Nonunion of fractures

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INTRODUCTION

Since the beginning of the nineteenth century nonunion of fractures has been recognized as an important surgical problem. The vast amount of literature on this subject attests the fact that it is a difficult condition with which to deal. Great progress has been made in the last century and a half in the unravelling of the processes involved in repair of fractures and in the treatment of fractures toward preventing deformity, malunion, and impaired function. Yet absence of bony union still presents a surgical catastrophe which we should do our utmost to prevent.

The occurrence of nonunion of fractures is apparently on the increase (1). This fact may be attributable either to a poorer general care of fracture cases than we had formerly or to an increased severity of injuries produced by modern machinery. The latter factor is probably the greater. However, even if this is true, we then must admit that our treatment has not kept pace with the increased demand and that renewed effort is necessary on the part of the surgeons handling fractures if we are to reduce the incidence of this unfortunate malady.
DEFINITION OF NONUNION

Nonunion must be differentiated from delayed union primarily. Nonunion is said to exist when the physiological processes of repair of a fracture have ceased to be active and still no bony union results. The gap between fragments is filled with an inactive fibrous tissue and raw ends of the fragments are sealed over, the marrow cavity obliterated (2). Some authors have set an arbitrary time limit after which they claim nonunion exists if there is no bony union (3). However, without regard to time elapsed, if the physiological processes of repair are still active the condition is one of delayed union rather than nonunion.

The differentiation between the two is important because in delayed union prolonged immobilization will result in union and lack of it may lead to nonunion (2).
INCIDENCE OF NONUNION

The number of cases of nonunion is not great in comparison to the number of fractures treated. It is rather difficult to be sure that all cases reported as such are really nonunion rather than delayed union. Amesbury in 1829 (4) reported that he had seen fifty-six cases of false joint after fracture. This was a great many more than most other observers of the time had seen. Malpaigne (5) had no false joints occurring in patients treated by himself and saw only eleven in other patients. He mentions the following cases seen by other surgeons. Walker of Oxford saw only six or eight cases out of one thousand fractures which he treated. Hammich saw only three cases; Liston had but one; Pierson had one out of three hundred and sixty-seven cases. At the Pennsylvania Hospital among nine hundred and forty-six fracture cases admitted between 1830 and 1840 union failed in but one. During the same period thirteen cases of nonunion came in after treatment elsewhere. At the Middlesex Hospital out of four thousand fractures observed in ten years, nonunion occurred in only five or six cases. Owen (6) reviewed eleven thousand six hundred and eighty-three fractures treated at the Philadelphia General and Jefferson Hospitals from 1921 to 1931. Out of this number, one hundred and one were treated for nonunion. Henderson (7) reported two hundred and twenty-one cases which he had observed. Cowan (8) reported forty-two cases. Hellstadius (9) states that 23 percent of uncomplicated simple fractures result in nonunion with closed treatment. However,
if open reduction is performed, the incidence rises to 2.4 percent. He also says that 7 percent of compound fractures fail to unite by bony union. Cubbins and Scuderi (10), in their work on fractures of the humerus, found that 3 percent of the cases failed to unite.

Statistics available are not conclusive as to the percentage of fractures which result in nonunion yet I believe they do support the opinion that nonunion is on the increase as stated before. With the exception of Ameshury the older authors' series show only a fraction of one percent of fractures resulting in nonunion. The observers of the modern era find in some series one percent failure of bony union in fractures.

That failure of union has a predilection for particular situations in the skeletal system has been recognized for many years. In fact one author states that nonunion is a matter of situations not person (11). In a number of cases a patient with two fractures is found to have a union in one and nonunion in the other (8, 11). Norris (12) drew up a table of one hundred and fifty cases of nonunion. The bones involved in these cases are as follows: humerus, forty-eight cases; femur, forty-eight cases; tibia, thirty-three cases; radius and ulna, nineteen cases; jaw, two cases. In the eleven seen by Malgaigne the distribution was the following: humerus, four cases; radius and ulna, two cases; femur, one case; leg, one case; clavicle, two cases; rib, one case.

Gueretin (13) worked out a series of thirty-five cases of non-
It was his idea that more cases of nonunion would occur in the end of a bone away from the nutrient artery. His findings supported the idea since he found that only ten of the false joints occurred in the end of the bone traversed by the nutrient artery and twenty-five nonunions occurred in the opposite end. However, in reviewing the table compiled by Norris, we find that of forty-one cases in which the sites of the fractures were definitely determined only fourteen were in the ends of the bone opposite the nutrient arteries. Estes (14) has found that nonunion is most likely to occur in the following situations: middle third of the humerus, distal half of radius and ulna, upper third of ulna, neck and distal third of femur, upper and lower thirds of the tibia.

Moore (15) in 1859 observed that the nearer the trunk a false joint occurred the more serious it was. They occurred more frequently in the upper arm, next in the thigh, and then in the tibia.

In Henderson's (16) two hundred and twenty-one cases of nonunion, the distribution was as follows: femur, seventy cases; tibia, forty-four cases; radius alone, twenty cases; radius and ulna in eighteen cases; ulna alone in eight; the humerus in forty-one; the patella in nine; clavical in one case. The commonest site in the femoral shaft was the middle and lower third; tibia, lower one third; humerus, equal in middle and lower thirds; radius and ulna together, commonest site was the middle third; radius alone, lower third; ulna alone, middle third.

The largest percentage of nonunions occur in males in the active
period of life. Carlisle (17) in 1801 reported three cases of nonunion in males twenty to forty-five years old. Malgaigne (5) reported that all his cases were males except one three year old girl. Cowan's (13) patients were all robust men in the prime of life except two. Norris (12) believed that age was a factor in some cases of nonunion although the greater number occurred in young males. Owen (6) has concluded that fractures due to muscular action were not as often complicated by nonunion as fractures due to direct force. In his one hundred and one cases he found the following distributions as to age: first decade, five cases; second decade, nineteen cases; fifth decade, sixteen cases; eighth decade, seven cases; ninth decade, two cases.

