THE EFFECTS ON BONE OF THE PRESENCE OF METALS; BASED UPON ELECTROLYSIS

AN EXPERIMENTAL STUDY

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THE reasons for undertaking these experiments on the reaction of bone to metals were, in the first place, the fact that extremely variable bone changes and clinical end-results have been observed when various metals recommended by research workers or by instrument houses have been used indiscriminately in the fixation of fractures. In the second place, we found much confusion in the reports of those who have performed exhaustive experiments to determine which metal or combination of metals was the most consistently tolerated by bone. Moreover, the directly contradictory opinions, and totally variable findings, of previous experiments gave us no clue as to the ideal metal or combination of metals for bone repair, upon which complete dependence could be placed.

Doisy,[4] in 1894, experimented with the then new metal, aluminum, and found that it produced irritation of the bone like any other foreign body. He concluded, however, that its salts were of weak toxicity and therefore that the metal was safe to use.

LeFort,[13] in 1918, observed that the body tissues reacted differently to bullets of different metals in spite of the absence of infection or other extraneous cases. He felt that the variations could possibly be explained by the action of the different metals used in alloys.

Algave[1] used silver wires in his experiments and stated that he was able to produce a chloride of silver which was harmful to the repair of bone.

Hey-Groves[8] claimed that nickel-plated steel did not produce any irritating effects on the tissues, and that magnesium produced destruction of bone if it was in contact with the cortex alone instead of in the medullary cavity. These experiments were quite rudimentary and were not checked by microscopic examination.

Rugh[19] experimented with 16 different types of metal, of which tiny pieces were placed in cultures of *Staphylococcus aureus* and *B. pyocyaneus*. He found that iron, steel, copper, zinc, and nickel, which are readily oxidized by body fluids, frequently cause aseptic suppuration. Silver, gold, and tin were unaffected by the body fluids.

Zierold[21] operated upon a number of dogs in which he drilled holes in numerous bones in various parts of the body and placed pieces of these metals in the holes: Gold, silver, aluminum, zinc, lead, copper, nickel, carbon, steel, stellite, *etc.* The tissues about the pieces of copper showed much discoloration and marked overgrowth of the bone. About the gold, silver, and aluminum there was excessive subperiosteal growth of bone. Lead caused indifferent bone reaction. Nickel produced marked irritation and some stimulation of new bone. Iron and steel caused discoloration and soft tissue reaction. Gold, aluminum, and stellite were readily tolerated by bone and became encapsulated early. Silver and lead, which are easily corroded, caused more connective tissue reaction. Zinc was corroded readily and interfered markedly with bone regeneration. Zierold concluded that steel and iron definitely inhibit bone regeneration and that stellite causes the least reaction of all the metals used. (Stellite is an alloy containing 58 per cent cobalt, 35 per cent chromium, 4 per cent tungsten, plus small amounts of iron, carbon, *etc.*).

Trout[20] inserted steel screws in the bones of young rabbits and noted an arrest of growth of bone.

Leriche and Policard,[16] in their elaborate studies of the physiology of bone, found constant necrosis of bone under the metal plates which were used to immobilize fractures. After excluding injury, pressure, and infection as possible causes, they still found evidence of destruction which they assumed was due to the chemical nature of the fluids about the metals.

Jones and Lieberman,[9] in a recent thorough study, have shown that varying reactions of bone to metals result from the use of impure metals or from alloys of unknown composition. They experimented with small tacks of various types of rustless steels, which were placed in holes in the femurs of dogs. Five dogs were used. As the tacks were removed they were weighed to compare their weights before and after the experiments. Tacks of the same metals used in the dogs were soaked in Ringer's solution and kept at body temperature for 30 days to serve as controls. It was observed that there are many alloys in use which vary notably in chemical composition and that it is necessary to understand their composition to get the best clinical results. This is especially true of the new alloys known as rustless steel. It was suggested that no metal should be used in bone which is corroded rapidly by immersion in Ringer's solution. It was noted that there was much reaction in the soft tissues about all the screws which were used. Such soft tissue reaction seemed to be related in some way to metallic corrosion. The authors decided that chrome-nickel rustless steel was the best metal to use in bone, since corrosion of this metal was minimal. However, this alloy did irritate the bone somewhat.

Only an occasional observer has mentioned the possibility that electrolytic reactions between various metals used in bone repair surgery might be an explanation for the interference with bone growth which occurs in the presence of metallic fixation devices. A few French experimenters have proposed this idea, although they have failed to substantiate their inferences by careful chemical studies. Rolland,[18] for instance, experimented with silver, bronze, iron, and galvanized iron in bone and believed that the plates of metal were eroded by electrolytic action. However, he did not attempt to prove that this explained the toxic effect of metals on the healing bone. Le Grand[14] repaired a fractured radius with a plate of steel and two circular wires. An excess of callus formed, and he wondered if the presence of these two metals bathed by the organic fluids of the body might not have formed a true electric couple which irritated the bone. He later performed several experiments in rabbits using copper, iron, and zinc, and even though there were few experiments, and these superficial, there was strong evidence that, with the two different metals in contact with bone, certain phenomena were produced which interfered with bone growth. Zierold,[21] whose work has been referred to before, suggested that the soft tissue reactions were mainly dependent upon the disintegration of the metals used. He did not, however, suspect electrolytic reaction. Galfre[7] assumed that electrolytic couples were to blame for all complications in the use of metal appliances in fracture work. He wondered if some of the unfavorable tissue destruction might not be due to the reaction of the metal and the calcium of the bone itself. He then erroneously concluded that the action of bone upon metal and the metal upon periosteum was the cause.

Cretin and Pouyanne[2, 3] attempted to explain the cause of variable reactions of metals on bone on a basis of cellular stimulation. They, therefore, were careful to experiment on normal bone with a minimum of trauma. They also studied all their specimens microscopically. Since the conclusions previously reported were so contradictory, they felt that much obscurity had been introduced into this problem. They operated upon guinea-pigs and placed metals such as aluminum, silver, copper, iron, magnesium, nickel, lead, and zinc in the bones. First they tried to see what action the metal would have if it were placed in the medullary cavity. Next they tried to see what action the metals would have if they were placed at the site of a fracture. They found that all the metals excited some degree of destruction which retarded growth of bone. This action also was essentially independent of location whether the metal was placed in the medullary cavity or directly on the bone surface. They tried to demonstrate that cellular reaction and calcification were inversely proportional to each other and that a metal which affected one did not affect the other.

In all these previous experiments, interpretations of results have depended upon macroscopic findings, tissue reactions, microscopic study which was but a magnification of the macroscopic detail, and some roentgenologic studies. Table I is arranged to show the wide variance of opinions resulting from these studies and the many inconsistencies thus far expressed as to the reactions of bone to metals.

