REACTION OF BONE TO VARIOUS METALS

Arthur A. Zierold, B.S.,B.M.,M.D.

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O U T L I N E

Very early in the history of surgery and when surgeons were more concerned with the closure of wounds than in their making, metal was being implanted in the tissues. Fabricius in 1647 wrote at length upon the use of iron wire sutures, limiting their use however to the soft parts. Surviving with the blind progress of the times, iron wire is again memorialized by Icart who in 1775 cut down upon a fractured bone and approximated the ends by suture. Lâlöy also relates the practise of wire sutures by Flaubert of Rouen and the literature of the period records various similar reports. However, it remained for Levert to make the first deliberate inquiry into the method and in 1829 he performed a rather extended series of experiments on dogs to determine the tolerance to metallic sutures, using gold, silver, lead and platinum. The last he found to be the least irritating. From this time until that of Lister and the advent of a new surgery the literature merely records the dull comment of a few ambitious but unoriginal workers in this particular field.

With the coming of antisepsis and later of asepsis, improvement was rapid. Lister had successfully employed buried silver wire sutures for fracture, and Kittredge and Wolff were using metal rivets in bone. Late in the nineteenth century Lane had been using wire and screws with varying success and was on his way to perfect the fixation of fractures by means of steel plates,which he reported in 1905. In the same decade Steinbach had employed silver plates and galvanized iron screws with varying success while Lambotte reported good results with brass plates and copper and iron wire. From this ground work,but chiefly by reason of the ardent championing of Lane, there arose the tremendous vogue of the buried metal plate; a vogue, perhaps more notable in this country than abroad.

It has been the observation of medical historians that the life cycle of an idea is predetermined; it arises first on a wave of enthusiasm only to sink into an obscurity from which it is rescued by some rational individual who recognizes its limitations and puts it to its proper use.

Naturally then, the first reports such as Sampson's, who recorded an unbroken series of 104 successes, were invariably favorable, and surgeons good and bad proceeded to insure their future employment by buring metallic substances in some form. The reaction swiftly followed and in 19__ was authorized the British Fracture Commission whose report formulated the already growing doubt of the propriety of treating fractures in this manner. Once well begun the controversy elicited a variety of opinions and dates. John B. Murphy, always an unbiased observer, remarked upon the frequency of non-union as compared with the preoperative period. Others, notably Albee, Hessert, Lexer, and Brickner, maintained that buried metal pieces not only failed in fixation but were noxious to the tissues involved and inhibited their regeneration; while Hallopeau, Dujarier, Fredet and Alglave proclaimed them, not only harmless and well tolerated, but actual agents for good. More recently a few have attempted to varify these clinical observations by experimental means. Trout inserted steel screws into bones of young rabbits and noted an arrest in bone growth, and Albee in another paper presented similar conclusions but from rather inadequate material. Stanley and Gatellier in an extended article with considerable clinical and X-Ray evidence developed some points of considerable value, inasmuch as their work was almost entirely concerned with the Parham band.

Their observations were, that in contact with the band early ossification was delayed but that no necrosis was discernable nor was there any evidence of oxidation or the toxic action of iron salts. Leriche and Policand, by histologic examination and chemical analysis of the tissues involved, determined that not only was the bone adjacent to a buried steel plate necrotic and rarified, but that there likewise occurred a marked impregnation of the underlying structure with iron salts.

Mann in a short series of experiments on dogs to determine the tolerance of joints to steel nails and screws, found them well imbedded at four weeks and showing only a slight rarefaction of the surrounding bone. But by far the major research was performed by Hey Groves. To arrive at the comparative merits of the various methods of fixation of fractures he employed a large series of experimental animals over a considerable period of time and planted various metals in the form of plates, ferrules, and intra-medullary pegs. His conclusions, based upon microscopic observations are as follows:

1. Nickel plated steel has no irritating effect on tissues.
2. Magnesium is rapidly absorbed and acts as a powerful stimulant to bone formation.
3. Indifferent aseptic foreign bodies are readily tolerated by the tissues.

From the foregoing it may be seen that much of the research while primarily aimed at an evaluation of fracture prosthesis has not been systematically conducted. There has been sufficient observation of end results but the lack of uniformity of material makes analysis difficult , and this same lack of uniformity and absence of accurate controls detracts from the value of the experimental data. In determining the merits of a given procedure it seems only logical to examine closely the materials employed and to ascertain the degree to which their inherent qualities will modify their utility.

The object of the following research is to determine whether metal per se, when implanted in bone, exerts an influence other than that of any foreign body and if so, whether this is a property common to many metals or varying with each individual.

To attain this within reasonable limits of error it is obvious that modifying factors must be rigidly excluded. To this end mature dogs have been employed as the most suitable laboratory animals, and in each series an effort was made to use animals of the same size and condition.

To make the data more comprehensive and observe the reactions of different types and structures of bone the experiments included the skull, tibia, and the ribs, the observation time ranging from two to six weeks in the different series.

In order to obtain a bony defect wherein to place a metal implant unaffected by pressure or mobility, holes were drilled in the various parts and metal plates of the exact depth and diameter were inserted. This was varied somewhat in the skull and ribs as will be noted later in the operative record, but with the aforementioned intent in mind. Aseptic procedure necessarily obtained throughout and was checked by culture and smear at autopsy; the infected specimens being rejected. Although wound hemostasis was uniform and easily obtained, medullary bleeding was a variable factor and a few animals were exluded from the records because of large hemotomata.

After considerable experiment with fixatives and tissue stains it was found that decalcification was more uniform and rapid with 5 per cent nitric acid, and that preliminary fixation in ten per cent formalin was adequate for the stains required. With Hematoxylin and eosin it was possible to differentiate the structures quite as well as with the special stains, although Van Giesons was employed routinely to emphasize the connective tissue changes, and Mallory's hemosiderin stain was used to delineate the iron pigment. Some difficulty was experienced in obtaining thin sections intact and finally ten mu. celloidin sections were cut for orientation and thinner fragments for detailed study.

The following catalogue includes the details of the operative procedure:

Under ether, six series of mature normal dogs were operated upon with the usual surgical aseptic precautions.

Series I. Ten dogs.

Preliminary, to rectify technical procedure and determine optimum time of obtaining specimens.

Series II. Fifteen dogs.

The middle third of the tibia was exposed through a three inch incision and a five mm. hole drilled through the cortex. A metal implant five mm. by eight mm. by .5 mm. was inserted in the hole, flush with the surface of the bone and fitting exactly but without pressure. The overlying fascia was closed with 00 catgut and the skin was closed with interrupted linen sutures. No dressing. In the control animals, the wound was closed after drilling the bone without the implantation of a metal. In the remainder the following metals were implanted:

1. Gold	4. Zinc	7. Nickel
2. Silver	5. Lead	8. High carbon steel
3. Aluminum	6. Copper	9. Low carbon steel

10. Stellite
11. Copper Aluminium Alloy
12. Magnesium
13. Iron

At the end of six weeks the dogs were killed, the tibiae removed and sectioned with a fine saw under running water. The metal implants were withdrawn from the cut end of the bone and region of the implant cut (as before) into two mm. cross sections. These sections were fixed in formalin for five days , then washed and placed in five per cent nitric acid and left until decalcified, the solution being changed daily. After imbedding in celloidin sections were cut and stained.

Series III. Fifteen dogs.

The knee joint was exposed by a three inch skin incision, parallel to the long axis of the leg and the joint cavity opened by a two inch lateral incision. The patella was dislocated medially and the condyle of the femur exposed by flexion of the knee. A hole 2 mm. in diameter and 3 mm. deep was drilled directly in the long axis of the femur and a metal implant 2 mm. by 3 cm. inserted flush with the articular cartilage.

The patella was then replaced and the joint capsule closed with linen sutures. The skin was closed with interrupted linen sutures. Beside the controls in which there were no implants, the following metals were implanted: Silver, gold, alumbnum, zinc, lead, copper, nickel, hight carbon steel, low carbon steel, stellite, copper altminum alloy, magnesium, iron.
At the end of two weeks the animals were killed and the femora removed. The metals were removed and the region of the implant cut with a fine saw into 2 mm. cross sections. These sections were fixed for five days in ten per cent formalin, then removed, washed and placed in five per cent nitric acid, and allowed to

decalcify. Later after imbedding in celloidin sections were cut and stained.

Series IV. Four dogs.

A six inch skin incision exposed the lower ribs in the axillary line. The superficial fascia and musculature were divided and the mid portion of the sixth, seventh, eight and ninth ribs exposed. A 2 mm. hole was drilled through the cortex of each rib and metal implants 2 mm. by 4 mm. by .5 mm. inserted, flush with the surface of the rib. Overlying muscle and fascia were closed with number two plain catgut and the skin closed with interrupted linen sutures. At the end of four weeks the animals were killed and the ribs removed. At autopsy it was found that the rib, because of its size and structure, was not suitable for this type of implant and that the factor of error due to mobility, fracture and operative trauma was so great as to make the results valueless. Gross observations only were recorded.

Series V. Fifteen dogs.