Henderson (18) found that of two hundred and fifty-nine un-united fractures operated at the Mayo Clinic in the six years from January 1919 to January 1925 one hundred and sixty-three were true nonunion. Eighty-one percent of them occurred in males between twenty and forty-nine years of age.

From this evidence we see that nonunion occurs mostly in males during the prime of life when they are exposed to more dangers of severe injury than are the very young or very old.
PATHOLOGY AND REPAIR OF FRACTURES

The problems presented by nonunion of fractures can be understood only after a clear conception of the histological and chemical processes underlying repair of fractures has been gained. It is then easier to comprehend how deleterious influences may operate to prevent bony union of a fracture.

The earliest descriptions, (before 1880) of the mechanisms resulting in repair of bone did not include intimate details of cellular structure or chemical changes at the fracture site. The discussions were mainly concerned with the formation of callus and its fate from a macroscopic standpoint (5). The first, or Hippocrates'ian idea, attributed the formation of callus to the bone marrow. Galen believed callus was formed of excess nutritive juices brought to the injured area by the blood. At the beginning of the seventeenth century, Jacques de Marque showed that the marrow could not form callus and from that time Galen's theory was accepted until in 1684 Antoine de Heide advanced the theory that callus was formed as a result of the coagulation of blood effused about the ends of fractured bones.

The real foundation of our knowledge of bone repair comes mainly from the work of Duhamel and Haller who lived in the eighteenth century (19). Up to their time the repair of bones generally considered a simple matter as expressed by Cheselden (20): "In a fractured bone, in which the same kind of matter which ossified the bones at first, is thrown out from the broken ends, there is formed a mass
of callus matter".

Duhamel's (21) theory was evolved in 1741 after his madder feeding experiments had led him to the belief that periosteum was the mother tissue of bone. He was the first to have this idea. At about the same time Haller (22) advanced the theory that bone was produced by arteries which could deposit bone in cartilage or under the periosteum. He considered the periosteum as a vascular covering for bone to which it carried nourishment. From his studies of fracture repair he concluded that the callus was formed from the bone itself and periosteum played no essential part.

Since the work of Duhamel and Haller was published nearly two centuries ago there has been a great deal of research and controversy on the subject of bone repair but even now we have two schools of thought on this subject. There have been modifications of and additions to the two theories and the histological and chemical features of bone repair have been investigated, but the difference of opinion concerning the role of the periosteum in bone growth and repair still exists.

Hunter (23) repeated the experiments of Duhamel and came to entirely different conclusions than the latter. He considered that the first important step in repair was the growth of blood vessels into the uniting blood clot. Now since he believed with Haller that any arteriole could deposit bone it made no difference whether they came from bone, periosteum, or muscle. He found
that bone was first deposited at the broken ends of the diaphysis but some centers might occur in the callus. So he differed entirely from Duhamel who considered the callus as a product of the periosteum. He agreed with de Heide as to the effusion of blood about the fracture site.

Syme (24) became a firm believer in the periosteal theory of bone repair after his experiments on dogs. But shortly after this, Good sir (25), in his microscopic studies of bone, identified bone corpuscles which he believed laid down bone. He was convinced then that periosteum played no part in bone growth or repair but served only as a limiting membrane for bone. With the findings of Good sir he became the first to realize that living units were involved in the changes seen in bone growth and repair.

In 1868 Ollier (26) had completed his experiments on the growth and repair of bone. He concluded that periosteum played the greatest role in formation of callus, marrow took a minor part, and bone itself was the least important. His views were accepted until Macewen (27) challenged his ideas. By his researches Macewen found that bone would regenerate without periosteum, and that growth of the shaft of the bone downward from the diaphyseal discs would fill a gap in the bone. He discovered again what Good sir had contended, that the periosteum was a limiting membrane, and that bone was regenerated from bone corpuscles or osteoblasts. Thus we see again the Duhamel-Haller dispute between Ollier and Macewen. The work of these two men, although at odds in some respects, gives us much of
our modern knowledge of the growth and repair of bones.

The events taking place at a fracture site have been followed and described by a good many authors. The main difference of opinion centered about the role of the periosteum as described above. However, there have been other controversial points. Most of the older theories of fracture repair admitted of an effusion of blood or lymph immediately after fracture, formation of provisional callus which changed to cartilage then ossified, and formation of a definitive callus between the ends of the diaphysis. After the latter formed, the provisional callus was absorbed (12, 5, 29). Andre' Bonn (29) first disputed the idea that there was a cartilaginous stage of callus in fracture repair. He said that plastic lymph was changed to fibrous tissue and then directly into bone.

It is interesting to note here that Leriche and Policard (30) have advanced the idea that bone is formed directly from embryonic connective tissue and that an intermediate cartilage phase is not essential to the process of ossification. Malgaigne (5) doubted the resorption of provisional callus. He believed that callus became molded in response to muscle pressure.

After Goodsir's discovery of the osteoblast, the cellular theory of bone growth and repair was accepted by the followers of both Haller and Duhamel. They merely accepted the osteoblast as the agent by which bone was laid down. The argument continued then as to whether or not the periosteum produced these cells. Ollier (26) was the main exponent of the periosteal theory.
He believed there were two layers of periosteum, an outer fibrous one, and an inner cellular one next to the diaphyseal bone, which produced the osteoblasts responsible for bone formation. MacEwen (27) believed the inner layer of periosteum described by Ollier belonged to the diaphysis and the fibrous layer was the whole periosteum. The latter view was supported by Ely (31), Bancroft (32), Leriche and Policard (33), and Murray (11) insofar as it denied any osteogenetic function of the periosteum. Ollier's theory has been accepted by Kolodny (34), Hamilton (35), Campbell (36), Haldeman (37), and Blaisdell and Cowan (38).