Because of the wide difference of opinion resulting from former experiments and because of certain unpredictable clinical phenomena when metals are used in bone surgery, we assumed that there must be a variable factor yet undetermined. Our experiments therefore were undertaken to study the possibility that electrolysis might be the variable factor. In order to demonstrate this it was necessary first to study the reaction of normal bone to

TABLE I

CONTRADICTORY CONCLUSIONS OF VARIOUS AUTHORS ON THE EFFECTS OF METALS ON BONE

Metals Used	Metal Is Resorbed	Metal Is Not Resorbed	Indifferent Reaction	Partially Indifferent Reaction	Bone Growth Stimulated	Toxic Reaction on Bone	Bone Growth Inhibited	Bone Reaction Favorable
Aluminum	Duval,[5] Elsberg and Danborn[6]	Zierold,[21] Cretin[2]			Cretin[2]		Cretin[2]	
Silver		Metal oxidized	Lemerle[15]	Zierold,[21] Cretin[2]				
Copper		Rugh[19]	Cretin[2]		Cretin,[2] Zierold[21] (distant)	Cretin,[2] Zierold[21] (contact)		
Iron		Rugh[19]	Rolland,[18] Trout[20]			Leriche and Policard,[16] Cretin[2]	Zierold[21]	Lange[12]
Magnesium	All observers				Lambotte,[10,11] Cretin[2]		Zierold,[21] Cretin[2]	
Nickel	Zierold[21]	Rugh[19]	Potarca,[17] Cretin[2]			Zierold,[21] Cretin[2]	Zierold[21]	Hey-Groves[8]
Lead			Zierold,[21] Cretin[2]			Cretin[2]		
Zinc		Rugh[19]		Rolland[18]	LeGrande,[14] Cretin[2]		Zierold,[21] Cretin[2]	
Steel	Zierold[21]						Zierold[21]	
Stellite			Zierold[21]					Zierold[21]
Chrome-nickel			Jones and Lieberman[9]					Jones and Lieberman[9]

various basic metals, plated metals, or combination of metals (alloys) in a control series of dogs. Two screws made of similar metal were placed in the bone where they would be bathed by the same electrolyte (body fluids) and where no electrolytic action would be expected.

In two subsequent series of dogs, screws of these same metals were placed in duo in the bones in different combinations to find whether or not there would be an electrolytic reaction between them. As the experiments proceeded, we performed biochemical examinations of the tissues and tissue fluids, screws, liver, and in some instances kidneys, of the dogs as they were sacrificed. This was done because we observed that simple macroscopic, microscopic and roentgenologic observations were too variable and inconclusive to be of value. It is obvious that the proof of electrolysis of tissue depends upon evidence of electrolytic action according to the laws of the electromotive force of metals either in the solution about the individual screws or upon the interchange of metal ions between the screws. A criterion for proof of electric activity was that, in the presence of different metals in duo in the same bone, if ions of one metal should be carried to the other, according to the laws of the order of electromotive force of metals, it would be due to electrolysis. The body fluids in these experiments acted as the electrolyte and biochemical analyses were performed to demonstrate the presence or absence in the electrolyte of one or the other of the metals in solution adjacent to, or adherent to, the other metal, ad seriatum, in accord with this law.

TABLE II

THE ORDER OF THE ELECTROMOTIVE FORCE OF METALS

Metal	Electromotive Force (E.M.F.)	Conductivity	Melting Point Degrees C.
Aluminum	1.7000	324,000	659
Zinc	0.7618	186,000	419
Chromium	0.5570	83,200	1,615
Iron	0.4410	63,000	1,535
Cadmium	0.4010	95,000	321
Cobalt	0.2780	10,300	1,478
Nickel	0.2310	144,200	1,452
Tin	0.1360	76,600	232
Lead	0.1220	50,400	327.4
Antimony	0.1000	27,100	630
Copper	0.3440	591,000	1,083
Silver	0.7978	681,200	960.5
Platinum	0.8630	91,200	1,773.5
Gold	1.3600	468,200	1,062

In all of these experiments, of which upwards of 50 were made, each radius of each dog was used. In the right foreleg the radius was fractured obliquely with an osteotome (to produce a condition of traumatized bone), and the fracture fixed with the two screws. The left radius was not fractured and two screws were placed in the bone similarly to those in the fractured right radius. The wounds were closed, the legs were fixed in plaster encasements, and the dogs maintained under especially favorable conditions for periods of four, six, and eight weeks.

At the time the dogs were sacrificed the macroscopic changes in the tissues were noted and photographed in color. Roentgenologic examinations of the legs were made, also biochemical studies of tissues, of liquid exudates adjacent to the screw holes, and of the screws themselves. Chemical examinations of the livers and kidneys were also made in many of the experiments. Finally sections of bone, at the screw holes, were removed for microscopic study.

In several of the experiments we found evidence of a migration of ions of one metal to another, which in each case was in accordance with the sequence of the electromotive force of metals. We found in a few instances an actual deposit of particles of one metal upon another. In one animal the transference of ions had involved two separate processes: a deposit of the copper ions from a brass screw onto the chromium of the chromium-plated screw and a deposit of chromium ions from this latter screw onto the zinc of the brass screw, all in accord with the order of electromotive force of metals. In several experiments, we found chromium in the livers and kidneys of dogs in which we had used the chromium-plated screws, and copper in large excess in the livers and kidneys in which brass or copper screws had been used. In dogs into which any form of steel had been inserted, whether plain or plated or in alloy, there was an excess of iron in the liver. Two of the dogs that died 15 to 20 days after operation had had chromium-plated steel screws used and a large amount of chromium was found in their livers. It is possible these deaths were due to chromium poisoning, since there was no other cause found at the autopsy, which included a careful analysis of the stomach contents.

In determining the electrochemical character of a given combination of metals, the volume of each piece of metal, the distance between them and the difference in potential of the electrolyte must be taken into detailed consideration. Thus the body fluids of each individual, though essentially the same qualitatively, differ quantitatively.

When pure metals are used alone in the body, there is some direct chemical action by the body fluids. In the instance that only one metal is used, any ensuing structural changes are due solely to chemical influence, because, of course, no electrolysis can occur in the presence of only one metal. But if impure metals are used in the body, singly or with other metals, there is a greater tissue reaction due to electrolysis between the various ions.

Thus our experiments with plated metals showed the greatest reaction of all because it was from plated metals that we were able to demonstrate the transference of metallic ions from one plated screw to the substance of another screw of different metal in compliance with the law of E.M.F. The reason is that when plating becomes eroded or chipped the body fluids can come in contact with the two metals side by side and a battery is at once established. This is forcibly illustrated in our experiments with chromium-plated steel screws.

Proof of electrolytic activity in the tissues is the fact that we have been able to recover chromium from the zinc of a brass screw, copper from the chromium of a chromium-plated steel screw, copper from a silver-plated steel screw and zinc from the substance about a galvanized iron screw, *etc.*, which is shown in the detailed description of the experiments. In such cases, the very great reaction of soft tissue and destruction of bone at the screw site we believe to be due to the electrolytic action engendered by two metals rather than to the intolerance of the tissue and bone to a single meal. For instance, a galvanized iron screw is a mixture of iron and zinc, about which there is invariably a marked reaction, whereas there is little change in the tissues about either iron or zinc alone. This fact has confused many other observers since they could not explain the great variance in the changes that were discovered.

In the use of alloys of "rustless steel" which are made of metals more resistant to body fluids it is impossible to prove electrolytic action by the transfer of the integral metals of one onto the metals of the other. Such alloys are actually different metals. But in direct accord with the law of electromotive force of metals, if there is a marked disturbance about an alloy due to one element being put into solution in the given electrolyte, the action is undoubtedly due to electrolysis and the effect is due to hysteresis. (Hysteresis is a molecular disintegration of metals in an alloy due to variations of local electrical resistance.)