A skin incision was made over the mid-temporal region extending from the saggittal suture for two inches. The underlying temporal fascia was incised in the same line and the muscle retracted to expose an area on the skull of about 2 cm. in diameter. A button of bone 1.5 cm. in diameter was removed with a trephine and the dura exposed. A metal disk exactly filling the opening was inserted and the deep temporal fascia and pericranium closed with interrupted 00 chromic catgut. The outer temporal fascia was closed with interrupted linen sutures as was the skin. The following metals were implanted: silver, gold, aluminum, zinc, lead, copper, nickel, high carbon steel, low carbon steel, stellite, copper aluminum alloy, magnesium and iron.

Series VI. Four dogs.

A six inch skin incision in the axillary line and incision of the underlying, superficial musculature exposed the fifth, sixth, seventh, eighth and ninth ribs. The periosteum was incised in the long axis of the ribs for a distance of 3 cm. With a periosteal elevator, the periosteum was loosened from the upper half of the rib and retractors inserted. With sharp chisels a section of the upper border of the rib was removed, 1.5 cm. by .5 cm. by.5 cm, and a metal implant inserted in such manner as to have its ends buried in the medullary bone substance thus, The usual controls and metals were implanted. The periosteum was closed with OO chromic catgut and the overlying tissue closed with plain catgut. The skin was closed with interrupted linen sutures.

At the end of four weeks the desired ribs were removed and X-Ray photographs taken.

Animal Experiment - Dog.

Series I. Control - Tibia, six weeks.

There is a slight amount of scar tissue over the wound. The periosteum is continuous over a slightly raised fusiform protuberance. There is no evidence of infection.

II. Gold - Tibia, six weeks.

There is no inflammatory reaction. There is a slight amount of scar tissue over the bone. Slight fusiform protuberance over implant, perceptible as a slight bulge in contour. The periosteum is continuous over the implant.

III. Zinc - Tibia, six weeks.

There is a moderate amount of scar tissue overlying the implant area. Muddy discoloration to soft tissue for an area of one cm. There is a slight protuberance over the area of the implant with an oval crater-like depression in the center. The periosteum does not cover the implant. The metal is markedly corroded and half absorbed. There is no evidence of infection.

IV. Copper - Tibia, six weeks.

There seems to be a marked bony proliferation. A moderate amount of scar tissue overlies the region of the implant. There is a bluish discoloration of the implant area for a distance of two cm. The region of the implant is the center of a very large fusiform bony enlargement. The periosteum is continuous over the implant which is bright and shows evidence of absorption. There is no evidence of infection.

V. Nickel - Tibia, six weeks.

There is a slight increase in the fibrous connective tissue overlying the implant, and a slight protuberance over the area of the implant with an oval central depression. Dark discoloration extends for an area of five cm. about the implant. The periosteum is continuous over the implant. The metal is discolored and corroded. There is no evidence of infection.

VI. Aluminum Bronze - Tibia, six weeks.

There is a slight increase in fibrous connective tissue over the area of the implant. Dark discoloration extends over an area of one cm. The periosteum does not cover the implant. The area of the implant is noticeably depressed. There is no evidence of infection.

VII. Magnesium - Tibia, six weeks.

There is a slight fusiform protuberance with a central depression over the area of the implant. The periosteum is continuous over the implant. The metal is three-fourths absorbed. There is a slight grayish discoloration about the implant for five cm. There is no marked productive change and no evidence of infection.

VIII. Aluminum - Tibia, six weeks.

There is a very slight fusiform protuberance over the implant, and the periosteum is intact. The metal is not discolored or absorbed. There is a very slight productive change with no evidence of infection.

X. Silver - Tibia, six weeks.

There is a slight increase of overlying fibrous connective tissue. The periosteum is intact. There is a slight protuberance. The metal is dark and slightly corroded. The surrounding tissue is not discolored. There is slight productive change and no evidence of infection.

XI. High Carbon Steel - Tibia, six weeks.

There is a slight depression over the area of implant. The periosteum is not intact over the implant. The area surrounding the metal is discolored for one cm. The metal is markedly discolored and corroded. There is moderate destructive change. There is no infection.

XII. Low Carbon Steel - Tibia, six weeks.

There is a slight increase in the overlying fibrous connective tissue. There is noticeable depression in the area of the implant. The periosteum isnot intact over the implant. The tissue surrounding the metal is discolored for one cm. The metal is markedly discolored and corroded. There is no evidence of infection. There is a slight destructive change.

XIII. Lead - Tibia, six weeks.

There is a slight increase in the overlying fibrous connective tissue. There is a slight protuberance at the site of the implant over which the periosteum is intact. There is no discoloration of the tissue although the metal is discolored. There is slight productive change.

XIV. Iron - Tibia, six weeks.

There is a slight increase of the overlying fibrous connective tissue, and a slight protuberance over the region of the implant with a shallow central depression. The periosteum is intact, and there is no tissue discoloration although the metal is discolored. There is slight productive change.

XVI. Stellite - Tibia, six weeks.

There is a slight protuberance over the region of the implant. The periosteum is continuous over the implant, which is bright and not corroded. There is slight evidence of any reaction.

Ribs.

Series II. Control, four weeks.

There is a moderate fusiform enlargement at the site of the drill hole. The periosteum is thickened.

II. Gold - Ribs, four weeks.

There is a moderate fusiform swelling at site of the implant. The metal is covered with thickened periosteum. There is no discoloration.

III. Silver - Ribs, four weeks.

There is a moderate fusiform swelling at the site of the implant. The metal is covered with thickened periosteum. There is no discoloration.

IV. Zinc - Ribs, four weeks.

There is a large fusiform swelling, and the periosteum is much thickened over the region of the metal. There is slight discoloration although the metal is partly absorbed and discolored. The swelling can be cut with a knife, and is friable on section. There is definite fracture at the site of the implantation.

V. Copper - Ribs, four weeks.

There is a large fusiform swelling, and the region of the implant is overlaid with a moderately thickened periosteum. There is a .5 cm. zone of discoloration. The metal is bright and roughened.

VI. Magnesium - Ribs, four weeks.

There is a large nodular swelling at the site of the implant. The metal is covered by thick periosteum, and is nearly absorbed. The discoloration is slight. The tissue is friable on section. The periosteum is markedly thickened. There is a definite fracture at the point of injury.

VII. Aluminum - Ribs, four weeks.

There is a moderate fusiform swelling at the site of the implant. The metal is bright, and there is no evidence of absorption. The periosteum is moderately thickened and covers the implant.

VIII. Lead - Ribs, four weeks.

There is a large fusiform swelling at the site of the implant. The periosteum is moderately thickened. The metal is corroded but covered. There is slight discoloration. There is a fracture at the site of the implant.

IX. Iron - Ribs, four weeks.

There is a moderate fusiform swelling at the site of the implant. The metal is discolored. The periosteum is moderately thickened, and slightly discolored about the implant.

X. High Carbon Steel - Ribs, four weeks.

There is a moderate fusiform swelling at the site of the implant. The metal is not covered and is markedly corroded. There is a marked reaction of the surrounding connective tissue.

XI. Nickel - Rib, four weeks.

There is a moderate fusiform swelling at the site of the implant. The metal is not covered, and the surrounding periosteum is moderately thickened. The metal is corroded, and there is moderate discoloration of the tissue.

XII. Al Bronze - Rib, four weeks.

There is a slight fusiform swelling with a central depression at the site of the implant. The metal is not covered. The periosteum is slightly thickened. The metal is bright, but the surface is roughened. There is slight discoloration.

XIII. Low Carbon Steel - Rib, four weeks.

There is a moderate fusiform swelling at the site of the implant. The metal is not covered and is markedly corroded. There is a marked reaction of the surrounding connective tissue.

XIV. Stellite - Rib, four weeks.

There is a moderate fusiform swelling at the site of the implant. The metal is covered with thickened periosteum. There is no discoloration.

Knee

Series III. Control, two weeks.

There is a slight discoloration about the drill hole, and a thin layer of cartilage over the opening.

II. Gold - Knee, two weeks.

There is a slight discoloration about the implant which is covered with a thin layer of dense connective tissue.

IIII Silver - Knee, two weeks.

There is a moderate discoloration about the implant which is covered with a thin layer of dense connective tissue.

IV. Aluminum - Knee, two weeks.

There is a slight discoloration about the implant which is covered with a thin layer of dense connective tissue.

V. Copper - Knee, two weeks.

There is very marked discoloration about the implant. the end of which is not covered.

VI. Copper Aluminum - Knee, two weeks.

There is very marked discoloration about the implant, the end of which is not covered.

VII. Zinc - Knee, two weeks.

There is very marked discoloration about the implant, the end of which is not covered.

VIII. Magnesium - Knee, two weeks.

There is very marked discoloration about the implant, the end of which is not covered.

IX. Stellite - Knee, two weeks.

There is very slight discoloration about the implant, the end of which is covered with a thin layer of dense connective tissue.

X. Lead - Knee, two weeks.

There is moderate discoloration about the implant, the end of which is not covered.

XI. Iron - Knee, two weeks.

There is moderate discoloration about the implant, the end of which is not covered.

XII. Nickel - Knee, two weeks.

There is marked discoloration about the implant, the end of which is not covered.

XIII. High Carbon Steel - Knee, two weeks.

There is marked discoloration about the implant, the end of which isnot covered.

