon, streptomycin acts rapidly in the presence of blood and is relatively nontoxic.

Penicillin is placed third. It is nontoxic, but penicillin is readily destroyed by changes in pH and possesses a very narrow range of bacterial activity. Resistant strains are not infrequently encountered and this antibiotic becomes almost worthless in the presence of a mixed infection. Penicillin does not destroy mixed bacteria, and conversely, penicillin is destroyed.

The mixture of sulfamylon five per cent and streptomycin is nontoxic, relatively stable in the wound, and has almost a complete range of bacterial activity including the anercbes of gas gangrene. Soft white healing is obtained. This mixture was used unsuccessfully, however, in the treatment of open wounds containing slough and sequestra. The mixture did not prevent the regrowth of pyocyaneus over the surface of wounds or burns.

Tyrothricin, parachlorophenol, and zephiran have a toxicity which permits their use only on granulating wounds.

Much experimental work has recently been done on the effect of various local agents in regard to their beneficial and stimulating action on wound healing. Unusual healing effects were obtained some years ago when living blowfly maggots were placed directly into chronic nonhealing wounds. Announcement of the success of this novel treatment attracted a good deal of interest. The question then arose as to how blowfly maggots can promote healing. Baer,(3) apparently, was the first to state his belief that these results are not due entirely to the scavenger action of the maggots in cleansing the wound. He conceived the idea that in addition, "some biochemical exchange takes place between the maggot and the tissues of the patient". It was later found that allantoin, a metabolic product present in the maggot secretion, and urea stimulate healing.

Maggots secrete comparatively large quantities of ammonium bicarbonate directly into the wound. It is this compound which is responsible for the stimulating effect.

A catalyst with a background of unusual chemical interest, namely, the enzyme urease, is apparently the agent responsible for the production of ammonium bicarbonate in maggot secretions. This enzyme which has been known since 1860 has recently been found to occur abundantly in the tissues and excretions of surgical maggots. Urease hydrolyzes urea and produces ammonium carbonate by means of two successive reactions. A molecule of urease first combines with one of urea. Then it immediately disrupts the urea molecule. From this reaction the enzyme emerges free, and if another molecule of urea is available urease at once reacts upon it without any measurable loss of time. The carbonate is unstable and with a loss of one molecule of ammonia it becomes ammonium bicarbonate.(86)

Schaeffer(88) of the University of Southern California has been studying the effects of local instillations of amino acids on the rate of healing of experimental wounds on the corneas of guinea pigs and rabbits. Both superficial and deep incised wounds were made on the corneas of these animals. One eye was treated with an amino acid solution while the other eye received a boric acid preparation. Schaeffer concludes that the same phase of healing is reached after two days in the amino acid accelerated eye that is reached only after six days in the nonaccelerated control eye. This is equivalent to a threefold speed-up of wound healing as a result of the forced instillation of amino acid.

In any wound, areas of local acidity may result from stasis and carbon dioxide accumulation, or from the production of organic acids by cells suffering from oxygen want. Various observers have measured the pH values of healing wounds and found that they varied over a very wide range.(24) There is little agreement as to the values required for optimum healing. Robinson(86) observed that alkaline solutions (ammonium carbonate) promoted wound healing and reduced the number of stitch abscesses.

It has been shown that oxalic acid hastens the healing of normal noninfected wounds. In combination with sulfathiazole the gain in time averages twenty per cent.(27)

It has been shown that chlorophyll has definite bacteriostatic properties,(92) and under suitable environmental circumstances apparently even some bactericidal capacity. The action of chlorophyll seems to be more in the nature of enhancing tissue resistance by relative acceleration of the normal repair mechanism. It has a definite stimulating effect upon normal fibroblastic proliferation.

Further investigation using chlorophyll in conjunction with some of the newer antibacterial has been done.(91) The topical use of penicillin ointment combined with one per cent chlorophyll gave spectacular results. The sulfa compounds in combination with chlorophyll showed some acceleration of healing but not nearly as much as did the penicillin mixture.

LOCAL MECHANICAL AGENTS

Turning now from the local effect of drugs on wound healing, the effect of mechanical agents will be briefly discussed. The favorable influence of selective, purposeful mechanical pressure on wound healing has been discussed by Blair(13) who lists the four basic ends to be gained as: Elimination of dead spaces; control of oozing; limitation of stasis; limitation of the amount of plastic substance that pours into the wound. Of more fundamental interest was the demonstration by Twymon(98) that epithelium proliferates readily when subjected to pressure that restrains the growth of connective tissue. Hence by regulating the bandage pressure to an amount which corresponds to that required to blanch the finger nail, the granulation capillaries are compressed or collapsed and the tissue is repressed, while epithelial growth proceeds unaffected.