We have accepted the findings of Zierold[21] and of Jones and Lieberman[9] in their reports of their experiments with the rustless steels, and believe with them that these new metals, for such these alloys are, are more resistant to body fluids and so cause less reaction. But we differ with them in their resulting recommendations because of the presence in all rustless steels of such a high percentage of iron, which is so subject to the action of body fluids and which sets up hysteresis and local electrolytic changes in the alloys. Our experiments with an alloy called vitalium, which contains no iron, showed complete resistance to body fluids and no changes whatever in either the surrounding tissues or in the bone. This metal was used in many combinations

TABLE III

CHEMICAL COMPOSITION OF VARIOUS ALLOYS USED IN BONE WORK

STELLITE	"NICKEL FREE" RUSTLESS STEEL	"HIGH NICKEL" RUSTLESS STEEL	"LOW NICKEL" RUSTLESS STEEL	VITALIUM	PROPOSED POSSIBLE ALLOY
Cobalt 58% Chromium 35% Tungsten 4% Iron 3% Carbon	Chromium 15% Manganese .4% Silicon .3% Sulphur .5% Molybdenum .5% Carbon Phosphorus Iron 80%	Chromium 8% Nickel 22% Copper 1% Silicon 1.5% Phosphorus Carbon Iron 65%	Chromium 18% Nickel 9% Manganese .4% Iron 70% Carbon	Cobalt 65% Chromium 30% Molybdenum 5% Manganese Silicon	Cobalt 65% Vanadium 30% Molybdenum 5% Manganese Silicon
Contains iron, so increases electro-activity in alloy with added variance of E.M.F. because iron more subjected to action of electrolytic organic acids.	Chromium 15% 0.5570 E.M.F. Iron 0.4410 E.M.F. about 80% Containing high per cent of iron	Chromium 8% 0.5570 E.M.F. Iron 65% 0.4410 E.M.F. Nickel 22% 0.2310 E.M.F. Conductivity Chromium 83,200 Iron 63,000 Nickel 144,000 High electrolyte potential with variance conductivity	Chromium 18% Iron 70% Nickel 9% Lower per cent of chromium and nickel less E.M.F. Smaller per cent of nickel less conductive potentiality	Chromium 0.5570 E.M.F. Cobalt 0.2780 E.M.F. Molybdenum Conductivity Chromium 83,200 Cobalt 10,300 Melting Points Chromium 1615 Cobalt 1478 No iron Least subject to action of electrolyte	

with other metals with uniform results as may be seen in the detailed report of our experiments.

These experiments show that the various chemical, tissue, and bone reactions are changes due to electrolysis, when two metals are used in couples in the same bone, and explain why there has been so much tissue disturbance locally and such variable results clinically.

In clinical orthopedic work electric couples are created by the use of plates, bands, wires, washers, lock nuts, *etc.,* in conjunction with screws, nails, or other appliances so that two different pieces of metal are used in the same bone. Here Ohm's law becomes effective; *i.e.,* that an electric current is directly proportionate to electric conductivity and inversely proportionate to resistance. Conversely, metals that are more nearly of the same electric conductivity offer less resistance to a current between them.

For example: The usual Lane plate furnished by instrument dealers is nickel-plated or chromium-plated steel, in which the iron is exposed at the holes into which screws of plain steel, chromium-plated steel, rustless steel, or galvanized iron are to be placed. What happens? Immediately an electrolytic action is started at the point of contact of each screw with the metal plate and the current is carried by the contacting plate to each other screw. There is then produced a progressive proliferative reaction in the tissues that is protective against the current. A necrosis and destruction of bone cells also takes place and an accumulation of discolored exudate, which contains elements of the metals in solution, forms about the metals and enters the circulation. In two weeks these screws, which were placed in the bone with forcible resistance, may be picked out with the fingers.

As we have shown, we have recovered chromium from the livers of dogs that had only small chromium-plated steel screws in each radius. The suggestion implied by this finding, which was incidental, seems very important because of the extreme toxicity of chromium. Looking back on our clinical experience, we are sure we have seen patients, in whom devices plated with chromium had been introduced, become much more ill than seemed warranted by the operation itself, which makes one wonder if chromium poisoning may not have been responsible. We feel that further investigation of this factor is important because of the wide and indiscriminate use of chromium in plating or alloy in so many appliances used in osteosynthesis.

Wire nails and galvanized nails are made of iron and zinc, and possibly some lead; copper nails and screws are usually copper with zinc or iron; steel screws commonly contain some zinc, while galvanized screws are usually made of iron plated with zinc. All of such metal devices as these have an electrolytic action whether used singly or in multiple, and if they are coupled together by like, or different material, the action is, in electrical terms, "stepped up."

Most of the nickel-plated and chromium-plated appliances sold today are not even electroplated, but instead are plated by chemical dipping. The outer coating of metal is easily chipped or rubbed off, or if the appliance is drilled after plating, the two metals are exposed to direct contact at the screw holes with resulting electrolytic action. Such an assortment of materials courts the disaster we have so often seen clinically.

Electrolytic reaction to the different metals causes the collection of thin, brownish serous exudate about the site of the foreign metal *in vivo*, which, when chemically tested, contains the salts of the metals present in solution. The fluid collection is not due to infection, because this fluid, as well as the surrounding tissue, is microscopically bacteria free. As we have said, though, when metal ions from one screw are recoverable from another of different metal consistently with the law of E.M.F., it is due to electrolytic action and not solely to the chemical action of body fluids upon the metals themselves.

When screws have been placed too far apart in the bone to allow direct interchange of metal ions, there is a local electrolytic action in the screw itself between the metals of which it is made. This can be proved by a biochemical analysis of the tissues about the sites of these screws. To us this explains the interference with healing of fractures in which metal fixation of bone has led to necrosis and destruction of osseous tissue.

Finally, we believe that an alloy should be sought and developed that is entirely inert in the presence of, and unaffected by, biologic salts, to the extent that there will be no electrolytic action: and that it shall have the strength to resist such stress or strain as it may have to bear.

EXPERIMENTAL PROCEDURES

In dogs anesthetized with intravenous nembutal, two screws, consisting of the various metals, alloys, and combinations as described, were placed in the bone about 1½ cm. apart. The right radius was fractured in all the animals and the left radius was not, in order to check the reaction in each dog with and without trauma of the bone. Before the screws were placed, drill holes about two-thirds the size of the screw were made, in order to obviate the possibility of undue or variable pressure.

After the operations all wounds were closed with silk and the extremities fixed in a plaster encasement. The dogs were kept for observation in a well drained, shady corral, and fed separately with a selected, balanced diet.

EXPERIMENTAL RESULTS

CASE REPORTS

Dog 1.—Operation May 29, 1936. *Chromium-plated* screws used throughout. Died June 22, 1936. Autopsy showed no infection, although there was extreme loss of weight. Stomach analysis was negative except for chromate test which showed suggestion of chromium poisoning—more suspicious in subsequent experiments.

Roentgenologic Examination.—Necrosis of bone around all the screw holes. There was considerable tissue reaction about both operative sites. The fracture of the right radius was united. All the screws were loose one plus.