The osteoblastic theory was generally accepted until Leriche and Policard (30, 33) published their new metaelastic theory of bone formation. They denied the existing belief that the osteoblast was the agent of osteogenesis. At the beginning of their researches they were strict believers in the principles laid down by Ollier but ended up denying nearly every conclusion he had laid down. They have found support in this country from Murray (11) and Bancroft (32), mainly. Thus we have a third theory of bone repair to consider. The two older theories accept the osteoblast as the important factor in osteogenesis but differ as to their origin from periosteum or cortical bone. The newer one denies any specific activity of the osteoblast or the periosteum.

Since the current concepts of the methods by which changes incident to bone repair are effected differ in several respects, it seems advisable to trace the steps in the process and discuss
the different theories which explain the mechanism involved.

All the modern investigators agree that after a fracture there is an extensive hemorrhage at the fracture site. Blood comes from the periosteal vessels, medullary canal, and surrounding soft parts which have been damaged. The periosteum is stripped up from the cortex by hemorrhage and the fracture itself. The blood clots around the ends of the diaphysis and fibrin is found in the clot three to five days after the fracture. From this point on, differences of opinion exists as to just what happens.

The Osteoblastic Theory

Organization of the clot proceeds by invasion with granulation tissue from the periosteum, endosteum, Haversian canals. As early as three to five days after fracture, small areas of ossification begin in the angle formed by periosteum and diaphysis (32). Ely (31), describes the formation of cartilage and fibrocartilage in the space under the periosteum. He believes the function of the periosteum is important only up to the formation of cartilaginous cells. He says that it probably acts as a membrane to help the hemorrhage from escaping and the granulation tissue undisturbed. In this belief he agrees with Macewen (27) but disagrees with most other observers who hold to the osteoblastic theory. Cowan (8), Ham (35), Holdeman (37), Kolodony (39), and Cowan and Blaisdell (38) believe that the periosteum plays the most important part in the repair of fractures. According to their view the cellular layer of the periosteum shows marked activity very promptly after fracture. The cells, called osteogenic cells by Ham (35), proliferate
actively, and within two days have increased greatly in number. Cells of the same type are found in the endostea, and lining of the Haversian canals but they play a much lesser role in the repair process since they are less easily mobilized.

At the end of a week the procallus is well developed and vascular communication is re-established between the fragments, the vessels running at right angles to the length of the shaft. Meanwhile bone formation near the old shaft has continued after the fashion of membrane bone formation. The bone is laid down in an area around the new blood vessels so that cylinders of bone are formed with primitive marrow spaces between them (8, 35). At the same time, close to the fracture line, in an area where osteogenic cells are proliferating very rapidly, a beginning differentiation to cartilage is seen in the callus. There is no incorporated blood supply here, only an occasional vessel is found. Ham (35) believes that cartilage forms in an avascular area where osteogenic cells are rapidly proliferating and bone forms in an area where osteogenic cells proliferate at a moderate rate accompanied by blood vessel formation. Cowan (8) states that pressure on procallus is an important factor in causing it to form cartilage. He says that medullary procallus often ossifies without a cartilaginous stage if properly treated.

With lifting of the periosteum and hemorrhage into the medullary and subperiosteal area, cortical bone becomes necrotic for a variable distance above and below the fracture line within a few
days after fracture. By the ninth day the lacunae in this area are empty and this portion of the diaphysis becomes a foreign body to be removed. Above and below this area some five to ten millimeters from the fracture line, normal bone cells are found occupying the lacunae. They show no tendency toward proliferative activity. In other words, adult bone cells play no part in fracture repair (38). The dead bone is invaded by new cells and vessels so that it appears eroded, the Haversian canals become large and irregular. At the same time new bone is deposited on their walls, continuous internally and externally with medullary and subperiosteal callus.

After the ninth day the cartilage at the center of the callus is mature and it begins to degenerate so that the matrix becomes a good medium for replacement by bone. The old cartilage matrix is invaded by osteogenic cells and vessels from the new bone already formed nearer the shaft. The osteogenic cells differentiate into osteoblasts which lay down new bone in the old cartilage matrix. Within a month at least half of the cartilage is replaced.

When function has been restored to the bone involved, the part of the bony callus which lies outside the pressure lines is gradually absorbed so that the marrow returns to its lymphoid state and the diaphysis is molded to shape (40). The new cylinders of bone which lie at right angles at first are arranged by "creeping replacement" (32).

It is well agreed among the authors who hold the osteoblastic
theory of bone repair, that the external callus plays the major role in fracture repair. Most of them attribute this to the activity of the osteogenic cells of the periosteum. Macawen (27) and Ely (31) have said that most of the osteogenesis is from the outer part of the cortical bone. There is no real difference of opinion here since the same result is anticipated no matter whether the osteogenic cells are considered a layer of the periosteum or of the cortical bone.

The Metaplastic Theory

Leriche and Policard (33) have led the way in their statement of the metaplastic theory. They have described it in detail after extensive researches into the problem of bone formation. In this country Bancroft (32) and Murray (11) have been the foremost supporters of the theory. According to their concept, bone repair results from several processes which are not necessarily peculiar to bone at all. These phenomena are a result directly of trauma, and primarily are no different than reparative processes set up anywhere in the body as a response to injury. The only difference is the fact that the changes take place next to bony tissue where there is an excess of calcium produced by rarefaction of the fragment ends. It has been postulated that the requisites for ossification are embryonic connective tissue, edema of the fundamental supporting substance, and a 'calcific surcharge'. These conditions are fulfilled at a fracture site.