The effect of cooling on wound healing has been investigated.(64) It has been found that certain harmful effects result from prolonged refrigeration of living tissue, such as is advocated by some for amputation of gangrenous infected extremities. The results show that during the cooling period there is no reaction on the part of the tissues to the injury, and that subsequently there is a definite lag in the healing of the wounds, the degree of delay varying with the duration of the cooling period. In wounds treated by delayed suture after cooling for twenty four or forty eight hours the incidence of infection is much greater than in control incisions maintained at normal temperatures.

LOCAL IRRADIATION

The effect of irradiation on wound healing will next be discussed. That the recorded experiences with relation to irradiated wounds are somewhat conflicting is not astonishing in view of the different experimental conditions under which the several tests have been conducted. Ritchie(84) concludes from a review of the literature that, in spite of conflicting evidence, it appears that small doses stimulate the healing process. On the contrary, he believes that when larger doses, approximating those used in the treatment of malignant tumors, are administered within forty eight hours of the incision there is a definite retardation. The retarding effect is less on epithelium than on connective tissue. Moreover, a retardation was found in all wounds exposed to any dose twenty four hours after the incision, the degree of slowing varying directly with the dosage. In addition, wounds subjected to varying doses forty eight hours after the incision were retarded only by the larger doses whereas no change followed smaller ones.

SUTURE MATERIAL

The principle of suturing wound edges together with various types of thread is not new. 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, and to secure primary healing.(90)

Henri de Mandeville, Parecelsus, and Pare' studied the problems involved in suturing wounds quite thoroughly. The latter recommended that the foreign bodies be removed and the divided parts be united with fine linen. Halstead in America and Kocker in Europe were not satisfied with the high percentage of wound infections and experimented with silk. Finally in 1913, after several years of research, Halstead published his classical paper on the uses and advantages of silk.

The controversy over the type of suture to be used in approximating wounds has been oscillating from absorbable to nonabsorbable to absorbable types for years. It is still one of the most prominent questions for research today.

Many prerequisites have been advanced for an ideal suture but tissue reactivity should be the cardinal factor in the choice of the ideal suture material. Halstead(37) believed, "the merits of sutures should be based entirely upon the reactivity in tissues, wound strength and ease with which they can be handled". By tissue reaction we mean the type and degree of response of various tissues to a foreign body. Nonirritating sutures will not induce the inflammatory changes which retard wound healing. Sutures causing the least reaction facilitate wound healing by reducing the inflammatory changes. Nevertheless, catgut, which causes the greatest reaction, is still the suture of choice, but the trend is changing to nonirritating sutures. Catgut wounds have a longer quiescent or lag period, lasting from four to eight days, than wounds sutured by other material. There is a definite relationship between the microscopic picture of healing and the strength of the wounds. They are inversely proportional, the greater the reaction the weaker the wound. In attempting to find an ideal suture material, Large(63) has compared the tissue reactions of nylon, catgut, silk, cotton, and stainless wire. He found that wire, cotton, and silk led to reactions of considerably less intensity than catgut or nylon.

Cotton, one of the most important vegetable fibers, is readily available as suture material in the form of ordinary thread. It is inexpensive, pliable, fine, and is easily sterilized. Cotton, a cellulose material, consists of unicellular hairs which occur attached to the seed of various species of plants of the genus Gossypium. Each fiber is formed by the outgrowth of a single epidermal cell of the testa or outer coat of the vessel. Microscopic examination of the mature cotton shows that the hair is twisted and flattened. This characteristic is of considerable technical importance, the natural twist facilitating the operation of spinning the fibers into thread and yarn. It also distinguishes it from silk and linen which have no natural twist and consequently have more of a tendency to fray out. Cotton thread is made from the long fiber Egyptian or Sea Island cotton. When spun, it is usually made up of six cords which do not become unraveled as easily as twisted silk or linen. In addition to the plain cotton there is a mercerized thread. The latter, as will be shown, is somewhat stronger, size for size, than the plain thread, although it contains but three cords. The process for its production was devised by Mercer in 1813 and consists essentially of putting cotton thread in a warm twenty five per cent solution of potassium hydroxide for an hour, which produces a quick shrink and at the same time a glossy sheen. Following the immersion in the alkali, the cotton is either washed in running water until neutral, or the alkali is neutralized by acid. When finished, the pH of the mercerized thread varies between 6.8 and 7.2.(72)