Dog 2.—Operation May 30, 1936. *Plain Steel* screws used throughout. Sacrificed July 20, 1936.

Roentgenologic Examination.—*Right:* There was nonunion of the fracture with destruction of bone and proliferation of callus.

Left: Destruction of bone about the screws with proliferation of new bone over screw heads. All screws were loose four plus.

Autopsy.—*Macroscopic: Right:* Nonunion of fracture with inflammatory soft red tissue over screw head and about the fracture site for 2 or 3 cms.

Left: There was much bony destruction with soft tissue necrosis for ½ to 1 cm. beyond screw heads. Other bone normal. Much excess bone for about ½ cm. around the screw.

Dog 3.—Operation May 29, 1936. *Vanadium Steel* screws used throughout. Sacrificed July 29, 1936.

Roentgenologic Examination.—Fracture united. Slight reaction in the shaft with destruction of bone at the screw heads and proliferation of new bone.

Autopsy.—*Macroscopic: Left:* The screws were tight in their sockets and both were covered with much fibrous tissue. Rim of bone was beginning to cover heads of screws. No discoloration of soft tissue near proximal screw. Excessive scar tissue near distal screw head.

Right: The screw head was completely covered by loose, adherent transparent fibrous tissue with faint brownish discoloration. Screw was loose. Fracture was united without excess callus. Slight necrosis over the head of screw.

Dog 4.—Operation June 3, 1936. *Silver Wire* used throughout. Sacrificed August 7, 1936.

Roentgenologic Examination.—*Right:* Fracture was united. Excessive proliferation of new soft bone.

Left: Silver pegs had worked out of place. Destruction of bone at the sites of both pegs.

Autopsy.—*Macroscopic: Right:* There was firm bony union of the fracture with an excess of firm callus. There was a slight accumulation of tan-colored fluid in a bursal sac immediately over the wire head. Excessive fibrous tissue was present for about 1 Mm. about the wire.

Left: Both wires had apparently worked out of the bone and become encysted. No necrosis at the holes. Holes were nearly filled with proliferation of new bone. Light brown discolored fluid about the wires. No infection.

Dog 5.—Operation June 3, 1936. *Silver-Plated Steel* screws used throughout. Sacrificed August 7, 1936.

Roentgenologic Examination.—Showed necrosis of bone at all screw sites with a marked proliferation of soft callus.

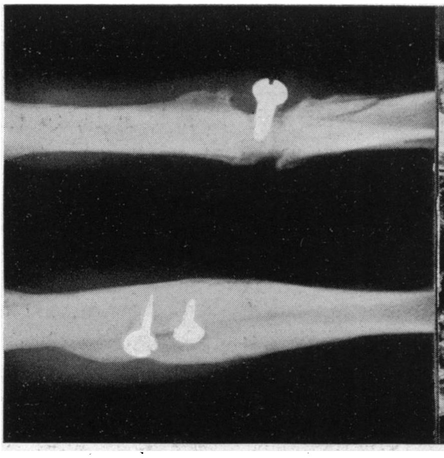


FIG. 1.—Dog 5: Silver-plated steel throughout. Roentgenogram showing marked necrosis of bone at all screw sites; note destruction about single screw.

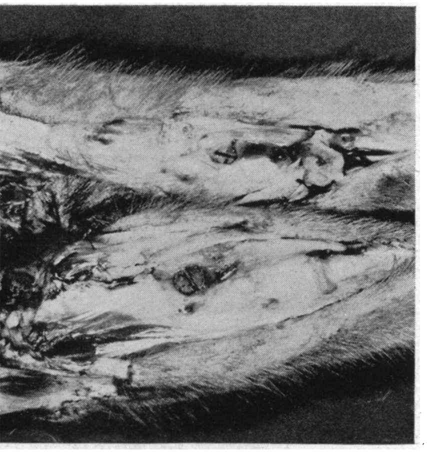


FIG. 2.—Dog 5: Silver-plated steel throughout. Showing tissue reaction: Fracture ununited. Soft encapsulated seminecrotic tissue; tannish discolorations around heads of screws, all of which were very loose.

Autopsy.—*Macroscopic: Right:* Fracture was ununited. Screw was loose. The hole was covered with an excess of fibrous tissue for 2½ Mm. There was soft seminecrotic tissue lining an encapsulated area over the head of the screw. There was a moderate increase of soft callus.

Left: There was an excess of soft callus about the screws. Proximal screw was very loose. Distal screw was engaged. Bluish-tan discoloration over heads of screws which were encapsulated by fibrous tissue 2 Mm. thick.

Dog 6.—Operation June 3, 1936. *Copper Nails* used throughout. Sacrificed August 5, 1936.

Roentgenologic Examination.—*Right:* Union of fracture. Peg had worked out of bone. Necrosis with excessive proliferation.

Left: Necrosis with excessive proliferation. All pegs were loose four plus.

Autopsy.—*Macroscopic: Right:* There was fibrous union of the fracture with excessive fibrous tissue about the fragments. The copper nails had been displaced and were resting parallel to the bone. There was an excessive amount of fibrous tissue about the operative wound. About one nail there was a good deal of tissue necrosis with brownish fluid and tan discoloration. No pus.

Left: There was destructive necrosis near the holes where the copper nails were placed. There was marked necrosis also about the heads of the nails for 1½ cm. Beyond this was an area of marked proliferation of new bone. There was an excess of fibrous tissue almost completely covering the heads of the nails. This extended to 1 Mm. beyond the head of the proximal copper nail. The same was true of the distal nail, although the hole was about twice the size of the nail. There was a slight soft tissue necrosis about the heads of both nails.

Dog 7.—Operation June 10, 1936. *Copper* nail distal and *Steel* screw proximal on the left side. Reversed in the fractured right radius. Died July 16, 1936.

NOTE: In all the subsequent experiments with different combinations of metals in the same bone the arrangement of proximal and distal screws was reversed in the two legs to avoid any possible effect of gravity, or of contact of the solution of metals.

Roentgenologic Examination.—*Right:* Union of fracture. Necrosis of screw site and screw loose three plus.

Left: Slight change. Screws loose one plus.

Autopsy.—*Macroscopic: Right:* There was a sinus in the operative wound with evidence of a small abscess at the operative site and nails had worked out of the bone. Fracture was solidly healed in spite of infection. Tissue was necrotic around the wound.

Left: The copper nail was tight in the bone. Its surface was shiny. There was no apparent tissue necrosis in the region. The steel nail was not tight in the bone and it appeared tarnished. The soft tissue about the steel nail was discolored a dirty gray. Also this tissue showed evidence of liquid necrosis.

Dog 8.—Operation June 10, 1936. *Copper nail* proximal and *galvanized iron screw* distal on the left. Reversed on the right. Died June 22, 1936. No autopsy, cause of death unknown.

Roentgenologic Examination.—Much destruction of bone.

Autopsy.—*Macroscopic:* In both legs there was much tissue proliferation with excess of tan-colored fluid. No infection.

Dog 9.—Operation June 10, 1936. *Chromium-plated* screw proximal, and *copper nail* distal on right. Reversed on the left.