XIV. Low Carbon Steel - Knee, two weeks.

There is marked discoloration about the implant, the end of which is not covered.

SKULL

Series IV. Control, six weeks.

There is a slight increase in fibrous tissue. The margins of the trephine opening are slightly rounded and smooth. The periosteum is continuous over the bony defect which is not covered by bone but by dense fibrous tissue. Negative to culture.

II. Gold - Skull, six weeks.

There is a slight fibrous tissue increase. The metal is covered by a dense fibrous tissue layer one mm. thick. The overlying periosteum is continuous. The metal is not corroded. There is slight reaction.

III. Silver - Skull, six weeks.

There is a slight fibrous tissue increase. The periosteum is continuous over the metal. The metal is covered by a one mm. layer of dense fibrous tissue which contains no bony tissue. There is a zone of bluish discoloration over the metal and two or three mm. from the circumference. The metal is slightly corroded.

IV. Zinc - Skull, six weeks.

The metal is lying exposed under the superficial fascia. The periosteum is not continuous over the metal but only to the edge of the bony defect. There is a .5 mm. zone of marked connective tissue increase about the metal. The metal is badly corroded and slightly absorbed. The margins of the bony defect show marked fibrous tissue increase.

V. Magnesium - Skull, six weeks.

There is a moderate increase in the connective tissue over the metal and in a zone extending one cm. or more from the margins of the bony defect. The metal is overlaid by a dense fibrous tissue layer two or three mm. thick, containing no bony tissue. There is a notable protuberance of tissue over the metal. The metal is half absorbed.

VI. Aluminum Copper - Skull, six weeks.

The metal is lying exposed under the superficial fascia. There is a moderate increase in the connective tissue. There is an area of dark discoloration for one cm. about the metal. The metal is very slightly discolored and the polish is dulled.

VII. Copper - Skull, six weeks.

The metal is lying exposed under the superficial fascia. The periosteum is not continuous. There is a zone of moderate connective tissue increase. There is a zone of discoloration for .5 cm. The metal is bright, but showing signs of absorption.

VIII. Nickel - Skull, six weeks.

There is a slight increase in the connective tissue, and a zone of discoloration of one cm. There is a thin layer of fibrous tissue over the metal which is discolored and corroded.

IX. Aluminum - Skull, six weeks.

There is a slight increase in the connective tissue. There is a bridge of bone .5 cm. wide and 1 mm. thick across the center of the metal which is bright and not corroded. There is no discoloration.

X. Stellite - Skull, six weeks.

There is a slight increase in the connective tissue. There is no discoloration. The metal is covered by a one mm. layer of very dense fibrous tissue, and is bright and not corroded. There is slight reaction.

XI. Lead - Skull, six weeks.

There is a noticeable increase in the connective tissue. The metal is covered by a 2 mm. layer of dense fibrous tissue, and there is a zone of connective tissue proliferation for .5 cm. There is a slight surrounding discoloration. The metal is discolored and corroded.

XII. Iron - Skull, six weeks.

There is a slight increase in the connective tissue. The zone of connective tissue increase is .5 cm., and there is a moderate discoloration for a distance of .5 cm. The metal is covered by a one mm. layer of dense fibrous tissue. The metal is slightly discolored.

XIII. High Carbon Steel - Skull, six weeks.

The metal is lying exposed under the superficial fascia.

There is moderate connective tissue increase for a zone of .5 cm. and a moderate discoloration for a zone of one cm. The metal is discolored and corroded.

XIV. Low Carbon Steel - Skull, six weeks.

The metal is only partially covered by a narrow thin zone of fibrous connective tissue. There is moderate discoloration for a distance of two cm. The metal is discolored and corroded.

Ribs

Series V. Control, four weeks.

X-Ray of the injured portion of the rib shows the defect nearly filled with bone of the same density as normal. There is a slight shallow depression at this point and no callus formation is to be seen.

Aluminum: About the region of the implant is a moderate fusiform bony overgrowth which is more marked on the side opposite the point of injury. Directly through the area is a thin line of rarefaction which might be indicative of fracture. The metal is well encapsulated in bone of normal density and there is no discernible callus formation.

High Carbon Steel: The bone of the specimen appears rarefied throughout its length and particularly in the neighborhood of the distal end of the metal. There is a very small amount of callus a short distance from the proximal end, but this is barely noticeable. There is no attempt at bony encapsulation of the metal and only a very slight bone regeneration at either end of the implant.

Zinc: About the region of the implant is a slight fusiform thickening, more noticeable on the side opposite to the injury, where it appears as subperiosteal. About the ends of the metal there is a small amount of callus which is partly calcified. The metal is not encapsulated by bone but near the ends there is some evidence of regeneration.

Silver: In the region of the implant there is a fusiform mass of callus which is somewhat excessive. Opposite the point of injury there is a moderately thick layer of subperiosteal bone. The metal is covered by bone in its distal half but in the proximal portion this is deficient, probably because the implant is bent so that the tip points outward. There is considerable bone regeneration and a definite tendency to encapsulation.

Magnesium: About the region of the implant is a large fusiform mass of callus which shows but little evidence of calcification. There is no bone filling the defect and the metal has entirely absorbed. The rib is relatively dense in structure but apparently actual bone growth is negligible.

Copper: The region of the implant shows a moderate fusiform enlargement which consists chiefly of new subperiosteal bone which is as dense as the normal structure. The metal lies well imbedded and completely encapsulated in new dense bone.

Low Carbon Steel: Over the rib defect is a slight amount of callus showing no evidence of calcification. There is no bone overlying the metal and apparently there is no attempt at new bone formation. The rib appears slightly rarefied toward its proximal end.

Nickel: At either end of the metal are small callus masses which appear to be undergoing calcification. On the opposite side of the rib is a fusiform mass of callus not calcified. The metal is not covered by bone but at the extreme ends there appears slight evidence of bone growth.

Lead: Over the region of the implant is a moderately thick fusiform mass of callus which is slightly calcified near the metal ends. One end of the metal is displaced outward and held in what appears as new bone growth. There is slight bone regeneration and no tendency to bony encapsulation.

Stellite: The bony contour is normal, and there is no callus or bone overgrowth. The metal is deeply imbedded and covered with new bony slightly less dense than normal.

Gold: There is a very slight shallow depression at the site of the implant, and a large mass of callus near one end. The callus is not calcified. The metal lies covered with a thin layer of bone of the same density as normal. The whole bone and particularly that portion underlying the implant appears denser than normal.

Iron: There is a shallow depression at the site of the implant and on the opposite side of the bone a narrow fusiform mass of uncalcified callus. There is a small mass of new bone at either end of the metal, but there is no tendency to encapsulation.

Copper Aluminum: There is a moderate fusiform mass of uncalcified callus about the region of the implant. At either end of the metal there is a moderate sized hump of subperiosteal bone nearly as dense as normal. No bone covers the greater part of the metal and there is no bony encapsulation.

Microscopic Findings

Series I. Silver - Tibia, six weeks.

The implant is surrounded by a closely applied narrow zone of dense fibrous tissue.

Medulla ⊖ The quadrant opposite the implant is filled with thick trabeculae of new bone and large sinuses engorged with red blood cells. The interstices are filled with a few shrunken and small fat cells, supported by fine reticulum of connective tissue cells. The marrow cells are chiefly of connective tissue and endothelial types. The rest of the medulla and cortical defect is filled with new bone interspersed with large irregular Haversian spaces and well filled blood sinuses. The cortical bone is normal except opposite the internal end of the implant and at the margin of the cortical defect where many enlarged Haversian canals are found lined with osteoblasts.

Periosteum - The quadrant of the region of the cortical defect overlies a thick crescrent of new subperiosteal bone continuous over the implant. A thin layer of subperiosteal bone completely surrounds the section. The periosteum is thick and lined with osteoblasts.

Zinc - Tibia, six weeks.

The implant is surrounded by a thin layer of dense fibrous connective tissue which is closely approximated by new bone.

Medulla - The medullary cavity contains a few thin trabeculae of new bone which are more numerous in the region of the implant. Interspersed are a few fat cells and adult connective tissue cells and masses of marrow cells of leucocytic and endothelial types.

Cortex - The region of the cortex is filled with new bone with relatively small Haversian spaces, filled with a reticulum of connective tissue and osteoblasts. There are numerous blood sinuses. Cortex elsewhere is normal.

Periosteum - The periosteum is slightly thickened over the region of the implant and dips down to meet the outer end of the implant. There is a moderately thick mass of subperiosteal bone on either side of the implant but not covering it.

Copper - Tibia, six weeks.

The implant is surrounded by a thin, closely applied zone of fibrous connective tissue which in turn is completely surrounded by rather dense new bone.

Medulla - The medullary portion is almost completely filled with moderately dense new bone interspersed with a few fat cells and masses of marrow cells chiefly of the endothelial type and connective tissue cells to form a network of collagen fibrils. The whole medullary cavity is more completely filled than in other sections.

Cortex - The region of the cortical defect is filled with new bone of the same character as that in the medulla, and completely covers the outer end of the implant. The remainder of the cortex is normal except for a general increase in the size of the Haversian canals which contain many osteoblasts and a few giant cells.