Among the important articles that have been published advocating the use of cotton thread as suture are those of Meade and Ochsner,(72) Thorek,(97)(96) Crile,(22) and others.(26)(34) Meade and Ochsner showed that while unsterilized cotton has not quite the tensile strength of silk of equivalent size, after sterilization of cotton by boiling, there is an eleven per cent increase in its tensile strength, compared with only four per cent increase in silk. In their experimental work on animals it was found that there were moderate inflammatory reactions in the cutaneous tissues about both plain and chromic catgut, the latter somewhat more pronounced than the former. The edema was much greater than that surrounding either silk or cotton sutures. They emphasize the disadvantages of catgut in that the preservatives used in preparation of catgut are deterrents to wound healing, that they produce a local inflammatory reaction characterized by increased exudation, bringing about what Gage(35) has termed a wet type of healing, whereas silk, linen, and cotton produce but slight inflammatory reaction and result in a dry type of healing associated with early fibroblastic proliferation.(17) Halstead emphasized the use of fine suture material, the obliteration of dead space, and the combined use of absorbable and nonabsorbable material should be avoided. Apparently the compact structure of cotton prevents the ingrowth of tissue and lessens the incidence of suture sinuses which are rather common with the use of silk, particularly when used in superficial locations. It has long been known that the formation of sinuses incidental to the use of silk is much more frequent with continuous than with interrupted sutures, probably because infections are able to traverse the entire length of a wound along the track formed by a continuous suture. Due to its high coefficient of friction, cotton is not likely to slip after the first throw of a square knot. Furthermore, it can be tied with reliable square knots. After implantation in a wound, catgut, silk, linen and cotton decrease in tensile strength in the order named. It has been found that catgut lost thirty per cent of its original tensile strength in four days, fifty per cent in seven days, and sixty per cent in ten days.(56) Wounds sutured with cotton showed the least reaction and healed in a shorter length of time.

In the research department of Temple University Medical School extended studies have been made by Large in regard to the relative values of suture materials. He found that among ordinary suture materials the tolerance of the tissues to sutures is in accordance with the following listing: Fine stainless steel wire, cotton thread, silk, nylon, and catgut.

Hinton and Localio(45) state that various objections have been raised against the use of catgut. Among the more important of these are difficulty of sterilization, allergic sensitivity, variable absorbability, deleterious effects of chemicals, such as the production of serum, delayed fibroblastic activity, and delayed wound healing. Other well founded criticisms are increased incidence of wound infection, wound disruption, postoperative hernia, and unreliability of the square knot tied with catgut.(54)(99)

Experiments by Large(63) showed that anastomoses and wounds sutured with catgut were weaker than with any other kind of suture. The tissue through which it passed showed all signs of foreign body reaction from the fourth day until the catgut was absorbed. The reactions from chromic and plain catgut were highly cellular with a prolonged destructive phase characterized by giant cells, polymorphonuclear leucocytes, and round cells. In many sections the central zone of reaction revealed loss of cell structure and beginning necrosis. From these observations it would appear that patients whose wounds have been united with catgut are allowed out of bed when their wounds are the weakest, from the seventh to the fourteenth day, during the lag period.

The use of large amounts of foreign material both as ligatures and in the repair of divided tissues predisposes toward prolongation of the exudative phase, delays healing, and promotes infection. The suture is the most important of the foreign bodies which the surgeon introduces into a wound and in most instances the only one.