Roentgenologic Examination.—Showed marked bony necrosis at all screw sites, more marked with much more destruction at site of copper nails.

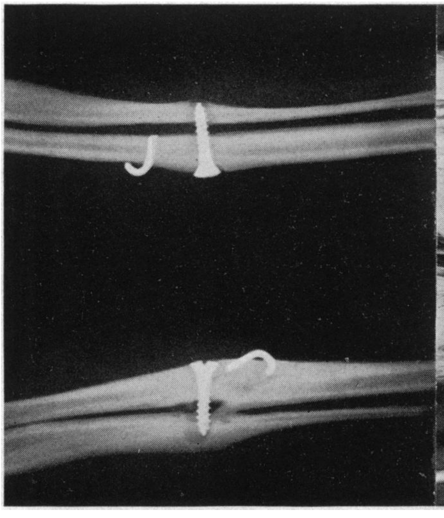


FIG. 3.—Dog 11: Silver and chromium-plated steel. Roentgenogram showing bone necrosis around the chromium but none is present adjacent to the silver.

FIG. 4.—Dog 11: Silver and chromium-plated steel. Showing tissue reaction: Marked reaction evident around the chromium plated steel screw which was loose. Very slight if any reaction present around the silver.

Autopsy.—*Macroscopic: Right:* Bony union of the fracture in good position. There was some destructive necrosis about the chromium-plated screw throughout its entire length. There was more destruction about the copper nail. There was apparently more new bone proliferation distal to the copper. Copper nail was loose. Necrosis over the head of it. Chromium-plated screw light. No excess callus or fibrous tissue.

Left: Decidedly more absorption of bone about the copper nail. Apparently no destruction about the chromium-plated screw. There was an excess of callus and fibrin about the copper nail. The screw was moderately loose and free in the hole. Slight amount of necrosis. The chromium-plated screw was tight. There was no excess of fibrous tissue and no discoloration.

Dog 10.—Operation June 13, 1936. *Plain steel screw* proximal, and *chromium-plated screw* distal on the right. Reversed on the left. Sacrificed June 21, 1936, because of compound fracture and gross infection. Not suitable for chemical study.

NOTE: At this stage of the experiments biochemical studies were begun of the tissues of the legs adjacent to the different screws, of the screws themselves, and of the livers and kidneys of the dogs as they were sacrificed.

Dog 11.—Operation June 13, 1936. *Chromium-plated screw* proximal, and *silver peg* distal on the left. Reversed on the right. Sacrificed September 1, 1936.

Roentgenologic Examination.—Showed marked necrosis about chromium-plated steel screws. None about the silver pegs.

Autopsy.—*Macroscopic: Right:* Around the distal chromium-plated screw there was soft reddish-tan fibrous tissue. Screw was loose two plus. Brown discoloration around the margin of the hole with excess callus. About the proximal silver peg there was no discoloration, no necrosis, no looseness, no callus.

Left: The head of the proximal chromium-plated screw was completely covered flush with callus. There was very dark brown necrotic material over the screw head. Soft tissue around the bone was dark brown and necrotic. Screw was loose three plus. The distal silver peg was out of the hole in the bone and was encapsulated in soft fibrous tissue.

Biochemical Analysis: The soft tissues of the leg were positive for chromium about the chromium-plated screw on the left. The liver and both kidneys showed positive chromium tests.

NOTE: The discovery of chromium in the liver in this dog suggested the possibility that Dog 1 may also have died of chromium poisoning, particularly since the stomach contents showed a positive chromate test although strychnine was not present.

Histologic Examination.—Right proximal screw; silver: Moderate periosteal reaction with formation of moderate amount of chronic granulation tissue. No suppuration present. No evidence of bone regeneration about edges of screw hole. Moderate amount of bone degeneration present, however.

Right distal screw; chromium-steel: No periosteal reaction noted. No granulation tissue formation present. Bone undergoing marked degenerative changes.

Left proximal screw; chromium-steel: Marked periosteal reaction around edges of screw hole with thickening and increased vascularity. Large collections of plasma cells, lymphocytes and multinucleated cells. Marked production of granulation tissue. Some bone degeneration. No osteoplastic activity noted.

Left distal screw; silver: Marked granulation tissue formation with thickening and increased vascularity of periosteum. Some callus formation with moderate osteoplastic activity and with numerous

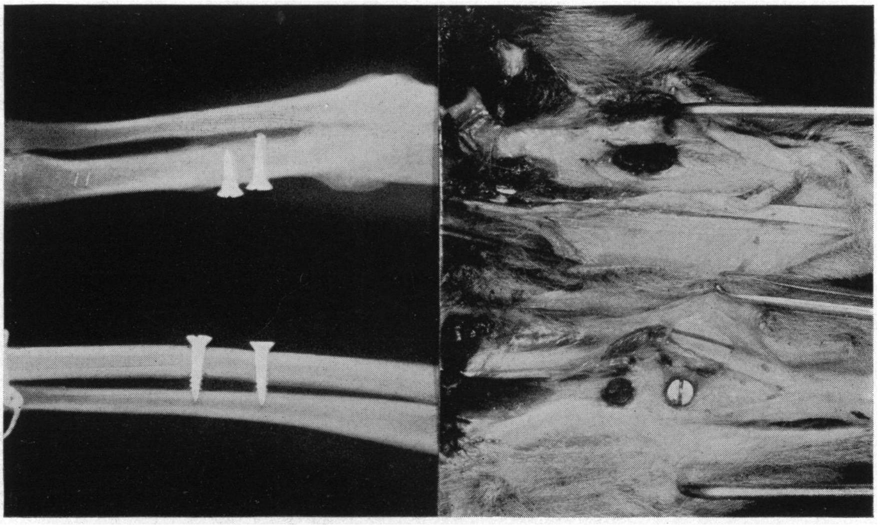


FIG. 5.—Dog 12: Silver-plated copper and steel. Roentgenogram showing moderate bone necrosis evident around all the screws.

FIG. 6.—Dog 12: Silver-plated copper and steel. Showing tissue reaction: There is tan to black discoloration about the silver-plated copper screws. All screws are loose except the steel one in fractured radius.

osteoblasts scattered throughout granulation tissue. In one area there appears to be a chronic suppurative process.

Dog 12.—Operation June 13, 1936. *Plain Steel screw* proximal, and *silver-plated copper screw* distal on the left. Reversed on the right. Sacrificed September 1, 1936.

Roentgenologic Examination.—There was union of the fracture with moderate necrosis about all screws.

Autopsy.—*Macroscopic: Right:* In the bone about the proximal silver-plated copper screw there was brownish black discoloration and semifluid degeneration. Screw was loose one plus. Around the distal steel screw there was black discoloration. The screw was tight and there was no fluid.

Left: About the distal silver-plated copper screw there was much thin, pale tan fluid with similar tan discoloration of the tissue. Screw was very loose: three plus. There was liquefying necrosis. About the proximal steel screw there was black discoloration but no fluid. Screw was loose two plus.

Biochemical Analysis: There was an excess of copper in the liver and kidneys. There was erosion of the silver-plated copper screw in several places with traces of copper in solution in the adjacent tissues.

Histologic Examination.—Right proximal screw; Steel: Mild general reaction with small amount of granulation tissue formation. Mild bone necrosis. Regenerative changes slight.