Organization of the clot occurs by ingrowth of embryonic con-
nective tissue from all possible sources about the fracture site, the most important being Haversian canals, endosteum, and periosteum. At the same time there is a marked regional hyperemia due to a paralytic vasodilation which causes edema of the soft parts and decalcification of the superficial bone. The medullary tissue reverts to a young fibrous type for some distance above and below the fracture line. The conditions necessary for ossification are present from this time forward. By the sixth day after fracture, bone has started to form in the region of the callus where the periosteum and cortex meet. According to their theory, bone is laid down in a presosseous substance which forms first in the callus. This substance is not chemically defined. It appears to be a coagulation or gel material forming in the fundamental ground substance with no specific activity on the part of the cells. In fact, the metaplastic theory ascribes only an opposing action to the cells. The osteoblast is described as a reactive form which attempts to overcome the thickening of the medium in which it lives. As the process goes on, the cell is overcome and entrapped so that it becomes a mature bone cell with sluggish metabolism living in an ossified matrix.

Calcification

The fact that calcium is deposited in the formation of bone at a fracture site has been mentioned above with no description of the method by which it occurs. The process of calcification is not absolutely clear, even today, but a brief review of the current con-
cepts is in order. It is quite generally accepted that the calcium source for fracture repair is a local one derived from the decalcifying bone (32, 41, 42). The decalcification is due to circulatory stasis and changes in pH to the acid side at the fracture site (30, 43). The calcium supply thus released from the bone is held in the area. It is in the form of complex molecules containing calcium phosphate. After the fracture the fluid at the site has a pH of 7.4 which has changed to 4.5 by the fourth day. However, it then rises until at the tenth day it is 8.2 (18). Now these pH changes are probably useful in calcification by effect on phosphatase. Phosphatase is either derived from osteoblast metabolism (44) or from breakdown of cells of non-specific type (32, 33). It increases in amount in serum. The enzyme acts upon the calcium salt complex and splits off certain phosphates thus liberating more phosphate ions in a region already saturated, thus calcium phosphates together with other calcium compounds are precipitated and taken up by the bone matrix which has a physico-chemical affinity for it (44).
PATHOLOGY OF NONUNION

The pathology of nonunion is explicable only on an anatomical basis, since it is purely a local condition as far as can be determined. Investigations have been made of general conditions which might underlie nonunion, but no definite conclusions have been reached. It was believed by some observers that calcium and phosphorous metabolism might be found to be abnormal in cases of nonunion. However it is fairly well agreed today that no true relationship can be established (41, 42, 45).

In his experiments upon dogs Kolodony (39) found that perhaps endocrine disturbances had some effect on union of fractures. It has not been established that endocrine upsets have any effects on healing of fractures toward causing nonunion in human beings.

On an anatomical basis nonunion may be divided into three types, namely, atrophic nonunion, fibrous union and pseudarthrosis.

Atrophic nonunion results when there has been a loss of bone substance either by the injury or by disease. There is a large gap between the fragments and no attempt at union is found. The ends of the diaphysis at the fracture site become thin and transparent. The marrow cavity is enlarged and filled with fat. In the gap between the fragments a dense scar tissue forms (46). Roentgenograms show marked atrophy of the fragment ends. In fact they are almost radiolucent. A large gap is seen with no sign of bone between the fragments. Some authors believe this is due to lack of blood clot (47). In that case no fibrin is found at the site and according
according to some views fibrin is a stimulant to granulations necessary to form a base for the callus. Another idea is that autolysis continues (11) and gives wide separation with no subsequent filling by callus. One author has attributed a continued bone decalcification of the fragments to irritation of the peripheral nerves (48).

Fibrous union occurs in a majority of cases of nonunion. The ends of the fragments are joined by fibrous tissue. The union may be either a loose or firm union depending upon whether or not there has been much motion at the site (8). The fibrous tissue is continuous with the fibrous periosteum and fills the gap between fragments. The ends of the diaphysis are sclerotic, the medullary canal is obliterated by dense callus (46). The ends of the fragments become aburnated and are usually rounded.

In the true pseudarthrosis is found an extreme change in altered bone repair. This type is really a late result of fibrous union. With use of the part, pressure causes formation of cartilage and fibrocartilage so that the ends of the bone become covered with a cartilaginous layer (8, 33). Then small spaces or breaks appear in the fibrous tissue between fragments and finally a cavity is formed which fills with a fluid resembling synovial fluid. The ends of the diaphysis are either both convex, or, one convex, the other concave. Thus a structure very much like a diarthrodial joint is formed (8).

Here is one factor common to all nonunion. This is separation
of fragments. Some observers claim that another factor common to nonunion is laceration or complete disruption of the periosteum at the fracture site (8, 33). Ely (27) states that when the periosteum is completely divided, union may not be expected and when it is slit, bony union may or may not occur.
ETIOLOGY OF NONUNION

The causes given for nonunion of fractures have been many and varied, both constitutional and local.

General conditions given as predisposing factors in nonunion are: advanced age, pregnancy and lactation, state of nutrition, endocrine disorders, acute fever producing diseases, faulty metabolism, lues, vitamin deficiencies, paralysis.

The effect of age in healing of fractures is apparently not significant in production of nonunion, age incidence of the malady was discussed in the section on incidence.

Pregnancy and lactation have been considered factors in some cases of nonunion (5). If it is a significant cause, evidence has failed to verify the fact (6). One author states that it may be a predisposing cause by the debility which it produces (1).

Cachectic states from poor nutrition is mentioned by several authors (15, 5, 1). It is conceivable that it may play a part in an occasional patient but the very fact that most of nonunions occur in males during the active part of their lives makes this a factor of doubtful importance. There is no mention of malnutrition as a cause in the more recent literature.