As has been stated the excellent results which Halstead obtained in his operative work were due to his great attention to careful gentle surgery, meticulous hemostasis, and the use of fine suture material. He chose silk, and today many surgeons are using silk in clean operative work of all sort. Suture material causes foreign body tissue reaction because of its size and quantity and because of its own chemical composition. Silk has shown itself much less irritant than catgut and may be used in much finer sizes. The work of Whipple has shown without doubt the superiority of its use in clean surgical work. The experiments of Howes on the strength of wounds sutured with catgut and with silk have shown that the exudative reaction lasts longer with catgut, and that the full strength of the wounds is gained somewhat earlier with silk than with catgut. Fewer complications follow the use of silk, as has been shown by Shambaugh's complications and nearly ten times as many minor ones after catgut, as after silk suture. This, however, does not tell the whole story since the use of silk usually requires a different technique of handling tissues than catgut. Silk is finer and the strands are more easily broken so that the surgeon must perforce be gentler in handling tissues, and there is less tendency to suture under tension. The knots of silk may be cut very short, since they do not swell and untie like those of catgut. Because of this factor alone less foreign material is left in the wound. There is, however, some misunderstanding about the type and sizes of silk which should be used and the manner of silk usage. Silk should be used in the fine grades, the finer the better, but since no two manufacturers use the same system of grading silk and since there is no standard, it is not possible to state sizes definitely. As a general rule the surgeon who starts to use silk after using catgut tends to use the silk in sizes comparable to those of catgut. This is quite unnecessary even if we wish to have sutures of equal strength. The heaviest silk used should not be as coarse as 0000 catgut. With reference to catgut in wound healing, we must also recognize the work of Kraise, Kesten, and Cimiatti on catgut sensitivity, and the experiments of Jenkins on rates of absorption of different types and brands of catgut. There is no doubt that in some wounds catgut disappears very rapidly, apparently as a result of specific reaction of the tissues to it. On the other hand, Jenkins has shown that the rate of absorption is quite variable and does not correspond to the anticipated rate. The length of stay of catgut in a wound is uncertain and its premature absorption may lead to separation before healing is firm. Whatever the type of suture material used it should be the finest in size that will hold the tissues in apposition.

The suturing of skin or other tissues under tension is another factor which predisposes to delay in healing. Suture should not have greater strength than the tissues sutured, since if tension becomes too great the tissues will tear through. Particularly disastrous are tight skin sutures where a linear necrosis of the opposed edges may lead to a serious infection. In instances in which closure cannot be accomplished without tension the surgeon should have recourse to the various types of skin grafting in order to close the wound. The same constricting type of necrosis may occur in deeper tissues.

With regard to the old question of absorbable versus nonabsorbable suture it seems that the pendulum at the present time is swinging toward the nonabsorbable sutures. This, however, may be only another temporary shift. As Fallis has said, "It is probably true that care in suturing is more important than the suture material used."

INFECTION AND ANTISEPTICS

Of the other local factors which interfere with wound healing, infection has probably received too great an emphasis at the expense of other equally important ones. Since this is such a large subject in itself, only the factors directly pertaining to wound healing will be briefly discussed.

The prevention of infection is not synonymous with the use of antiseptics. Whether or not infection will develop in a wound or operative incision will depend upon the nature of the contaminating microorganisms and upon whether or not the soil within which they find themselves is favorable for growth. The development of infection will depend to a large extent upon those things which lead to disturbances of healing, so that we can look upon infection simply as a complication of healing. Whether or not infection will occur will depend in turn upon our success in ridding the wound of a sufficient number of bacteria and leaving the tissues in a condition able to combat successfully the bacteria that remain.

We may begin with the assumption that every wound regardless of how it is made, operatively or accidentally, is contaminated. It has been shown that even in a well appointed operating room, bacteria fall on a Petri dish at the rate of from one to two per minute.

The bacteria which contaminate a wound vary in virulence and pathogenicity, and in their ability to accommodate themselves to growth in the host. We can seldom predict just how readily a certain strain of bacteria will grow in a particular human host. For clinical purposes, however, we may divide the sources of wound contamination into two categories: Contamination with bacteria from their natural habitats, and contamination with bacteria from human or analogous sources. To the first category belong such organisms as gain entrance to wounds at time of injury from an object not recently contaminated from human sources. To the second category belong those organisms which are transferred directly to the wound from a human host, from a culture, or from certain animals.

The distinction between the two sources of wound contamination is important. It has been shown that the incubation period for bacterial growth in human tissues varies with the organisms and with the recentness with which they have been in contact with human hosts or appropriate culture media. When organisms gain entrance to tissues they do not at once begin to grow but lie dormant for some time until they become acclimated to their new environment. During this period of acclimatization or incubation they remain localized to the site of entrance and the wound is merely contaminated. If proper measures are taken, the bacteria may be mechanically removed before infection occurs. After the period of incubation has passed growth occurs and the wound is infected. Mechanical cleansing cannot then be accomplished; in fact, local surgical measures may be extremely dangerous.

The following approach to the question of wound healing is new. It deviates from the histopathologic description already presented. There is inherent in the healing of all wounds a physical law of repair. A wound can be defined as a break in the continuity of tissue. All things being equal, so long as continuity exists function is normal. Immediately ensuing a break there are certain definite changes which take place. These changes are at first physical and mechanical and later chemical and bacterial. It takes time for chemical changes to occur and time is required for the incubation of bacteria, both of which inhibit the perfect healing of a wound. The proper way to eliminate these is to repair the wound while it is still in the mechanical and plastic state.