Right distal screw; Silver-plated copper: Mild degree of granulation tissue formation. Mild degree bony degeneration. General reaction very slight.

Left proximal screw; Silver-plated copper: Moderate degree of bone necrosis. No evidence of granulation tissue formation or callus formation.

Left distal screw; steel: Marked granulation tissue formation. Callus formation with some bony regeneration present.

Dog 13.—Operation July 28, 1936. *Vitalium screw* proximal and *Vanadium Steel screw* distal on the right. Reversed on the left. Sacrificed August 7, 1936, because of severe screw worm infection of mouth.

Roentgenologic Examination.—Fracture united with solid bony union. Vanadium steel screws loose. Vitalium screws firmly in place. In the left leg there was no bony necrosis about the vitalium screw. About steel screws much bone necrosis and tissue reaction.

Autopsy.—*Macroscopic: Right:* Fractured ulna found to be solidly healed. Both vanadium steel screws were in place snugly. Vitalium screws were very tight and considerable force was required to remove them. There was very slight soft tissue reaction about the vanadium steel and none about the vitalium.

Left: Essentially the same findings as on the right.

Biochemical: Examination negative.

Histologic Examination.—Right proximal screw; Vitalium: Periosteum moderately thickened, but no granulations noted. Periosteum dense, relatively acellular with few blood vessels present. No bone necrosis noted, but there is a large wedge of what appears to be new bone present. General tissue reaction is of slight intensity.

Right distal screw; vanadium-steel: Moderate degree of periosteal thickening with a moderate granulation tissue formation about edges of screw hole. This tissue is undergoing extensive liquefaction necrosis. A few small foreign body giant cells are noted along junction of periosteum and granulation tissue. No bone necrosis is noted. General tissue reaction is one of moderate degree.

Left proximal screw; vanadium-steel: Mild periosteal reaction with a very small amount of granulation tissue present. Tissue reaction slight although there appears to be a slight amount of bone necrosis.

Left distal screw; vitalium: There appears to be little tissue reaction of any character, although a small amount of granulation tissue is observed. No bone necrosis.

Dog 14.—Operation August 21, 1936. *Galvanized iron screws* used throughout. Sacrificed November 2, 1936.

Roentgenologic Examination.—*Right:* Fracture ununited and angulated. Much necrosis and bony atrophy. All screws loose four plus.

Left: Necrosis at the screw sites. Screws loose four plus. No new bone growth.

Autopsy.—*Macroscopic: Right:* There was nonunion of the fracture in poor position. There was much fibrous tissue over the ends of the bone. About the proximal screw there was much destruction of bone. The distal screw was out of the bone in a cavity surrounded by amber fluid.

Left: There was very little proliferation of soft fibrous tissue with some pale tan discoloration. Both screws were loose four plus, with destruction of bone about the tips of the screws. Periosteum about the margin of the screw heads and between the screws was completely destroyed.

Biochemical Analysis: Zinc present in adjacent fluids. Liver was not tested for zinc.

Dog 15.—Operation August 21, 1936. *Vitalium screw* was placed proximally, and *galvanized iron* distally on left. Reversed in right leg. Died September 17, 1936. Cause of death unknown.

Roentgenologic Examination.—*Right:* Union of fracture. Destruction about proximal screw. No change about distal vitalium screw.

Left: No destruction near proximal screw. Destruction about galvanized screw.

Autopsy.—*Macroscopic: Right:* There was an hematoma in the leg about the proximal galvanized iron screw and the screw was loose two plus. The distal vitalium screw was tight.

Left: There was a small abscess over both screws in the field of the operation. The vitalium screw was covered with a transparent membrane and both screws were tight.

Biochemical Analysis: Negative.

Dog 16.—Operation July 18, 1936. *Chromium-plated steel screws* used throughout. Sacrificed September 8, 1936.

Roentgenologic Examination.—Showed moderate destruction of bone about heads of all screws. Bony union of fracture.

Autopsy.—*Macroscopic: Right:* The fracture was solidly healed and there was deep brown discoloration about both screws. The proximal screw was tight. The distal screw was covered with brown transparent areolar tissue.

Left: The distal screw had marked black discoloration of the tissue for a wide area. The screw was tight, although there was destruction of bone about the head of the screw from 3 or 4 Mm. The proximal screw was tight with destruction of bone for 1 Mm. about the head.

Biochemical Analysis: Much chromium in soft tissues adjacent to screw. Trace of chromium in the liver.

Histologic Examination.—Chromium plated steel screws throughout.

Right proximal: Moderate degree of periosteal thickening which has a shredded appearance. Small amount of granulation tissue present. Mild degree of bone necrosis.

Right distal: Mild degree periosteal thickening. No granulation tissue formation present. No bone necrosis—irritative changes slight in degree.

Left proximal: Periosteum mildly thickened with a moderate degree of granulation tissue formation which is undergoing organization. A few foreign body giant cells are scattered through the granulation tissue. General irritative changes are of moderate degree.

Left distal: Moderate degree of periosteal thickening with a moderate degree of granulation tissue formation. No bone necrosis noted. General tissue reaction is slight to moderate.

Dog 17.—Operation July 18, 1936. *Plain Steel screw* proximal and *brass screw* distal on the left. Reversed on right. Sacrificed September 9, 1936.

Roentgenologic Examination.—Union of fracture. Destruction of bone about all screws, more marked about the brass.

Autopsy.—*Macroscopic: Right:* The distal steel screw was tight with some fibrous tissue over the head. The proximal brass screw was loose two plus with a slight amount of boggy tissue over the screw head.

Left: Both screws were very loose four plus. There was much new bone about both screws with erosion about the heads and much brownish discoloration over the proximal steel screw.

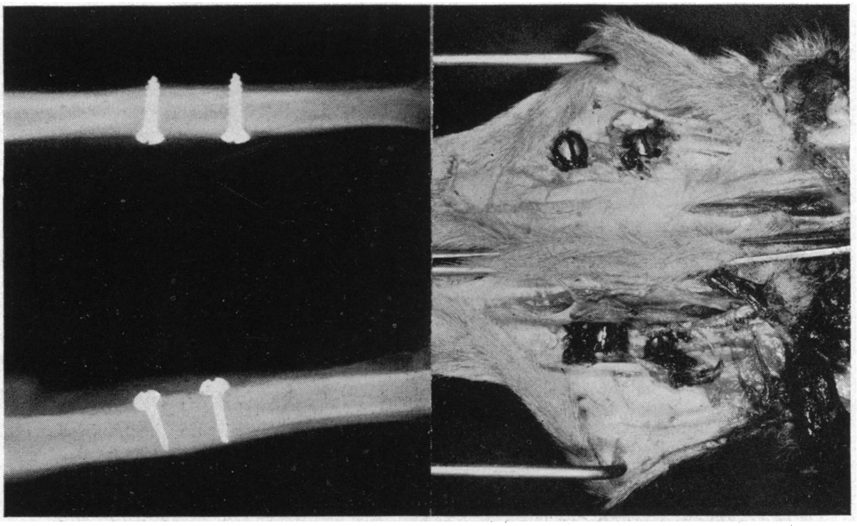


FIG. 7.—Dog 16: Chromium-plated steel. Roengtenogram showing moderate necrosis of bone about all the screws.