Periosteum - The periosteum over the half containing the implant is moderately thickened and underlying it is a very thick crescent of new subperiosteal bone which almost completely surrounds the cortex. In the outer portion of this crescent are several areas made up of dense masses of cartilage. The periosteum dips down in the region of the cortical defect to form a wedge of fibrous connective tissue.

Magnesium - Tibia, six weeks.

The implant is surrounded by a thick layer of fibrous connective tissue interspersed with marrow cells of the endothelial type.

Medulla - The medulla is made up of dense masses of marrow cells chiefly of the endothelial type interspersed with a moderate number of fat cells. New bone is present in thin anastomotic trabeculae and relatively small in amount.

Cortex - The region of the cortical defect is filled with thick, short anastomotic trabeculae of new bone forming large Haversian spaces filled with connective tissue cells and a fine collagen reticulum and lined with osteoblasts. The new bone does not closely approximate the implant nor does it cover the outer end. The remainder of the cortex is normal.

Periosteum - The quadrant overlying the implant is moderately thickened, the remainder being normal. There is a thick wedge shaped area of new subperiosteal bone on either side of the outer end of the implant.

Aluminum - Tibia, six weeks.

The implant is surrounded by a thin layer of fibrous connective tissue which contains a few large cells of the endothelial type.

Medulla - The medullary cavity is filled for the greater part with large clear fat cells and masses of marrow cells chiefly of the endothelial type. There is a loose reticulum of connective tissue cells with fine collagen fibrils. New bone is present in the form of thin anastomotic trabeculae which are more densely arranged as the cortical defect is approached.

Cortex - The cortical defect is filled with new bone having moderately large Haversian spaces filled with osteoblasts and a connective tissue reticulum. The outer end of the implant is not covered by new bone but is closely approximated. The remainder of the cortex is normal.

Periosteum - The periosteum is slightly thickened in the quadrant overlying the implant which it covers. Underlying this are two thin crescents of new subperiosteal bone. Elsewhere the periosteum is normal.

Nickel - Tibia, six weeks.

The implant is surrounded by a wide zone of densely arranged marrow cells chiefly of the granular leucocytic type interspersed with a few bands of fibrous connective tissue. Toward the medullary end are a few fat cells.

Medulla - The medulla is filled with several large masses of new bone with small Haversian spaces. The spaces are filled with a reticular connective tissue, and large marrow cells of the granular leucocytic type. Osteoblasts are numerous and there are occasional giant cells. The interstices between the masses of new bone contain a fine reticular connective tissue network holding marrow cells of various types and many shrunken opaque fat cells.

Cortex - The region of the cortical defect is filled with rather dense new bone with small Haversian spaces in which are intermingled marrow cells of the endothelial type and connective tissue cells with long collagen fibrils, also the usual osteoblasts. The new bone does not closely approximate the implant nor does it cover the outer end but rounds off, leaving a wedge shaped defect filled with connective tissue cells and marrow cells. The remainder of the cortex is normal.

Periosteum - The periosteum of the quadrant overlying the implant is markedly thickened and underlaid on each side of the implant by a half crescent of new subperiosteal bone. The remainder is normal.

Stellite - Tibia, six weeks.

The implant is surrounded by a closely applied thin layer of fibrous connective tissue. In many places this layer is absent and the endosteum of the new bone approximates the metal.

Medulla - The medullary space is filled for the most part with widely separated but-like processes of new bone. In the neighborhood of the implant these are anastomotic. The interstices are filled with a few large clear fat cells, but chiefly with dense masses of large marrow cells of the endothelial type.

Cortex - The region of the cortical defect is filled with a rather dense network of new bone. The interstitial spaces are filled with osteoblasts and a fine reticulum of connective tissue. Sinuses are few and well filled. The new bone is especially dense and closely applied to the outer half of the implant. The remaining cortex is normal.

Periosteum - The periosteum is normal except for a slight thickening in the quadrant overlying the implant. There is a moderately thick crescentic area of new subperiosteal bone in this region.

Lead - Tibia, six weeks.

The implant is surrounded by a closely applied thick layer of fibrous connective tissue interspersed with leucocytic marrow cells.

Medulla - The medullary cavity is filled with short thick budding trabeculae of new bone interspersed with large well filled blood sinuses and marrow cells chiefly of the connective tissue type. These are a few normal fat cells.

Cortex - The region of the cortical defect is filled with long anastomotic trabeculae of new bone running for the most part parallel with the metal and not completely covering the extreme end. The interstices are filled with marrow cells of the endothelial type and blood sinuses. The cortex is otherwise normal. The endosteum is thick and proliferating.

Periosteum - The periosteum over the implant is only slightly thickened and there is a narrow crescentic zone of new subperiosteal bone. The remaining portion of the periosteum is normal.

Iron - Tibia, six weeks.

The implant is surrounded by a moderately thick zone of fibrous connective tissue. At a few points close to the metal are giant cells reacting to a specific stain for hemosiderin. These are very few in number as compared to the high carbon steel sections and are not found in the surrounding tissues.

Medulla - The greater portion of the medullary cavity is filled with widely spaced thin trabeculae of new bone, the interstitial spaces being filled with small normal fat cells and densely packed marrow cells of the leucocytic type. Blood sinuses are not numerous nor large. The endosteum is thin and inactive.

Cortex - The cortical defect is filled about the implant with rather dense new bone with small Haversian spaces. The new bone closely approximates the metal at several points but does not cover the external end where it divides into two wedge shaped masses. The cortex is otherwise normal.

Periosteum - The periosteum does hot cover the implant but is slightly thickened in that region. The remaining portion is only slightly thicker than normal. On either side of the implant are two moderately thick wedges of subperiosteal bone.

Gold - Tibia, six weeks.

The implant is completely surrounded by new bone which is separated from it by a very thin layer of fibrous connective tissue.

Medulla - Greater porftion filled with thick buds and trabeculae of new bone. The region about the internal end of the implant contains numerous larger spaces filled with shrunken fat cells, marrow cells of the connective tissue type, and well filled blood sinuses. The endosteum throughout is thickened, as the region of the cortical defect is approached the new bone becomes denser and the Haversian spaces smaller. There is a marked overgrowth of new bone over the external end of the implant.

Cortex - The cortical bone is normal except for a few enlarged Haversian canals. In the region of the defect most of these are filled with osteoblasts, but a few contain fat cells.

Periosteum - Over the cortical defect is a large crescentic area of new bone over which the periosteum is markedly thickened ahd active. The remaining periosteum is only slightly thickened.

Copper Aluminum - Tibia, six weeks.

The implant is surrounded except for the extreme end by a thick, dense zone of connective tissue.

Medulla - The medulla is filled with anastomotic trabeculae of new bone interspersed with large dense masses of marrow cells chiefly of the endothelial type and areas of normal fat cells. There are some areas of shrunken and opaque fat cells.

Cortex - The cortical defect is filled with new bone interspersed with long narrow Haversian spaces lined with osteoblasts and numerous well filled blood sinuses. The cortical bone is normal except for a few enlarged Haversian canals in the region of the defect, filled with osteoblasts. As the periosteum is approached the new bone recedes from the implant to form an open V.

Periosteum - The quadrant over the implant is markedly thickened and the outer end of the implant is not covered. At each border of the cortical defect is a wedge shaped area of new periosteal bone. The periosteum about the remaining portion of the bone is slightly thickened.

Control - Tibia, six weeks.

Medulla - The half opposite the cortical defect is filled with thin asastomotic trabeculae of new bone, interspersed with marrow cells of the endothelial type and groups of large clear fat cells. The endosteum is thick and covers a thin layer of subendosteal bone. The cortical defect is filled with new bone trabeculae, which is continuous with a crescentic area of subperiosteal bone over the region of the defect.

Cortex - There is a slight increase in the number of large Haversian canals. On the borders of the defect and in the cortical bone directly opposite are numerous enlarged Haversian spaces lined with osteoblasts.

Periosteum - The periosteum is normal except for the third overlying the region of the defect where it is much thickened.

High Carbon Steel - Tibia, six weeks.

The implant is surrounded by a moderately thick zone of cellular connective tissue intermingled with large pigmented cells which react strongly to a specific stain for hemosiderin.

Medulla - The medullary portion contains a few small buds of new bone but for the most part is made up of fat cells and marrow cells of the leucocytic and endothelial types. Many of the fat cells are shrunken and opaque.

Cortex - The region of the cortex is only partly filled with new bone made up of rather thin anastomatic trabeculae and large interstitial spaces filled with a reticulum of connective tissue and marrow cells. On the whole the new bone formed is very small in amount and in no place does it approximate the implant. At the outer end it thins out and slopes away from the implant. The cortex elsewhere is normal.

Periosteum - The periosteum while slightly thickened in the region overlying the implant does not cover it but dips down on either side. There is a narrow half crescent of new subperiosteal bone on either side of the implant.

Low Carbon Steel - Tibia, six weeks.

The implant is surrounded by a thick zone of fibrous connective tissue interspersed with marrow cells chiefly of the endothelial types. Throughout this zone are numbers of large pigmented cells which react to a specific stain for hemosiderin.

Medulla - The greater part is made up of masses of marrow cells, mostly of the endothelial type interspersed with fat cells. Many fat cells are shrunken and opaque. There are a few thin trabeculae of new bone which are most numerous as the cortical defect is approached.