A piece of metal which suffers a complete fracture if welded while fresh results in good union. If left to rust or corrode, union is poor. So in the healing of a wound, it is conditioned upon early approximation. Early, it is a matter of simple mechanical coaptation. The time of election is the period from zero to six hours following injury. The law of repair then holds good and is: "The healing of a wound is directly proportional to the timeliness of its aseptic coaptation."(93) Primary union then occurs and brings early restoration of function.

The secondary period, chemical and bacterial, needs elucidation in order to stress this law further. The chemical and bacterial changes are due to nature's oxidation principle. Oxygen is the disintegrating principle of life, working night and day to dissolve, separate, pull apart, and dissipate matter. It is the prime factor in the law of conservation of energy. It is both upbuilding and tearing down.

The problem as to methods of removal of these organisms, once present, from wounds has been attacked from two viewpoints. First has been the attempt to destroy them with heat or chemicals. Boiling oil and the red hot iron have passed into the shades of medieval surgery; while chemical antiseptics as a more modern counterpart have still not reached that stage of perfection where they destroy bacteria without injuring also the delicate living cells upon which healing depends.

As far as fresh traumatic wounds are concerned we would be far better off with a total ignorance of all chemical bactericidal agents and if we only utilized our knowledge of bacteria and of wound healing by gentle mechanical cleansing of the surrounding skin and open wound of all dirt, foreign bodies, dead or devitalized tissue, and by flooding the invisible bacteria away by means of sterile salt solution.(81)

All of us have a very powerful antiseptic that we keep in our bodies and which we are apt to forget. That is the body cells. We are apt to forget that we have lots of cells which can phagocyte bacteria. It is by means of these that we probably get rid of most of our infections. Of course, just the picking up of a microbe by a cell doesn't mean that the microbe is dead. Most cells are greedy; at least they can be very greedy, and they can pick up more than they can digest. If cells digest too many microbes, the microbes destroy the cells, not the cells the microbes.

Chemical antiseptics may affect the natural defenses. This can be described and estimated by the use of a contraption called the slide cell.(33) Into a narrow cell you run blood, plus microbes, plus chemicals. Now suppose you run in blood, plus about fifty staphylococci, along with a little salt solution. You get two or three staphylococcus colonies; the blood kills the rest. Blood is a good killer of microbes as long as the leucocytes are intact. Then as you put in carbolic acid, beginning with a weak solution and making it gradually stronger and stronger, more and more staphylococci appear. At a dilution of one in six hundred and forty of carbolic acid, all the staphylococci grow. The antiseptic then has made the blood a first class culture medium. Carbolic acid has this effect because it kills the cells, the polynuclear leucocytes, in a concentration at which it won't injure bacteria. By this method it will be found that carbolic acid and all the other common antiseptics used kill leucocytes more easily than they kill the microbes.

Our profession is being deluged with pharmaceutical advertisements tant necrosis encourages too much the growth of the organisms not killed.(82)

The second method of removing bacteria from wounds has been that of mechanical cleansing. Debridement of dead or devitalized tissue and of foreign materials plus a careful flooding away of the bacteria with sterile water or normal saline solution will usually leave the tissues in such a healthy state that they can cope with the few organisms present without exhibiting the evidences of clinical infection. The harm which has resulted from pouring strong antiseptics into open wounds cannot possibly be estimated.

MISCELLANEOUS FACTORS

AGE

There are a certain number of general factors which have a direct or indirect effect upon wound healing. It is well known that age has a potent influence on the rate of healing. This relation has been investigated by du Nouy who has shown that the age of a person can be expressed in terms of a constant which in a formula of the healing rate corresponds to his physiological activity. Or, stated differently, the index of cicatrization of a wound indicates exactly the age of the patient.(1) Carrel has shown that healing of wounds occurs at a rate inversely proportionate to age and other investigators have confirmed this observation.(68)

The increased rapidity of healing which is characteristic of younger individuals is usually accepted as being due to an increased rate of cellular proliferation. Another interpretation, however, is that this may be the result of a diminution in the amount of retardation entering into the process. In fact, Howes and Harvey(49) interpret their experiments to indicate that healing in the young is less retarded, and not because the rate of fibroplasia is greater.

SYSTEMIC DISEASE

We are all familiar with the delayed healing that may occur in the aged, but we all know also that healing does occur in the aged as well as the young and that often the diseased condition rather than the age alone is the more important. Certain diseases such as diabetes and nephritis retard healing, but by what mechanism we are not always certain.