FIG. 8.—Dog 16: Chromium-plated steel. Showing tissue reaction: There is marked local reaction around all screws with excess proliferation and dark discoloration. The screws are tight.

Biochemical Analysis: Iron and copper present in the soft tissues adjacent to the screws. Greater quantity present on the left side because the screws were closer together. Much iron found in the liver.

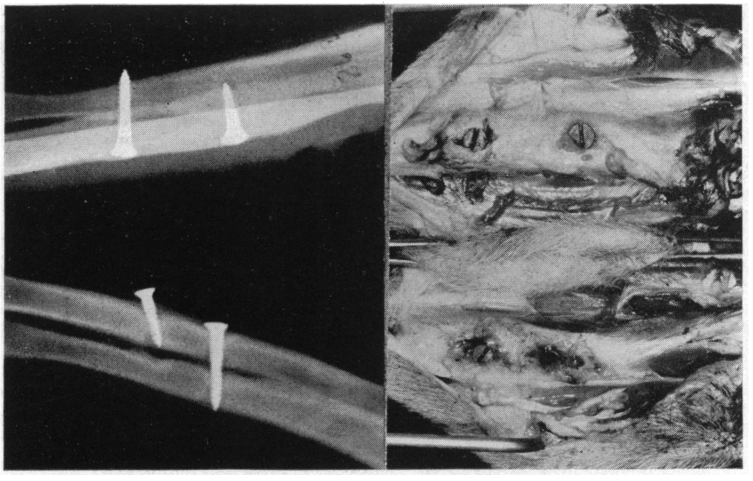


FIG. 9.—Dog 17: Steel and brass. Roentgenogram showing destruction of bone about all the screws with marked necrosis around the brass.

FIG. 10.—Dog 17: Steel and brass. Showing tissue reaction: There is much new soft bone with marked fibrous proliferation. All the screws are very loose except the steel one in the fractured radius.

Histologic Examination.—Right proximal screw; brass: Moderate amount granulation tissue formation with marked periosteal thickening. No bone necrosis. Some new cartilage present.

Right distal screw; Steel: Marked thickening and fibrosis of periosteum with moderate osteoblastic activity. Moderate degree of granulation tissue formation. No bone necrosis. Irritative changes not marked.

Left proximal screw; steel: Marked periosteal thickening and fibrosis with a very slight amount of granulation tissue formation present. No bone necrosis. Numerous osteoblasts present.

Left distal screw; brass: Marked callus formation with thickening of periosteum. No granulation tissue formation noted or has become organized into callus. New cartilage formation noted. Few irritative changes present.

Dog 18.—Operation July 18, 1936. *Brass screw* proximal and *galvanized iron* screw distal on the left. Reversed on the right. Sacrificed September 9, 1936.

Roentgenologic Examination.—Firm union of fracture. All screws loose except proximal brass in left. Much destructive necrosis of bone at all screw sites.

Autopsy.—*Macroscopic: Right:* The distal brass screw was loose two plus. There was no necrotic material. No fluid and moderate proliferation of new bone. The proximal galvanized iron screw was loose four-plus with a proliferation of new bone about the margin of the screw head.

Left: The proximal brass screw was firmly fixed in the bone. The distal galvanized iron screw was loose four-plus. There was much new bone about both screws with more about the proximal. There was brownish discoloration of the seminecrotic material around the distal screw.

Biochemical Analysis: Liver showed heavy trace of copper. Trace of copper and zinc in tissue adjacent to the screws.

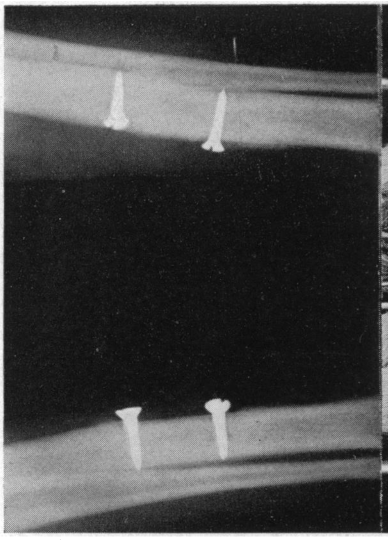


FIG. 11.—Dog 18: Galvanized iron and brass. Roentgenogram showing marked bone necrosis around all screws.

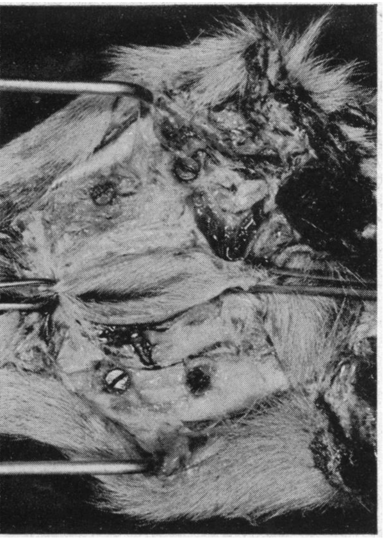


FIG. 12.—Dog 18: Galvanized iron and brass. Showing tissue reaction: There is present brown discoloration with proliferation of soft, fibrous tissue. All screws loose.

Histologic Examination.—Right distal screw; brass: Moderate degree of periosteal thickening around screw hole. No granulations present. No irritative reaction. No callus or bony regeneration. Process appears generally indolent with some necrosis in tissue lining the screw hole.

Left distal screw; galvanized iron: Mild degree of periosteal thickening around edges of screw hole with a marked degree of granulation tissue formation. Numerous large cells (osteoblasts?) scattered through granulation tissue which contains numerous inflammatory cells. Appearance is that of a marked tissue reaction of irritative character.

Dog 19.—Operation July 21, 1936. *Plain Steel screw* proximal and *vitalium screw* distal on the left. Reversed on the right. Sacrificed September 9, 1936.

Roentgenologic Examination.—Union of fracture. Distal steel screw on the right loose four plus with erosion about the head. Vitalium caused no reaction. On the left the vitalium screw was slightly loose, and the steel screw was loose three plus. There was a ridge of new bone 2 Mm. high on the medial side of the steel screw.

Autopsy.—*Macroscopic: Right:* The proximal vitalium screw was about 50 per cent covered with normal new bone. The screw threads were intact and the screw could be unscrewed easily. There was no discoloration and no abnormal bone. The distal steel screw was loose three plus. There was much excessive new bone around the margin of the head with a mass of encapsulated brownish soft tissue over the head.

Left: The proximal steel screw was loose three plus with a small amount of soft brown discoloration of the adjacent tissue. The distal vitalium screw had worked loose. On the medial side of the hole was a ridge of new bone about 2 Mm. high (? torn periosteum). There was no discoloration.

Biochemical Analysis: Vitalium screws showed no trace of iron about them. About steel screw was proliferation of iron into soft tissue. Excessive amount of iron in the liver. No trace of chromium or cobalt in the liver.