Cortex - The cortex is normal except for the region of the defect which is filled with anastomotic trabeculae of new bone. The amount of bone is relatively small and does not approach the implant closely. The cortex has several large Haversian spaces opposite the point of implantation. They contain some fat cells together with connective tissue cells and a few osteoblasts.

Periosteum - The periosteum is slightly thickened over the quadrant of the implant but is not continuous across it. There are two narrow segments of new subperiosteal bone on either side of the implant, but not continuous over the outer end of the implant. The remainder of the periosteum is normal.

Series III. Microscopic Findings.

High Carbon Steel - Femur.

Zone 1. The implant is surrounded by a relatively wide zone of densely massed, large, clear, polygenal cells with eccentric vesicular nuclei. Interspersed are many concentrically arranged fusiform cells with oval nuclei. Also in this area are a number of large giant cells which appear brown to hematoxylin and eosin, and react to a special stain for hemosiderin. This type of cell is found scattered throughout for some considerable distance from the implant. Bone trabeculae are somewhat thickened but few and scattering. The lamellar structure is well defined and there is little evidence of new bone formation. The endosteum while slightly thickened in a few places, is, for the most part, normal. There are no fat cells present in this region.

Zone II. Bone trabeculae are normal. The interstices are filled with large clear or finely granular cells with rounded, vesicular nuclei. The fat cells are fewer and smaller than normal.

Zone III. This region is normal except for a decrease **in** the number and size of the fat cells, and a slight predominance of the large clear cells noted in zone two.

Magnesium - Femur.

Zone 1. The implant is surrounded by a thick layer of concentrically arranged fusiform cells with oval nuclei. Interspersed are numbers of large polygonal cells with finely granular cytoplasm and round dense nuclei. The bone trabeculae are thick, numerous and anastomotic. There are many budding projections of new bone. The endosteum is thick and made up of two or three layers of cells. There are no fat cells present in this region.

Zone 11. The bone trabeculae are relatively thick and anastomotic. The included bone cells are large and oval. The laminated structure is not well defined. There are no budding projections of new bone, but the endosteum is thick and in places made up of two or three layers of cells. The interstitial marrow bells are in dense masses, the predominating type being large, polygonal, and with a finely granular cytoplasm and a dense round nucleus. The fat cells are few in number and smaller than normal.

Zone 111. This region approximates the normal except for slightly thicker bone trabeculae and smaller interstitial spaces. At one point there appears an irregular ring of cartilage.

Zinc - Femur.

Zone 1. The implant is surrounded by a closely applied dense zone consisting of several concentric layers of spindle shaped cells with elongated dense nuelei. This zone contains a number of sinuses well filled with red blood cells.

The bone trabeculae are thick, short and anastomotic. New layers of bone are well differentiated. Many large included bone cells are present and many budding projections of growing bone.

The endosteum is a thick single layer of oval cells with oval vesicular nuclei. There are many osteoblasts and numerous giant cells. The sinuses are markedly engorged with red blood cells. Of the fat cells the few present are shrunken, deformed and cloudy. The interstitial cells consist of many oval and spindle shaped cells with clear cytoplasm and oval vesicular nuclei. There are many rounded and polygonal cells with finely granular cytoplasm and round relatively dense nuclei. There are many similar cells with polymorphonuclear forms, and a few large oval and irregular cells with coarsely granular cystoplasm and eccentric round nuclei. A few red blood cells are present.

Zone 11. The bony trabeculae are slightly thickened and anastomotic and the laminated structure is well defined. There are many included elongated bone cells. The endosteum consists of a thick single layer of spindle shaped cells with relatively dense, oval nuclei. There are a few osteoblasts and an occasional giant cell. The sinuses are few and well filled with red blood cells. The fat cells are few in number, small, clear and distended. Of the interstitial cells the predominating types are large irregular cells with clear cytoplasm and large oval vesicular nuclei. Many polygonal and rounded cells with finely granular cytoplasm and round relatively dense nuclei are seen. A few red blood cells and a few large irregular cells with coarsely granular cytoplasm and round relatively dense nuclei are present.

Zone 111. Normal except for the interstitial cells, of which those predominating are large irregular cells with clear cytoplasm and oval vesicular nuclei.

Nickel - Femur.

Zone 1. There is a dense cellular exudate about the implant, consisting of many polymorphonuclear leycocytes. Many large irregular cells with eccentric, round, relative dense nuclei and finely granular cytoplasm are to be distinguished together with numerous large polygonal cells of a clear cytoplasm and oval vesicular nuclei. There are numerous red blood cells. Next to these is a thick dense zone of elongated cells with clear cytoplasm and oval vesicular nuclei and adjoining this are occasional buds of growing bone.

The bony trabeculae are widely separated, thin and short, with their laminated structure well defined. Numerous oval, isolated bone cells are to be seen in the new bone and many osteoblasts bordering the budding new bone growth.

The endosteum consists of single and double layers of large cells with large oval nuclei. Fat cells are not present.

Of the interstitial cells the predominating type is large, fusiform, and with an oval vesicular nucleus. There are many large polygonal cells with clear cytoplasm and round vesicular nuclei, and a number of large, irregular cells with finely granular cytoplasm and eccentric relatively dense nuclei. A few red blood cells are to be seen, and the sinuses are engorged.

Zone 11. The trabeculae are thin, widely separated, and anastomotic with a definite laminated structure. There are a few budding projections of growing bone and isolated bone cells in the usual number, small and oval. Osteoblasts are few.

The endosteum consists of a thin, single layer of cells with small, elongated, dense nuclei. The fat cells are very few in number, small, round and clear. The sinuses are engorged.

Of the interstitial cells the predominating type is of large polygonal cells with clear or finely granular cytoplasm and large, round or oval vesicular nuclei. There are many polymorphonuclear forms and a few red blood cells.

Zone 111. Zone III is the same as zone 11, except that there are more and larger fat cells and fewer polymorphonuclear forms.

Aluminum - Femur.

Zone 1. The implant is surrounded by a closely applied dense zone of spindle shaped connective tissue cells arranged in three or four layers. But for the new bone, the connective tissue layer comes very close to contact with the implant.

The bony trabeculae are somewhat thickened, short, and anastomotic. Many budding projections of new bone are seen and the lamellar structure is not well defined. There are many oval, large, isolated bone cells. Osteoblasts are numerous,as are also, giant cells.

The endosteum consists for the most part of a thin,single layer of cells with elongated dense nuclei. In places larger cells are present but in a single layer. The sinuses are moderately filled. Fat cells are few in number and small, clear and distended.

The predominating type of interstitial cell is moderately sized, polygonal, with round vesicular nucleus and a relatively clear cytoplasm. There are a few polymorphonuclear leucocytes and transitional types and a few large irregular cells with coarse granules together with a few red blood cells.

Zone 11. The bony trabeculae and fat cells are slightly smaller than normal. The endosteum is normal,as are also the sinuses.

Of the interstitial cells which occur in slightly greater masses than normal, about half are moderately sized and polygonal with clear cytoplasm and round vesicular nuclei. Some have a finely granular cytoplasm and relatively dense nuclei. There are a few red blood cells and a few large cells with coarse granules.

Zone III. Zone 111 is normal.

Lead - Femur.

Zone 1. The implant is surrounded by a closely applied dense zone of several layers of concentrically arranged spindle cells. In a zone between this and the surrounding bony trabeculae are many small sinuses engorged with red blood cells.

The bony trabeculae are thick and widely separated and there are many budding projections of growing bone in which the laminated structure is well defined. Many oval included bone cells are to be seen.

The endosteum consists for the most part of a thin single layer of spindle cells with elongated dense nuclei, although many areas of single and double layers of oval cells with oval relatively dense nuclei are to be noted. There are numerous osteoblasts in the growing areas, and occasionally giant cells. The sinuses are numerous and engorged with red blood cells. The fat cells are shrunken and distorted and slightly opaque.

The predominating type of interstitial cell is rounded and has a finely granular cytoplasm and a relatively dense round or polymorphic nucleus. There are many large cells with clear cytoplasm and oval vesicular nuclei and many spindle cells.

Zone 11. The bony trabeculae and endosteum are normal. The sinuses are many and engorged with red blood cells. The fat cells are normal in number, but slightly smaller than normal, round,

Zone 111 is normal.

Aluminum Bronze - Femur.

Zone 1. The implant is surrounded by a closely applied dense zone of cells, of which the predominating type is oval or fusiform with a clear cytoplasm and oval, vesicular nucleus. There are many rounded polygonal cells with finely granular cytoplasm and round, relatively dense nuclei, and a number of red blood cells. Surrounding this zone is a zone of short, thick, bony trabeculae, with few anastomoses. The laminated structure is not defined. There are many large polygonal included bone cells. Some trabeculae have endosteum consisting of a thick layer of large, oval, or spindle cells with large, oval, vesicular nuclei.

The sinuses are numerous and engorged. There are no fat cells present.

The predominating type of interstitial cell is oval or spindle shaped with clear cytoplasm and a large, oval, vesicular nucleus. There are a few rounded cells with finely granular cytoplasm and round, relatively dense nuclei.

Zone 11. The bone trabeculae are thin and widely separated. The laminated structure is well defined. The included bone cells are oval and small.