Frequently the circulatory disorders which may be present are the most potent factor, since it is general experience that the diabetic may be subjected to operation as may the nondiabetic, provided the condition is of nondiabetic origin, and healing may be confidently expected by first intention. Acute and chronic anemia unquestionably may interfere with wound healing, through what mechanism we cannot be certain, though we must think of hypoproteinemia, oxygen, and nutritional want.

EARLY POSTOPERATIVE WALKING

During the early days of modern surgery patients were kept in bed after clean laparatomies and herniorrhaphies for periods of three weeks or more. Immobility of the wound was felt to be so important that plaster spicas were applied after herniorrhaphies. Rehn,(80) in 1902 sensed the danger to the patient as a whole in contradistinction to the wound itself in this regimen of immobilization and proposed respiratory and muscular activity as well as a sitting position for the patient while still confined to bed.

The most violent break in traditional postoperative care had its inception in the chance observation of Emil Ries that a patient in Morrisiani's clinic had a wound which healed well in spite of the patient having walked across the room the night after operation. Ries(83) began to get patients up out of bed in twenty four to forty eight hours after vaginal hysterectomy and soon extended the method to laparatomies. He attributed his courage to Abel, who had demonstrated that the avoidance of incisional hernia depends upon accurate layer closure and the prevention of infection.

About 1906, Kummell of Hamburg was practicing and strongly advocating early postoperative walking. The method received rather general acclaim in Central Europe, so that a pertinent questionnaire sent to such surgeons as Bier, Koenig, Gaberer, Witzel, and Dederlein, among others, was published in 1912.(75)

From then on it has retained many adherents and lost some others. It received favorable notice in the famous surgical text of Bier, Broun, and Kummell and was discussed at many surgical meetings. The use of the method spread throughout all Europe and was reported from Africa and South America.

Rather remarkable, except for the Central European clinics about 1908 to 1912, university clinics have had no part in the development or evaluation of postoperative walking.

Andre' Chalier of Lyon has done much to popularize early postoperative walking in Latin countries. He considers this to mean getting patients out of bed from the second to the fifty day postoperatively. In contrast to him many others have by their example and publications, advocated what is called immediate arising; that is, walking from the operating table back to the room and continued activity out of bed until discharged. This method now has a fairly wide following.(73)

It is of more than passing interest that this method of early mobilization of patients after operation was forced on some surgeons by lack of adequate bed space in hospitals.

As indicated previously, the distinction between early and immediate postoperative walking is clear. The daily postoperative continuation of bodily activity, including walking, self care in matters of toilet, dressing, and feeding, and even actual gymnastics is considered an integral part of a regimen directed toward an uncomplicated and rapid convalescence. In those cases in which early postoperative walking is contraindicated, deep breathing and leg exercise in bed are substituted for it by most of those who have written on the subject. If an arbitrary temporal limit is set, early postoperative walking may be said to mean walking within the first twenty four hours postoperatively. The rationale for this time limit lies in Henle's demonstration in 1900 that pulmonary complications occur largely within forty eight hours after operation. The belief that other complications appear or have their silent inception within a few hours after operation, if not during the actual operation itself, and certain observations on the physiology of rest and exercise will be mentioned later.

Aseptic operations with firm closure of the incision are ideal for the use of early postoperative walking. Some men have extended it, however, even to drained wounds. Neither the length of the incision nor its location has any bearing on the problem. It is of importance mainly in laparotomies and herniorrhaphies because of the ensuing high incidence of the so-called postoperative syndrome.

Local anesthesia permits immediate or early postoperative walking at any elected time. Other anesthetics require a variable recovery period. None, however, except in the presence of complications, longer than twelve to twenty four hours. Some men consider a special suture technique imperative. This opinion, however, is not generally held. The need of scrupulous attention to hemostasis as well as to other surgical fundamentals scarcely merits mention.

The obvious contraindications to the use of the method fall into two categories, general and local. Cardiac insufficiency, shock, severe anemia or cachexia, hemorrhage, or the fear of hemorrhage, the presence or even possible presence of thrombi or emboli, as well as prolonged preoperative bed confinement make up the first group. To the second belong such suppurative conditions as peritonitis, cholangitis, pancreatitis, and liver infections. To these may be added potentially infected incisions and insecure gastroenteric anastomoses, such as occur, for example, in resection for exclusion of duodenal ulcer or in colon resections. Copious tamponade also precludes early postoperative walking, but a simple telltale drain through a stab wound, such as is commonly practiced after cholecystectomy, does not.

Such complications as postspinal anesthesia headache, unexpected wound infection, or other complications may force the return to bed of patients who have been up and walking.