Endocrine disorders have been investigated in latter years but their relationships to nonunion, if any, have not been proved. Kolodony (31), in his experiments on dogs, found that some of the animals in whom bones were broken suffered nonunion after removal of testis, thyroid or pancreas. Parathyroids were left intact.
The results of his experiments are not conclusive.

The violent febrile diseases have been named as a cause (1, 15). The cases reported are few and in recent times I have found none. It was found that, in several patients who suffered fracture and febrile disease concurrently, no evidence of repair was present when the bone was examined at autopsy. Malgaigne (5) described another effect of febrile diseases on the callus at the fracture site. He called it softening or "ramollissement" of the callus. This condition occurred weeks or months after the reparative callus had been laid down. After fever subsided the callus was thrown out again and union finally resulted.

Faulty metabolism of calcium and phosphorous and its effect on fractures has been investigated quite recently. The part it plays in nonunion is still uncertain however. There is ordinarily a significant relationship between levels of serum calcium and phosphorous and fracture repair, but in cases of nonunion an alteration of this relationship has not been found to be accountable for the failure of bony union (41, 42, 45, 49, 50). Attempts to change blood calcium had no effect in accelerating fracture repair and the amount of calcium in the blood was found to be no criterion in the prognosis of fractures (51).

Syphilis has been given frequently as a cause of nonunion (15, 1, 5, 52). Nutter has stated that it is the one general disease which will cause a failure of union (3). This view is not generally accepted today since it has been found that patients with
positive Wassermanns unite fractures as readily as others (6).

Deficiency diseases such as rachitis and scurvy have been re-regarded by some authors as important etiological factors in some cases of nonunion. Rachitis is immediately ruled out since it has been found that in patients suffering from that disease bones unite very readily (5, 12). Scurvy does have a retarding effect on bone repair but only delays union (5). In the more recent literature there is no mention of scurvy as a cause of nonunion.

Of the general causes given for nonunion from time to time, then, we must see that for all practical purposes, they may all be discarded while attention is directed toward local factors. Most authors today believe that they are all important in the causation of nonunion. Cowan (8) has stated that, of all the causes mentioned in the etiology of nonunion, all the general and most of the local ones may be discarded.

Anything which interferes with the normal processes of repair at a fracture site will cause a delay in union or prevent it entirely (43). A good many local factors have been mentioned, some due to the treatment of the fracture.

Interposition of soft parts, periosteum, or foreign bodies has been considered by most observers. When this occurs vascular re-establishment between the callus granulations is prevented and thus healing by osseous union is rendered impossible (8). Even though reduction has been made so that, radiographically, the alignment is perfect no union can result. Lucicke and Poliscar (30)
consider that interposition is the usual cause of closed pseudarthroses. They say that muscle is the interposed tissue in those cases and that although muscle can become calcified it does not in this situation because the fibers are transverse. If the fibers were placed longitudinally between the fragments calcification would proceed in the muscle. The patella is usually united by fibrous tissue after fracture, due, in some cases, to interposition of the aconeurosis covering it anteriorly (53). Cubbins, Callahan, and Scuderi (54) consider that in severe injuries continuance of the fracturing force causes interposition of soft parts and thus nonunion. They believe that the majority of nonunions are due to mutilating injuries in which the periosteum is torn and fragmented with much trauma to the soft parts.

In some fractures there is a loss of bone due to massive death of tissue or tearing away of the bone. In these cases nonunion will result only if the fragments cannot be brought into apposition (53). This may be due to traction used, or, in the case of the humerus, to the weight of the limb. This condition may also be found when there is an intact parallel bone which prevents the fractured bone ends from coming together as in the case of the tibia, fibula, radius, or ulna. Again, fusion of the vessels in the granulation tissue is hindered so that ossification cannot proceed. This is true in the adult but not in children, as shown by Macewen (27). Bones which are still growing may fill a gap in by growth at the diaphyseal side of the epiphysis. Norris (12) removed two
inches from the tibias of a twelve year old child with resulting union.

Interference with the blood supply to bone is one of the most important causes of nonunion (11, 12, 30, 41). Successful union is dependent on the fusion of new vessels in the granulations of the fragments. When the fragments are in good contact union is almost certain to occur (6). Lacy (41), in his study of nonunions, considered only those cases in which alignment and apposition were good. He believed that the blood supply was the most important in bone repair. At the time of injury there is trauma to the soft parts with consequent damage to the blood supply, causing a state of malnourishment of the fragments which will lead to nonunion, if severe enough. With tearing and fragmentation of the periosteum one of the main supplies of blood to the bone is destroyed. In fact, one of the most important structures in the repair of bone is damaged. Not only is the blood supply impaired, but the main sources of osteoblasts is taken away from the fracture site. Or to the adherents of the metaplastic theory, the main source of embryonic connective tissue is destroyed.

In the case of the head of the femur we find a situation not equalled anywhere else in the body. Fracture of the neck of this bone seldom unites readily. Brodie (55) called attention to this fact many years ago. He believed that it would not unite because of its intracapsular situation with no muscle attachments or cellular membrane, only a synovial membrane. He said that any bone in

art (59) says that it is the one important etiological factor and that all cases may be identified with it. In cases having an impaired blood supply the fragments are found to be white at operation (54). These dry fractures seldom unite without operative interference. There is no medium for ossification (30) and the pH of the area is not proper for the deposit of calcium (11). To those who believe that the blood stream is the source of calcium for fracture repair this also means that no proper amount of calcium is brought to the area (45).
Infection at the fracture site may delay union of a compound fracture, but if properly treated, the fracture will usually unite (5,12,60). If failure of union does develop in such a situation it is probably due to the fact that fibrin and growing cells are destroyed by the infecting agent. The medium necessary for ossification is then gone and a fibrous union results (11). There is also produced a large gap by necrosis of the fragment ends which remains to be filled.