The endosteum consists of a thin, single layer of spindle cells. A few osteoblasts may be noted on the ends of the trabeculae, also occasional giant cells.

The fat cells are relatively few in number. Some are large, clear and distended, and some small, clear and distended. Some are small, shrunken, deformed, and slightly opaque.

The interstitial cells are chiefly rounded cells, with finely granular cytoplasm and round, relatively dense nuclei. There are a number of large rounded cells with coarse granular and round exceedingly dense nuclei,and a number of polygonal cells with clear cytoplasm and oval vesicular nuclei.

The sinuses are moderately engorged with red blood cells.
Zone 111. Normal except that the fat cells are fewer and smaller and the interstitial cells are more polygonal with clear cytoplasm and oval vesciular nuclei.

Iron - Femur.
Zone 1. The implant is surrounded by a narrow zone of closely packed cells. The predominating type is large, polygonal and with finely granular cytoplasm and a round relatively dense eccentric nucleus. There are many smaller round cells with finely granular cytoplasm and polymorphonuclear and transitional types of nucleus. Many are oval and elongated cells with clear cytoplasm and oval vesicular nuclei. There are a few giant cells. There are numerous red blood cells.

The bony trabeculae are anastomotic, thickened, and the laminated structure defined except where new bone is laid down. Many budding projections of new bone and many included oval bone cells are to be seen.

The endosteum consists for the most part of thin and single layers of cells with oval nuclei. About the new bone areas the cells are larger and more oval and at times occurring in two layers. There are many osteoblasts in growing areas and occasional included giant cells. The sinuses are moderately filled.

The predominating type of interstitial cell is relatively large, polygonal and with clear cytoplasm and rounded vesicular nucleus. There are many large polygonal cells with finely granular cytoplasm and round eccentric relatively dense nuclei. The fat cells are few small, clear and distended.
Zone 11. The bony trabeculae are thin anastomotic and the laminated structure well defined. There are a few budding

projections of new bone. The included bone cells are small and oval.

The endosteum is of a thin single layer of cells with elongated dense nuclei. There are a few giant cells. The fat cells are few, small, clear and distended. The sinuses are moderately congested with red blood cells. The **interstitial** cells are the same as Zone 1, except for a few large, irregular cells with coarse granules and eccentric relatively dense, round nuclei.

Zone 111. Zone 111 is the same as Zone 11, except for the interstitial cells, of which many are irregular, polygonal cells with clear cytoplasm and large, oval, vesicular nuclei. Also there are many irregular cells with finely granular cytoplasm and round, relatively dense nuclei and a few large, irregular cells with large, coarse granules and eccentric, round, relatively dense nuclei.

Silver - Femur.

Zone 1. The implant is surrounded by a closely applied, dense zone of spindle shaped connective tissue cells arranged in several layers. The bone trabeculae are thin, short and anastomotic with many budding projections of new bone, in which the lamellar structure is not defined. There are many large, isolated bone cells and many budding processes with numerous osteoblasts and occasional giant cells.

The endosteum consists for the most part of a single layer of cells slightly larger and more oval than normal. In places two layers of cells are found. The fat cells are very few in number, small and distorted, but clear. The sinuses are engorged with red blood cells.

Of the interstitial cells the predominating type is fusiform, with an oval, dense nucleus. A number of polygonal cells with clear cytoplasm and rounded vesicular nuclei and a few red blood cells are noted.

Zone 11. The bony trabeculae are thin, anastomotic and the lamellar structure is defined. Isolated bone cells occur in normal number, elongated and oval.

The endosteum is of a thin single layer of cells with elongated dense nuclei. The fat cells are small, clear, distorted and not numerous. Of the interstitial cells the predominating type is large, polygonal, and with clear cytoplasm and a round, dense nucleus. Also there are a number of polygonal cells with finely granular cytoplasm and round, dense nuclei.

Zone III is normal.

Gold - Femur.

Zone 1. The implant is surrounded by three and four layers of concentrically placed connective tissue cells having elongated, fusiform, fibrillar form, and elongated relatively dense nuclei.

The bone trabeculae are for the most part, thin, but with a few thick budding areas. The anastomotic laminated structure is defined by additions of new bone. The isolated bone cells are relatively small and elongated. There are budding processes of new bone covered with a single layer of osteoblasts. New bone is in close contact with the implant in many places. There is an occasional giant cell to be seen.

The endosteum for the most part is made up of a single layer of fusiform cells with elongated nuclei, but about the new bone there is either a single layer of young cells or in places a double one. A few included giant cells are to be seen in the thicker new trabeculae.

The fat cells are clear and distended, but fewer and somewhat smaller than normal. The sinuses are engorged with red blood cells.

The interstitial cells are chiefly large, polygonal or elongated cells with clear or finely granular cytoplasm and rounded vesicular nuclei. A few adult red blood cells are to be seen.

Zone 11. The bone trabeculae are thin and anastomotic and the laminated structure defined. The isolated bone cells are fusiform and there are no budding growths or new bone layers.

The endosteum consists of a thin, single layer of closely applied cells with elongated dense nuclei. The fat cells are clear and distended but slightly smaller and less numerous than normal. The sinuses are engorged with red blood cells.

The interstitial cells are made up of a few large cells with finely granular cytoplasm and relatively dense nucleus, and a few red blood cells. The predominating cell type is large with clear cytoplasm and oval or rounded vesicular nucleus.

Zone 111. Zone 111 is much the same as Zone 11, except for the fat cells which are larger and more numerous, also the sinuses are less noticeably engorged, and the interstitial cells have a few polymorphonuclear forms.

Copper - Femur.

Zone 1. The implant is surrounded by a thick concentric layer of spindle cells with dense elongated nuclei. The bone trabeculae are thickened and have many budding projections. The lamellar structure is not well defined and there are many large included bone cells.

The endosteum is thick and consists of single and double layers of large cells with oval, vesicular nuclei. There are numerous giant cells in this region, but for the most part the cellular tissue is made up of fibroblasts in various developmental stages, together with a few polymorphonuclear leucocytes and a few red blood cells. There are no fat cells present.

Zone 11. This region is very similar to the first, differing only in degree. The predominating type of interstitial cell is large and polygonal, with a finely granular cytoplasm and a large, eccentric, relatively dense nucleus.

The fat cells are few in number and are shrunken, deformed and cloudy. The blood sinuses are engorged with red blood cells.

Zone 111. The bone trabeculae are normal but the interstitial marrow cells appear smaller than usual.

Normal Bone - Femur.

The bone trabeculae are of definite lamellar structure with included fusiform bone cells.

The endosteum is closely applied in usually one thin layer of cells with elongated dense nuclei. Occasional giant cells and a few osteoblasts are seen. Fat cells are numerous, large, clear and distended. The sinuses are filled with adult red blood cells. The interstices between the fat cells are filled with masses made up of large, irregular and polygonal cells with pale, finely granular cytoplasm and a rounded, eccentric, vesicular nuclei, small polygonal cells with clear cytoplasm and large, round, dense nuclei, and large, irregular cells with coarsely granular cytoplasm and an eccentric vesicular nucleus.

Control. Femur.

Zone 1. The regenerating area shows the new bone trabeculae in shorter fragments than normal and not anastomotic. The lamellar structure is not definite and there are many large polygonal included bone cells. The endosteum consists of single and of double layers of large cells with vesicular nuclei. The budding ends of the trabeculae show many osteoblasts and a few giant cells. The fat cells are fewer and smaller than normal, and the sinuses are engorged with red blood cells. The interstices are crowded with marrow cells, chiefly of the large finely granular type.

Zone 11 is normal.

Zone 111 is normal.

Stellite - Femur.

Zone 1. The implant is surrounded by a dense, narrow ring of connective tissue.

The trabeculae of bone are similar to those surrounding the regenerating area in the control, but thinner and anastomotic. The included bone cells are moderately sized and oval. There are numerous budding processes of new bone covered with osteoblasts.

The bony network closely approximates the connective tissue sheath of the implant.

The endosteum is relatively thin and inactive except at the points of new growth.

Fat cells are present, clear and distended, but slightly smaller than normal. The sinuses are engorged with red blood cells.

The interstitial cells occur in masses of the same nature as the control. The predominating type of cell is large and non-granular, although the smaller ones are present as are some coarsely granular.

Zone 11 is normal.

Zone 111 is normal.

Low Carbon Steel - Femur.

Zone 1. The implant is surrounded by a loosely arranged zone of connective tissue made up of oval and fusiform cells. Interspersed are numbers of large cells with clear cytoplasm and eccentric nuclei together with a number of giant cells which react to special stain for hemosiderin. These giant cells are chiefly in the region of the implant, although a few are scattered through the tissue as far as the second zone.

The bone trabeculae, are if anything, less in evidence than in the control. There are few budding areas of new growth and the endosteum is thin and inactive. No fat cells are present.

Zone 11. This region is normal except for a decrease in the size and number of fat cells and a slight excess of the connective tissue type of marrow cell.

Zone 111 is normal.

In an analysis of the foregoing observations it is obvious that a too minute scrutiny of all the variable factors involved will lead to confusion and a loss of the points at issue. The normal variation in the reaction of living tissue is great, and this is magnified by the inability to exactly repeat experimental conditions.