Although some merely admit the basic correctness of the principle of early postoperative walking, but apparently rarely use it, certain favorable results are almost universally cited. They are as follows:

1. Asthenia is avoided. This has impressed all who have used the method.

2. Morale of the patient is greatly lifted by the feeling that since he is up and leading a relatively normal life the dangers of the operation and the discomforts of the postoperative period are over or have been unduly exaggerated.

3. Economy to both patient and hospital is attained through the more rapid convalescence, discharge, and return to work, and through the reduction in the needed nursing personnel and the more efficient use of

bed space.

4. Simplification of postoperative care is attained.

5. Pulmonary complications are reduced four to five fold.(87) This marked diminution is readily credible since this same prophylactic course has been suggested by conservative surgeons for years in both elderly patients and after gastric resections where the danger of pulmonary complications is high. It is for this reason the more surprising, that recognizing the value of having patients out of bed in these restricted groups, this knowledge has not been applied to other groups of patients of only slightly less risk. Even with the lowering of mortality from pneumonia attained by use of the sulfonamide drugs and penicillin, a drop of morbidity such as is indicated from the use of early postoperative walking should be welcome.

6. A reduction in adhesion formation.

7. Many call attention to the absence of hollow viscus atony with the consequent avoidance of the use of catheter and laxative.

8. Still another contention is that laparotomy and herniorrhaphy wounds heal more benignly and rapidly with the motion of early postoperative walking than with immobilization has received experimental corroboration. Leithauser(65) attributes this shortened lag period to increased blood supply, improved lymphatic drainage and decrease of disuse atrophy of the repaired parts. It is believed that the greatest danger of evisceration is on the sixth to eighth day and that the surgeon following conventional rules will allow the patient some activity at that time.

9. Lastly the moot but most important question of reduction of

thrombosis and embolism is bound up with early postoperative walking. Of the three major factors commonly premised in the etiology of inferior caval tributary thrombosis, decreased rate of venous return is felt by many to be the most important and is the one affected by early postoperative walking. Vein wall trauma can be controlled only by careful operative technique. Through the use of heparin and dicoumarin, possibly along the lines indicated by Bergquist, changes in prothrombin time give promise of being brought under prophylactic restraint. Previous attempts and the rediscoverers' or modifiers' attempting to decrease venous stasis and thrombus formation by position or bed exercises have so far apparently failed. Barnes$_{(6)}$ found that after the use of measures directed at the prophylaxis of thrombosis and embolism, such as active and passive leg exercises in bed, massage of the lower extremities, and deep breathing, pulmonary embolism, over a ten-year period, still accounted for five and eight tenths per cent of surgical deaths despite the efforts of prevention. Actual walking, however, is said by many to minimize the occurrence of thrombosis, both the dangerous latent or silent kind and the classical saphenous and femoral. Possibly Chalier is correct in saying that if early postoperative walking does not entirely circumvent thrombus formation it surely does not assist in a cataclysmic accident but in the migration of embolic showers without danger to life. Actually those emboli that kill demand from the first a larger thrombus which does not form without a number of days of immotility. Workers with an extensive statistical background claim that postponement of early postoperative walking from the second to the third postoperative day increased the incidence of thrombosis. Further, the preoperative existence of thrombi in these fatal cases cannot be excluded and there is no reason to believe that the embolism might not have as readily occurred on the operating table as after early postoperative walking. Final judgment in this matter will rest on future well controlled clinical observations. Even if early postoperative walking does not prove to be a safeguard against thrombo-embolism, its other proved advantages would seem to make it worthy of extensive adoption.

Function and rest have both, paradoxically, been accorded great importance in growth and the healing of wounds. Larrey(81) has been cited as the outstanding early advocate of rest, yet the following passage from his works bearing on the evacuation of the wounded from the battlefield can scarcely be so construed: "The wounded should be removed to different places immediately after an engagement. The exterior and interior motion which takes place while transporting them excites and promotes the functions of the organs. All the muscles are in motion, the circulation is accelerated, and the secretions go on. Suppuration takes place in a proper degree; the sloughs are soon detached by the increased oscillation of the subjacent vessels, the wounds become clean, their edges develop, and approach each other by the gradual expansion of the vessels; and by this gradual excitement they close together, or contract adhesions by means of the slight inflammatory swelling which succeeds." Whether Larry did or did not hold rest as an essential in wound healing, Billroth unquestionably did, and it was probably he who most greatly influenced modern American and European surgeons.