Over and above nonunions due to the several local causes mentioned there are many nonunions which are apparently not caused by any of these factors. Amesbury was one of the first to say that, even those cases occurring in the face of supposedly irreproachable treatment always had a cause, and it was probably the treatment (4). He considered poor immobilization as a great cause. Callender considered that nonunion should never occur because he believed that it was always due to improper treatment (61). Malgaigne and Norris supported this opinion (5, 12). Henderson has reported that sixty-three percent of his cases of nonunion were due to improper immobilization (7). Jones and Roberts have gone so far as to say: "It may be categorically laid down that inadequate immobilization is the only cause for nonunion" (62). They point out that the great majority of cases occur at precisely the points in bones that are the most difficult to immobilize. With constant movements of the fragments, there is a shearing and twisting force brought to bear upon the callus, which ruptures the newly formed capillaries and
disrupts the continuity of the young connective tissue. Union cannot be completed without a continuous mass of connective tissue to fill the defect and an incorporated blood supply. Repeated trauma also gives rise to prolongation of the hyperemia and thus decalcification continues. A wider gap is left to be filled so that there is no continuous callus to recalcify. Sclerosis occurs across the ends of the diaphysis and no union is established.

Morris brought out the fact that ribs and clavicles unite even though perfect immobility could not be attained because of the situation of these bones. He said this fact needed explaining even though he believed that poor immobility was a factor in the failure of union in other bones (12). Bankart says that movement of fractured ribs is different than in other bones. When a fractured rib moves, the fragments move together and not upon each other. They maintain a constant relationship to each other, so, no shearing force is produced between them (59).

Ashhurst believes that slight movements between fragments are essential to stimulate the formation of callus and its subsequent transformation to bones (63). His contention is based upon the results of treatment by early mobilization of a fractured bone. However, it is pointed out that such treatment allows movement of the limb or at the joint and that no appreciable movement is allowed between the fragments of the fractured bone (53).

Faulty apposition of fragments has been found in many cases of nonunion. Dupuytren believed that most cases were due to obliqu-
ity of the fracture so that good apposition was defeated by muscle pull on the fragments (28). Amessbury and Malgaigne did not agree with this but believed that such cases were due to faulty apparatus which allowed the fragments to over-ride (4, 5). Macewen has named poor apposition as one of the main causes of failure of union (27). Hey Groves says that if the bone is so angulated that the fragments do not touch each other, or an adjacent surface of bone, that non-union will very likely occur (53). However, as Campbell points out, repeated manipulations under x-ray in an attempt to get perfect apposition may be a cause of nonunion (36). Speed says that malunion is much less of a tragedy than nonunion so that where it is not possible to get absolutely perfect apposition the bone should be allowed to unite and not tempered with further because of the danger of producing nonunion (64). Swart believes that good apposition of the fragments is most important for proper healing of fractures (65).

Cubbins, Callahan, and Scuderi reported cases in which no callus could be seen in the roentgenogram yet at operation a firm uniting callus was found (54). They recommend a careful clinical evaluation of x-ray negative cases. Repeated manipulations will break down the granulations and interfere with the blood supply producing new hemorrhages in the area and an increase in the size of the uniting mass of connective tissue so that fibrosis becomes predominant. The callus is crowded out and nonunion results.

It has been mentioned by several observers that lack of per-
fact anatomical reduction is one of the greatest causes of nonunion (32,65,66). This may be due either to an improper early treatment of the fracture or a delayed reduction of the fracture. In the latter case soft parts have become swollen and lardaceous. They tend to prevent a good approximation of fragments whereas they would tend to solint the bone if reduction had been done while the muscles were relaxed and pliable.

Albee (1) studied the effects of x-ray on the repair of fractures. He found that roentgen rays, in amounts used in fracture work, had no retarding affect on bone repair.

Practically all of the inadequacies of treatment which tend to produce failure of bony union after fracture may be identified with the lack of a proper blood supply in callus (41, 59, 67). Since union is dependent upon vascular fusion in the procalleus granulation tissue, anything which prevents this fusion will prevent union. Improper apposition, poor immobilization, too early use of the limb, constriction of the part by bandages all tend to disrupt or reduce the blood supply of the fracture site and the newly formed tissue there.

Pathological bone was believed by some to be a cause of nonunion (5,12,43). Some of the conditions mentioned are caries, cancer, osteitis fibrosa cystica, osteogenic sarcoma. Eliason made a study of this problem (68). He found that of all the causes of pathological fracture eighty-nine percent of them allowed ready union and that in most of them union was the rule. The fact that
few ununited fractures are seen in pathological bone is enough to
rule it out as a very potent factor in the etiology of this disease.

Nerve injury has been infrequently cited as a factor in non-
union. Campbell believes that vaso motor upset may be produced by
nerve injury (36). This would interfere with proper status of the
blood supply at the fracture site. Stimson believes injury to
nerves is important when the bone is thereby severed from its troph-
ic center (68). Most authors discredit this idea.

Turner has emphasized the importance of nerve irritation in
the production of nonunion (48). He says that the acute bone de-
calcification following fracture is due to nerve reflexes produced
by traumatic neuritis of peripheral nerves. When the irritation
ceases the process is stopped and replaced by deposition of lime
salts in the formed callus. In case this irritation is continued
longer that it should normally be, decalcification of the bone con-
tinues and a local deficiency of calcium is produced. With impro-
er amounts of lime salts at the fracture site union is prevented.
He ascribes a continued irritation in cases of nonunion to an un-
usual involvement of nerve branches due to trauma or treatment.
He reports successful treatment in many cases of nonunion after
sectioning or blocking a located sensitive nerve, thereby stopping
irritation of afferent fibers which had reflexly caused excessive
decalification.