The microscopic findings in the control specimen of Series I exhibit the phenomena of normal reaction to injury. The wound of the skin and underlying soft tissues presents the usual evidences of repair.

The scar tissue is not extraordinary in amount or extent. Inspection of the same tissues in the remaining specimens of the series shows a marked uniformity in behavior. In the control specimen the site of the bone injury is merely a smooth white swelling. This condition is approximated by only five members of the series; those bearing the gold, stellite, silver, lead and aluminum. These vary slightly among themselves, but the variation is well within normal limits. In the remainder of the series there is evidence that the implanted metals definitely interfere with the usual process of regeneration. Discoloration of the surrounding tissues, crater like depressions in the protuberances over the implants, or frank failure to cover the metal, occur singly or together as in the case of high carbon steel, low carbon steel, and copper aluminum alloy specimens.

The copper specimen while badly discolored, instead of showing an intolerance to the metal,exhibits a marked over-growth of the region. In fact so great was the reaction that the experiment was repeated in two other animals to observe the constancy.

The microscopic studies of these specimens as might be expected, afford a far better basis for conclusions than mere gross inspection. The slight swelling at the site of the drill hole in the control tibia is seen to consist of a slightly thickened periosteum and a mass of new bone; a crescentic periosteal protion blending with the endosteal growth from the cortical defect. In the medulla may be seen the trabeculae of new bone formation.

In establishing this control several animals were employed, although only one is reported in the protocol. It was found that in all cases the character of the reaction was the same, the variation lying in the degree.

The medullary reaction and that from the cortical defect were constant and uniform, but the thickness of the layer of new subperiosteal bone exhibited a variability of twenty per cent of the recorded specimen.

The section from the stellite implant shows the least departure from the normal. The type of reaction is similar and the degree is not outside the limits observed in the controls. Moreover, the new bone is so closely laid down about the metal that if a corresponding area be blotted out of the control section, they could not be identified. In fact, it appears in this section that the metal merely occupies space and affects in no way the regeneration of the bone and periosteum.

Very much the same picture is presented by the gold, silver and aluminum sections. The subperiosteal growth is somewhat excessive and the new bone does not conform to the outline of the metal quite so accurately, but these differences are very slight.

The section from the region of the lead implant is much like those previously mentioned, the chief difference occurring in the failure of the bone to completely cover the external end of the implant. Also, the encapsulation of the metal tends to be rather one of fibrous connective tissue than of bone.

In the case of the zinc implant the failure of the subperiosteal bone and the new bone of the cortical defect to cover the implant is marked and may be identified as the central depression noted in the gross. Although there is no attempt at bony encapsulation, there is a distinct fibrous connective tissue enveloped about the metal and little evidence of actual tendency to extrusion.

In the magnesium section the process is carried a step farther in that the enveloping connective tissue is more cellular and thicker. In fact as compared to the zinc section the new connective tissue is more in evidence than the new bone. Here again the trend is toward fibrous tissue encapsulation with but indifferent response from the bony structures.

The copper, copper aluminum alloy, and nickel specimens, while grossly dissimilar, should really be classed together as they present in different measures the phenomena of irritation and stimulation.

The copper section is unique in that it is the only one which shows excessive overgrowth of bone and bony encapsulation of the implant. In this section the medullary bone is more dense and more uniform than in any other, while the subperiosteal growth is tremendous. Even the cortex in the region of the defect, with its enlarged Haversian canals takes on the appearnace of the surrounding newer structure.

In the periphery may be seen several cases of cartilage, the significance of which is difficult to determine and which might be attributed to the stimulation of the copper. In a way the section appears as a process of inversion to the embryonic type of bone.

In the nickel section, while the stimulation is evident, it is not so intense and falls short of a bony encapsulation of the metal. From the space about the implant and the amount of cellular tissue surrounding it, it may reasonably be concluded that the process is a slower one than that of copper. In all events there is evidence of irritation and marked reaction of the tissue.

The copper aluminum alloy section while classed with the copper and nickel sections resembles them only slightly. The stimulation of the medullary bone growth is marked and the bone of the cortical defect is relatively dense but the subperiosteal growth is well within normal limits. Moreover, there is neither bony nor fibrous tissue encapsulation of the metal, the region of the implant being a wide open V. Stimulation there undoubtedly is, but not in sufficient degree to insure the retention of the metal.

The steels and iron have been left for separate consideration in that they have some phenomen peculiar to themselves alone. The iron section shows an implant surrounded by a relatively thick fibrous tissue layer in which are giant cells showing brown to hematoxylin and eosin and staining deeply with a specific hemosiderin stain. These cells lie near to the metal and are not scattered through the surrounding tissue. The medullary bone and the bone of the cortical defect are rather dense and uniform, and the subperiosteal bone is well within normal limits. There is no tendency to overgrowth and no tendency to bony encapsulation of the metal, while the regenerative process is not stimulated, neither is it greatly interfered with.

Both high carbon and low carbon steel when implanted in bone provoke the same type of reaction. The metal is incompletely surrounded by a thick zone of cellular connective tissue, its outer end free and uncovered by any periosteum. In this connective tissue and for a short distance in the surrounding tissue are to be found many giant cells staining specifically for hemosiderin. The new bone production in the medulla is negligible,while in the cortical defect it is more scanty than in any of the other specimens, failing to approach the metal by a considerable distance.

These several gross and microscopic observations of this series may be rendered somewhat more comprehensive in tabular form as follows: See Table I.

The second series of experiments although not of considerable value in determining the relative merits of the various implants, exhibits some interesting features which may aid in the analysis of other similar work. The intent was to employ the ribs of a dog in the same manner as the tibiae and compare the findings of the two different types of bone. The technical difficulties however, made this impossible as the maintenance of the same proportion between metal and bone and the use of a piece of metal sufficiently large to be workable was often followed by fracture.

Examination of the gross specimens reveals, as was noted in Series I, a similarity in reaction between the control and the gold, silver, aluminum and stellite implants, all manifesting only a moderate fusiform enlargement at the site of injury, The iron specimen is also of this character but the bone surrounding the tissue is discolored.

Copper implantation as in Series 1 is attended by a marked fusiform enlargement of the region with also the same discoloration.

The high carbon and low carbon steels together with the copper aluminum alloy and nickel all gave evidence of their irritant qualities by appearing uncovered by periosteum and accompanied by little bone stimulation.

The striking elements of the series however, lies in the behavior of the zinc, lead, and magnesium implants in that in these specimens the bone was fractured at the site of operation and all evidenced a large fusiform bony growth at this point quite in contrast to the reactions observed in the tibiae.

The three series of experiments involved metal implantations in the cancellous structure at the ends of the femora and was undertaken to determine the early stages of reaction in a very sensitive medium. In this way it was thought that the more strongly stimulant or toxic metals could be group. Gross examination of the autopsy material revealed little except for discoloration of the implanted regions, the joints and capsule and overlying tissues showing the usual scar formation of a recent wound.

The control, the gold, the aluminum, and the stellite specimens exhibited slight degrees of discoloration, and over the implant in each was found a thing layer of dense connective tissue. The silver specimen was similar but for a somewhat more marked discoloration.

The magnesium and iron implants also caused a moderate discoloration, but the ends remained uncovered by any tissues. This latter observation was made in the remainder of the series of which each was markedly discolored.

As in the first series, the gross evidence is not comparable as to the histologic and serves merely as a very rough means of classification. The microscopic studies, however, are attended by some considerable difficulties of which the technical are by no means the least. The tissue involved is briefly a network of bony trabeculae interspersed with marrow substance. To obtain bone sections sufficiently thin to allow of satisfactory study of the marrow cells, and yet of a thickness that would serve for orientation, proved a task which ended in compromise. The finer cell structure was sacrificed in order that the relationships of the various parts might be maintained, and as a result the recorded findings merely enumerate the general classification of marrow cell types without attempting a finer division which is difficult even with film preparations.

In entering upon the discussion of a subject so obscured by conflicting opinions it is not only advisable but necessary that some arbitrary standard of classification and nomenclature be adopted.

Accordingly the catalogued observations have been made as much as possible in keeping with Carnegie Dicksons monograph on the bone marrow. In this he has identified cells of the following orders:

I. Leucocyte Series.

A. Non-granular cells.
1. Large.
2. Small.

B. Granular cells.
1. Neutrophile
2. Eosinphile — myelocytes.
3. Basophile

II. Hemoglobin Series.

A. Normoblasts.

B. Megaloblasts.

III. Giant Cells.

A. Megakaryocoytes.

B. Polykaryocytes.

IV. Cells of the Connective Tissue Type.

A. Fat cells.

B. Reticulum cells.

C. Various phagocytic cells.

D. Ordinary connective tissue cells.

V. Endothelial Cells.

Examination of the section of normal bone in the region of the femoral epiphysis shows a network of adult bone trabeculae covered with a thin, inactive endosteum. Fat cells are numerous, large, clear and distended, and the blood sinuses are well filled with adult red blood cells. The interstices between the fat cells are filled with masses of large and small non-granular cells, also large cells of the granular type; all of the leucocytic series. Occasional giant cells, or polykaryocytes, are to be seen along with a few osteoblasts.