The present attitude of the majority toward this problem may best be epitomized by quoting Pool(78) to the effect that "a fairly prolonged stay in bed after celiotomy is recommended by most surgeons, largely that the coapted tissues may unite firmly before considerable strain is allowed to bear on them. On the other hand some surgeons (Kummel) advise getting patients out of bed as early as the first postoperative day. But it is manifest that a premature rising from bed is done at the sacrifice of proper wound repair which demands rest of the parts involved and this can be secured in many classes of operations only by confinement to bed for a reasonable length of time. The adoption of exercises during this period provides almost all the advantages gained by a shortened stay in bed without interfering with the best conditions for the repair of the wound." This prevalent fear of wound rupture as a consequence of early postoperative walking may well date from the tragic experiences of some of the early surgeons who were delighted when they could operate on the belly and even more delighted if they could operate during their office hours and treat their patients as ambulant.

Contrary to this orthodox opinion those who have used early postoperative walking have found no resulting deleterious effect, such as an increase in incisional pain, dehiscence, or incisional hernia while others have claimed even a smoother and more rapid healing.

SUMMARY

It is assumed that students of medicine are thoroughly familiar with all the details of wound healing. In my opinion this is a false assumption. An understanding of this phenomenon is absolutely essential to every student, especially if he is interested in surgery.

Many of the factors which we today know are essential to wound healing are not new but were recognized by medical men many years ago. Down through the centuries with the advent of new scientific instruments, experimentations, and theories, the influencing factors have been worked out in more detail, but still we have not yet reached the ultimate end point.

At the present time we understand fairly well how a wound heals, but we still do not know why it heals. Histologically, wound healing can be summarized fairly briefly. A fibrin clot forms in the wound. This fibrin clot will become permanent connective tissue. Granulations appear on the open surface and by their contraction the edges of the epidermis are brought closer together. Then the epithelial cells wander on the granulous tissue and by means of their centrifugal and stereotropic movement a new epidermis is formed.

Only in recent years has the medical profession appreciated the vital role which certain nutritional and biochemical factors play in regard to wound healing. Protein is necessary for the growth and repair of tissues. Hypoproteinemia may result from prehepatic, hepatic, or posthepatic causes. With hypoproteinemia the tensile strength of wounds is decreased and the incidence of wound disruption is greater. An in-

creased protein diet decreases the period of lag in wound healing and increases the velocity of fibroblastic repair. It has been definitely proved that an adequate concentration of vitamin C in the tissues is necessary for normal wound healing to occur. This vitamin is essential for the maturation of precollagen to the collagen of fibrous tissue. It is strongly urged that fluids in the postoperative period be primarily glucose in water and not glucose in saline because of the tendency toward edema formation in the wound with a resultant delayed healing and an increased incidence of wound disruption.

The sulfa drugs are sometimes placed in wounds with the objective of preventing or counteracting local infection. The general conclusion about the local use of the sulfonamides in wounds is that there is an increased inflammatory reaction and an initial delay in healing. These undesirable effects can probably be minimized by the use of small amounts of the drug in the microcrystalline form. Most surgeons today feel that there are more disadvantages to the use of the sulfonamides locally than there are advantages.

The long disputed question as to whether absorbable suture is better than nonabsorbable has not yet been definitely decided. At the present time cotton, which is a nonabsorbable type, is enjoying the most attention. Cotton produces a minimum of inflammatory reaction, early fibroblastic activity with a rapid dry type of healing. The main objections to catgut are its greater inflammatory reaction, a wet type of healing, delayed fibroblastic activity, and delayed wound healing. One principle which, unfortunately, has been overlooked is that care in suturing is equally as important as the type of material used.

Infection should be looked upon as a complication of healing. It is never possible to have a wound completely free of bacteria. Early mechanical cleansing with soap and water or saline is the treatment of choice. A truer statement cannot be found than, "the healing of a wound is directly proportional to the timeliness of its aseptic coaptation." The use of strong chemical antiseptics is absolutely to be avoided in open wounds.

The controversy of early postoperative walking versus rest is debatable. In the absence of the contraindications (cardiac insufficiency, shock, hemorrhage, and suppurative conditions) the evidence at the present time is definitely in favor of early postoperative walking. The definite major advantages are fewer pulmonary complications including thrombus and emboli formation, reduction in adhesion formation, better mental outlook for the patient, and more rapid wound healing.

As can now be seen, many factors are involved in wound healing. We have come to learn and agree with Paracelsus and Pare' that it is nature who heals the wounds and to man is left only the role of enhancing or hindering wound healing.

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