It is evident from the foregoing discussion that according to
present day concepts nonunion is above all a condition due to local
factors, some of which are present when a patient is first seen, and some of which are produced in the treatment of the patient.
THE TREATMENT OF NONUNION

The first consideration should be prevention of nonunion by proper treatment of new fractures. It has been emphasized that fractures should be treated as emergencies (6). The patient should not be moved without proper splinting. Early accurate replacement of the fragments should be carried out as soon as possible after fracture (11). X-rays should be used to determine the accuracy of reduction (64). Reduction should be completed in one attempt and before swelling of the part occurs (32). At the time of reduction it should be determined by palpation whether or not there are interposed soft parts. The blood and lymph circulation of the part should be restored as soon as possible by elevation of the part, physiotherapy, and functional activity. If manipulation, splinting and skin traction are not successful in giving proper reduction, skeletal traction should be used (64).

In compound fractures careful and thorough debridement should be carried out and the Carrel technic used to clean the wound (11). It is preferable in this case to use saline solution rather than Dakin's solution which carries calcium away from the fracture site. It may be desirable, in open cases, to fix the fragments with plates or screws at the time debridement is done. Motion at the fracture site is thus eliminated and chance for infection to set in is reduced (53). Many surgeons condemn the use of any kind of foreign material in fixation of these cases (1,60,70,71). They believe that a foreign body reaction is set up which leads to nonunion.
Some surgeons feel that if manipulation and splinting are not successful in giving a proper reduction that early operation should be elected (64). This treatment is particularly indicated in fractures with displacement at those sites where nonunion is known to occur most readily. The operation should be carried out so as to give rigid fixation and a proper source of granulation tissue. Early active use of the part is desirable.

Although the real value of constitutional methods of treatment cannot be demonstrated they should be used on theoretical grounds (42). Cod liver oil, calcium salts, sunlight, irradiated ergosterol, may all be used in attempts to prevent nonunion. There is some evidence, however, to show that increased vitamin D over a normal diet is of no value in augmenting bone repair. On the contrary a hypervitaminosis D may be produced which tends to delay union (72). Hyperparathyroidism should be corrected if the patient is subject to it (36). It has been suggested that metabolism studies may show abnormalities in some cases, correction of which may be useful in aiding union (14). Stuck (73) experimented with the effects of insulin on fracture repair but found that it was of no value clinically. It is, of course, obvious, that the patient should be treated as an individual and corrective measures taken for any other abnormal condition which he may have beside the fracture.

After nonunion has become established active treatment is necessary if the condition is to be cured. Liston (74) mentioned
a great variety of methods to be used. He recommended six procedures to be carried out. Compression and rest were his first considerations. Friction by manipulation of the fragments or weight bearing was his next step. If the fracture showed no progress then a seton was used with some good results. Application of caustics to the fragment ends was the next method of choice. If all these measures failed he resected the ends of the fragments. After a fair trial was given all the foregoing, and no union resulted, amputation was the last resort, if pain and deformity warranted it. Some of these methods are in use today although they are used mainly for delayed union and not nonunion.

Methods used today are; needling of the fracture site, injection of calcium salts at the fracture site, injection of whole blood, Bier's hyperemia, drilling, weight bearing on the lower extremity, massage, friction by rubbing the fragments together, percussion, section of sensory nerve, and open operation. Of all these, few are of any real use in nonunion. Most of them are designed to produce a certain amount of inflammatory reaction and change in the circulatory status of the part with the idea of stimulating bone formation.

The injection of calcium salts at the fracture site has doubtful value. Key (75) experimented with injections of both calcium salts and bone powder but found that neither one had any accelerating effect on osteogenesis. Albee (76) had suggested that repeated injections might be of value in cases of pseudarthrosis.
His results did not substantiate this contention.

Hyperemia caused by venous stasis as suggested by Bier was tried by Pearse and Morton. They found it of use in cases of delayed union but not in nonunion (77).

Drilling of the ends of the diaphysis has been used by some with a fair amount of success (2,35,53,64). Griswold reported results with this treatment in twelve cases. His patients had non-unions of from two months to two years standing. He used a subcutaneous drilling method whereby numerous small channels were made across the fracture site perforating the sclerotic bone ends and opening the medullary canal. Each one of these patients went on to firm union with no other treatment.

Turner (46) believes that section of peripheral sensory nerves, in some cases, is important in bringing about union after fracture. He reported that he had many successes with this treatment.

Of all the treatments suggested for nonunion it is generally believed that open operation and bone grafting is the only one consistently of value. It must first be accurately determined that union will not occur before resort is made to operative interference (64). Cases have been reported in which union by firm callus has been found at operation even though it did not show on roentgenographic examination (54). Ham, Tisdall, and Drake have shown that firm bony callus may be formed without calcification. Therefore, noncalcification is not nonunion (44). A proper period of immobilization should be allowed after reduction of a fracture.
The aim of treatment of nonunion is to reproduce the conditions of a new fracture, namely, adequate granulation tissue, proper circulatory status of the part, and a local source of calcium. It is generally agreed that bone grafting is the most effective means of producing these conditions surgically. They also give stability and more rapid healing so that earlier mobility of the part is possible.

After bone grafts had been introduced into the surgery of fractures a great deal of controversy arose as to their fate. It is believed by many that the grafted bone dies and merely gives a local supply of calcium (11,31,52,62). Murray says it is also a source of ferments for calcification. Others consider that the graft lives, becomes vascularized, and remains as an integral part of the host bone (27,54,71,78). In either case the graft promotes the desired repair.

Both autogenous and heterogenous grafts have been used, but it is agreed that the former are by far the most desirable. The main types are: medullary, osteoperiosteal, chip, inlay, and onlay.