In the control specimen the greater part of the section is identical with the character of normal bone but the immediate zone of the injury exhibits an active process of repair.

The new bone appears in short non-anastomotic fragments and the endosteal covering consists of single and double layers of osteoblasts, and about the budding ends of the trabeculae are a few giant cells. The blood sinuses are large and crowded with red blood cells, but the fat cells are few and smaller than normal, although clear and distended. The interstitial marrow cells are present in larger masses than in normal bone and consist chiefly of the large non-granular type.

All this is quite in keeping with our conception of reparative processes elsewhere, the unique feature being the increase in marrow cells. However, this is too to be expected as Dickson found the quantity of fat present to vary inversely with the activity of the tissue.

As in the first series, the specimens bearing the aluminum, gold, and stellite implants may be grouped together for consideration, their individual difference being slight and chiefly of degree rather than quality.

In each the metal is surrounded by a dense zone of connective tissue of three or four layers, closely approximated by new bone. Peripherally from this point the changes are well within the limits of the normal reaction as shown in the control,.

Next, in order of variance comes the magnesium specimen. In this the connective tissue zone surrounding the metal is slightly more cellular and more loosely arranged as well as being definitely thicker. Thicker too, and more actively proliferating are the bony trabeculae. This change extends well into the intermediate zone, the extreme periphery being normal.

Proceeding further on the scale of activity the implants of silver, lead and zinc range themselves in a closely related group. The bone proliferation in each is somewhat in excess of normal and the stage of regeneration seems farther advanced.

Moreover, while the zone of greatest departure from the normal is that in the immediate vicinity of the metal, it definitely extends into and involves the surrounding area. The interstitial marrow cells are of the granular and non-granular types with a few polymorphonuclear forms. Throughout the primary zone, however, and to a lesser degree the secondary zone, are found numerous cells of the connective tissue type of which very few were present in the control. The most interesting change occurs in the fat cells which are shrunken and cloudy and apparently degenerative forms. This condition is probably of the same nature as that described by Bizzozero, Jackson, Newmann and others. It occurs again in more marked degree in other sections, notably the copper, and may be considered as a degenerative process similar to that occurring in toxemias and in starvation.

In the case of the aluminum bronze and nickel implants this same excess of connective tissue is to be seen, but the bony regeneration is less marked. The reaction extends from the site of the implant into the secondary zone where it is less notable, also the fat cells are absent in the primary zone and only slightly affected toward the periphery. The entire process is an attempt at repair into which the bone does not enter to the degree manifested in the control.

In many respects the condition is similar to the fibrous marrow resulting from chronic disease processes, as noted by Dickson. The connective tissue element is probably derived from the reticulum cells described by Jackson.

In the copper specimen is seem the most marked reaction of the series. The bone and connective tissue proliferation are equally exaggerated at the expense of the fat cells and the blood cells of the marrow. The activity extends well toward the periphery and even at some distance from the implant, the fat cells occurring in degenerating forms. Throughout the greater part of the section there is evidence that the tissue has been stimulated to a tremendous activity.

The specimens bearing the iron and steel implants present phenomena very like those exhibited in the sections of the tibiae. In all, the implant is enveloped by a relatively thick layer of connective tissue surrounding which are the pigment giant cells. As noted before, these occur in greater numbers about the high carbon and low carbon steels, the iron apparently being less easily affected.

Again, as in the previous series, bone proliferation in the steel sections does not equal that of the control, while in the iron specimen it falls quite within normal limits. In fact, in these three metals of the three series the relative variation of the iron is much less than in the previously described Series 1.

Concerning the last two series of experiments little, if anything, need be added to the recorded observations. In Series IV the reaction is chiefly a connective tissue one and the results obtained are sufficiently obvious to require no further amplification. This also is true of the X-Ray findings of the last series wherein the degree of callus formation can be definitely measured from the photographs. In would be well, however, not to attach too great importance to the subperiosteal bone so frequently found opposite the implant in this series, as Gazzotti's experimental work would seem to show that the necessary extensive elevation of the periosteum over the circumference of the bone would in itself be sufficient cause for the subperiostel growth.

From the foregoing review of the findings it may be observed that in the different types oftissue examined there is a uniformity at least in the manner, if not in the degree of reaction to the various metal implants excepting in the second series involving the ribs. Here fracture of the bone at the point of injury has added a new and modifying factor in the mobility of the parts, and it is well to note that each instance of fracture is attended by an excessive bony overgrowth, which does not correspond to the findings in the other series. Consequently, it may be taken that the movement of the part is responsible for the bone stimulation and not the presence of the metal. This may serve to explain the findings of Groves, who noted excessive bony overgrowth when magnesium intramedullary pegs were used in experimental fractures, inasmuch as in these cases the absorption of the metal early allowed considerable mobility to the parts.

Excluding this first rib series as untrustworthy and technically defective, the remaining experiments constantly present one set of facts, viz., that bone is indifferent to the implantation of some metals and sensitive to others. In the first group the metal remains unchanged during its placement in the tissue, while in the second group there is definite evidence of varying degrees of corrosion. All other experimental factors being uniform the only conclusion permissable is, that the tissue reaction depends to a great extent upon the disintegration of the metal.

It must of course be recognized that the foreign body purely as such, affects the reparative processes to some degree, but the findings in the foregoing bone sections show it to be much less marked than in the connective tissue elsewhere. The endothelial cell proliferation and giant cell formation noted by Mallory is certainly poorly represented, although this might occur were the metal finely divided. Nor does it coincide fully with the observations of Herzog, Marchand, and others, in regard to the leucocytic infiltration, perhaps by reason of the disparity of the media and materials.

LeFort's observations on the tolerance of tissue to metallic masses even though concerned with the soft tissues coincide with the preceeding observations on bone, He says "when the mass is non-septic, non-irritating by its anatomic location or form of chemical nature, the organism tends to ignore it and the phenomena of defense do not appear. The usual reaction is the encapsulation in a dense wall of fibrous tissue."

Therefore, when the reaction exceeds this and involves the more remote tissues it must be by reason of something other than the mere presence of an inert foreign body.

It is axiomatic that, in mass form, a metal may modify other elements only at the expense of its own substance. In an electrolyte this is accomplished by the dissociation of metallic ions to the end that a colloidal solution is formed conforming to the solution pressure of the metal. This process underlies the phenomenon which we term corrosion, and recently A. N. Friend has advanced it in relation to steel and iron exposed to the action of electrolytes.

Gold and platinum are known as non-corrosive metals and do not pass into solution in this way, as has been shown by Naegeli and others. The same is claimed for stellite.

The preceeding experimental series however, have exposed the several metals to the action of living tissue wherein they are subject, not only to the inorganic solutes, but to their protein combinations. According to Benidicenti and Revello-Alves on shaking salt free albumin solutions with metallic, iron, copper, lead, nickel, or aluminum, portions of these metals go into solution and are bound by albumin in a masked or unrecognized form. Bechhold also states that in the presence of salts, albumin forms with heavy metals, precipitates whose chemical composition is not constant but depends on the concentration of the components at the time of precipitation. This gives intimation at least of the complexities which may arise from contact of metallic ions with living cells. Salus believes the influence of metals on living cells to be preponderatingly destructive, but that in some instances it may be a growth stimulant.

Robin on the contrary believes the action to be only stimulative,while Naegeli rather compromises the matter by saying that different cells react to different metals and in different manners.

Admittedly there is much confusion and the nature of the activity is not clearly understood. Baumgarten, Luger, and others, holding fast to a purely chemical explanation, and Saxl, together with many, claiming it to be a physical phenomenon.

But, whatever the process, the experiments here recorded appear to bear out Naegeli's conclusions, the most notable examples being copper and high carbon steel; the former attended by an excessive bony overgrowth and the latter remarkable for its inhibitory action.

CONCLUSIONS

In conclusion, but few statements can be made beyond a catalogue of the individual reactions as follows:

Gold, aluminum and stellite are readily tolerated by bone and tend to become encapsulated with but little hindrance to the reparative processes. They are inert materials, unaffected by the living cells and body fluids. This is contrary to the findings of Duval, Elsberg, and Dawborn, who observed that aluminum was absorbed when planted in the tissues.

Silver and lead are only slightly less tolerable to bone, but are easily corroded and evoke a slightly greater connective tissue response.

Zinc goes into solution readily and causes a slight connective tissue stimulation. It also interferes with bone regeneration and does not become encapsulated by it.

Contrary to Grove's findings, nickel has a distinctly injurious effect on bone growth. It is soluble in the tissue which make little attempt to retain it.

Also opposed to Grove's observations are those regarding magnesium. In the aforementioned experiments its behavior proves it to have little action other than a connective tissue stimulant. If anything, it retards rather than accelerates bone production.

Copper on the other hand causes definite stimulation to bone production although being slowly absorbed. Some specimens suggest that it may be toxic to the tissue in the immediate vicinity, but an active stimulant at a distance.

Alloying copper and aluminum seems to perpetuate this toxic action but without its far reaching irritant effect, for copper aluminum bronze frankly interferes with bone regeneration and tends to become extruded.

Steel, and to a less degree, iron, definitely inhibits bone regeneration. Poorly tolerated and readily soluble, steel seems least suitable of all to be employed in bone prosthesis.

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