The medullary graft has been discarded by most surgeons. It is objected to on the grounds that it interferes with the endosteal blood supply, which is important in repair, and that it gives incomplete fixation (6,36,71,76,79). It has been advocated by some, because with its use such wide exposure of the bone is not necessary and, lying in the axis of the bone, it gives strength (53,80).
It is not in general use today.

The inlay graft, as used by Albee, has given good results in some cases. It is best used in cases which have suffered no loss of bone substance (53). The main objection to this type of graft is the fact that it does not give much stability (7,15,26,79,81). Albee liked this type because it gave good contact so that healing was more assured (82).

The osteoperiosteal and chip grafts are used mainly as an auxiliary to other treatments. Lane used plates to fix the fragments, and chips to fill the spaces around the fracture site (83). Most surgeons use chips at the fracture site after any grafting procedure. Hallock has recently reported good success in the treatment of nonunion in children by the use of multiple small bone transplants (84). As a general rule these two types of graft do not give enough fixation to be used alone (79).

A massive onlay graft has been described by Campbell (36). It has found widespread use in recent times, and has been acclaimed as the best type of graft by several authors (7,18,71,79). It is particularly good because it is long, broad, and strong and when properly fixed to the fragments gives absolute immobility. Campbell recommended that the graft be fixed in place with bone pegs or beef bone screws. Henderson and Kirk have agreed with this, but quite recently Key recommended the use of metal screws instead. He has had better results with them because the graft can, more easily and more surely, be securely fixed to the host bone.
The best grafts for reconstruction of the long bones can be secured from the inner surface and crest of the tibia (18,36,71,79). These are particularly good for the massive grafts because relatively large pieces of the shaft of the tibia may be taken. Sometimes the fibula can be used for rather large grafts (71). The crest of the ilium is well suited for the taking of chip or osteoperiosteal grafts (53).

The general method of preparing a graft bed is agreed upon by all authors. The fracture site is exposed and all scar tissue removed from between and around the fragments (7). The ends of the fragments are freshened by cutting away the sclerotic, eburnated bone until normal, bleeding marrow is reached (36). In case the nonunion is of the atrophic type, the thin, decalcified bone at the fracture site is removed. In this case the use of an intramedullary, massive type of graft is justified (71). In the pseudarthrosis type of nonunion with much eburnated bone at the ends of the fragments, bone graft on or through it will not take well, so here it is best to remove all the involved portions of the bone and then fill the gap (79). In any case the medullary canal is opened. Next the rounded cortical bone is flattened by means of a chisel for an onlay graft, or, grooves are cut in the fragments for an inlay type.

The graft is taken from the tibia ordinarily, and split into spongy endosteal part and hard cortical part. The former is placed in the medullary canal and the cortical part fixed in place (38).
Any chips which are produced as a by-product of the operation are packed around the fracture site. The periosteum is then closed and the wound sutured in layers (36, 71, 79).

After operation secure plaster fixation is necessary (36, 71). This should be continued for at least six weeks or until roentgenograms show that the graft has become an integral part of the bone and good continuity of the bone is reestablished. After the plaster is removed convalescent splints or braces should be used until union is firm.

Other methods of operative treatment for nonunion in which there is no gap have been described. Hey Groves described two methods (53). In both, the fibrous tissue is first all dissected away from between the fragments. The first is a method of drilling or cutting the bone in several points parallel to its axis. The drill holes are made in both fragments and carried deep enough in each case to produce free bleeding. The bone ends are then placed in proper apposition, the wound closed, and the part put up in plaster for absolute fixation.

The second method given by this author is one in which the fragment ends are shaped so that one end is a projecting cone, the other a hollow cone into which the former fits. Or, to attain the same end, the bone ends may be step cut so that one fits the other. The fragments are then brought into apposition and, if necessary, fixed by wires or pegs. This procedure shortens the bone a certain amount so cannot be used where shortening would be a serious
detriment.

It is universally agreed that, after a compound, infected fracture, no operative procedure should be undertaken for at least six months. Kirk (71) had a great deal of experience with fractures and gunshot wounds during the war. He found it best, in infected cases, to wait at least six months and then until no sequestra are seen to be forming before operating. At operation all scar tissue is removed from the skin down to the bone. The bone ends are then freshened, covered by the scar free tissue, and the wound closed. If necessary, after removal of scar tissue from the skin, skin radiant light is used over the involved region for two weeks. if this produces no flare-up then it is reasonably safe to go on with a grafting operation. Extreme precaution is necessary because of the fact that there may be latent infection in the old wound which will light up at operation. If the grafting procedure were carried out in one stage, and an infection flared up, the whole purpose of the operation would be defeated and the situation made worse than before.

The results of operative procedures for nonunion have been fairly good generally. There are not a great number of statistics available because there are few men who have a series great enough to show any conclusive trend. In 1926 Henderson reported that eighty-three percent of the cases of nonunion treated at the Mayo Clinic from January 1919 to January 1925 were cured, and that sixty-four percent of them were treated with the massive bone graft (18). He reported again in 1938. In this series there were five
hundred and thirty patients who had been operated for nonunion, at the same clinic, in the period from 1912 to 1936. Of these, sixty-eight cases, making a percentage of about thirteen, received no benefit (81). In 1932 Campbell reported one hundred and four cases with nine failures (36). Kirk had one hundred and twenty-nine cases of nonunion after compound, infected fractures. Twenty-two of these failed to unite after the careful treatment which he advocates for such cases.
CONCLUSIONS

1. Nonunion of fractures is an important surgical problem.
2. Nonunion is found with the greatest frequency in men during the active part of their lives.
3. With the increase of severe mutilating injuries, nonunions after fracture increase.
4. Nonunion after fracture is a local condition, upon which general disease has little or no effect.
5. Many cases of nonunion could be prevented by the proper treatment of the new fracture.
6. The treatment of nonunion is always operative and the autogenous graft is usually the best procedure.
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