Histologic Examination.—Right proximal screw; steel: Little tissue reaction present. Periosteum

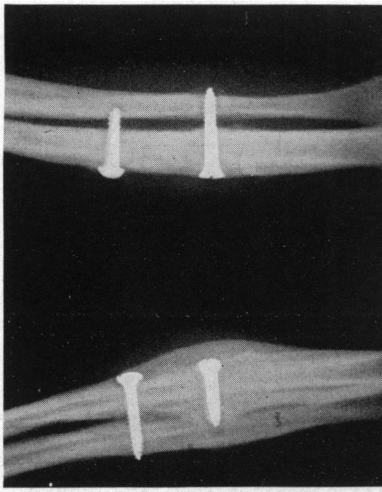


FIG. 13.—Dog 19: Vitalium and steel. Roentgenogram showing no bone changes about vitalium and erosion of bone around the steel screws.

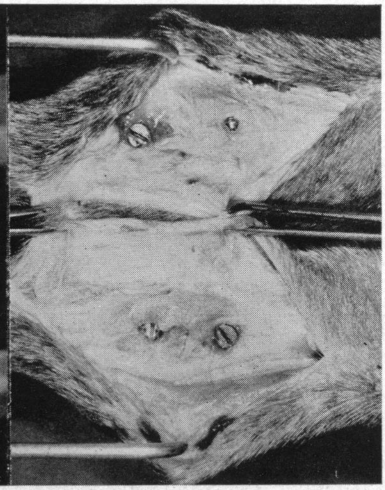


FIG. 14.—Dog 19: Vitalium and steel. Showing tissue reaction: No changes about vitalium; one vitalium screw is one plus loose; marked reaction about all steel screws, which are very loose.

not thickened, dense and relatively acellular. Small amount of granulations present which appear partially necrotic.

Right distal screw; vitalium: Mild periosteal thickening, small amount of granulation tissue present. Marked regeneration of bone, probably along fracture site.

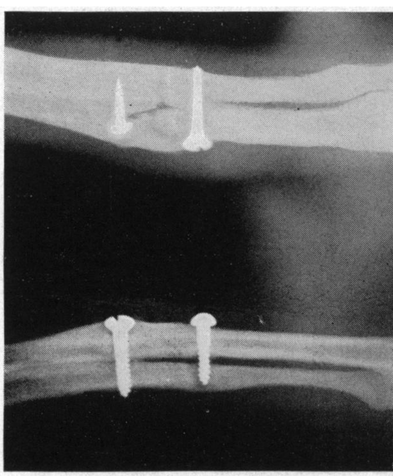


FIG. 15.—Dog 20: Vitalium and brass. Roentgenogram showing no change around vitalium screws; marked bone destruction about brass screws.

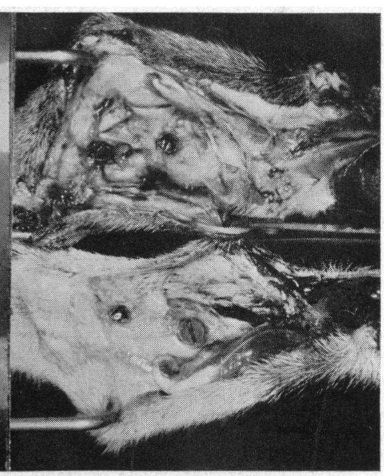


FIG. 16.—Dog 20: Vitalium and brass. Showing tissue reaction: No reaction adjacent to vitalium; tissue destruction with proliferation about both brass screws, which are four plus loose.

Left proximal screw; vitalium: No periosteal thickening noted. Periosteum covered with a moderately thick layer of granulation tissue which is undergoing early organization. No foreign body giant cells noted. General tissue reaction is not marked.

Left distal screw; steel: Moderate periosteal thickening with fibrocystic proliferation and formation of a few foreign body giant cells near periosteal attachment to bone. Lining the screw hole is a thick layer of granulation tissue undergoing organization. General tissue reaction is marked.

Dog 20.—Operation July 21, 1936. *Brass screw* proximal and *vitalium screw* distal on the left. Reversed on the right. Sacrificed September 9, 1936.

Roentgenologic Examination.—Fracture solidly united. No bony changes about either vitalium screws and they were tightly in place. There was necrosis of bone about both brass screws which were loose.

Autopsy.—*Macroscopic: Right:* Over the distal brass screw there was a large mass of reddish brown encapsulated tissue. All the neighboring soft tissue was boggy. The proximal vitalium crew was loose four plus. There were no threads in the hole and the screw had apparently been placed between the fragments of the fracture. There was no bony proliferation about the head.

Left: The distal vitalium screw was very tight. There was no discoloration and no destruction of the bone. The proximal brass screw was loose four plus, with much necrotic material around the screw. There was little proliferation of new bone.

Biochemical Analysis: Copper in tissue adjacent to screws in right foreleg. Trace of copper in the liver.

Histologic Examination.—Right proximal screw; vitalium: Mild periosteal thickening about edges of screw hole, but no granulations noted. Process here appears relatively indolent with what appears to be a mild degree of necrosis taking place. The bony elements show no necrosis and deeper there is a wide, dense callus in process of formation.

FIG. 17.—Dog 21: Galvanized iron and brass. Roentgenogram showing much destruction of bone about all screws.

FIG. 18.—Dog 21: Galvanized iron and brass. Showing tissue reaction: Soft brown granular tissue about galvanized-iron screw and soft fibrous tissue brass screws; all screws are loose except one of the brass ones.

Right distal screw; brass: Periosteum somewhat thickened, but is split up and shredded in appearance from exudative material. There appears to have been a marked granulation tissue formation but this is undergoing advanced liquefaction necrosis, and is not definitely recognizable as granulation tissue. There is a slight degree of bone degeneration just beneath periosteum. No new bone formation noted.

Left proximal screw; brass: Marked thickening and fibrosis of periosteum about edges of screw hole but only a very slight granulation tissue formation. No bone necrosis noted. No bone regeneration.

Left distal screw; vitalium: General tissue reaction very slight. Periosteum not thickened, but heavily infiltrated with cells similar to plasma cells and lymphocytes. A very slight granulation tissue formation is present. In one area at edges of screw hole there is a small area of bony necrosis while in another area there is a definite but slight degree of new bone formation.

Dog 21.—Operation July 21, 1936. *Brass screw* proximal and *galvanized iron screw* distal on left. Reversed on right. Sacrificed September 8, 1936.

Roentgenologic Examination.—Union at fracture site. All screws loose with much destruction of bone.

Autopsy.—*Macroscopic: Right:* Fracture solidly united. The proximal galvanized iron screw was surrounded by boggy tan granulation tissue on the proximal side. The screw was only slightly loose. The distal brass screw was tightly engaged with much slightly discolored new bone growth and dense fibrous tissue covering the screw.

Left: The proximal brass screw was loose two plus. There was some discoloration and erosion of the soft tissue about the screw but no fluid. The distal galvanized iron screw was loose three plus with a small amount of free fluid about it. There was destruction of the bone without metallic discoloration and considerable boggy fibrous tissue about the screw head.

Biochemical Analysis: Much iron in soft tissue adjacent to screws. Trace of copper deposited on galvanized iron screw.

Histologic Examination.—Right distal screw; brass: Marked periosteal reaction with moderate thickening. Moderate degree of granulation tissue formation with almost complete organization. Moderately advanced callus formation deep in bone along probable fracture line with new bone formation taking place. General tissue reaction of moderate degree of intensity.

Right proximal screw; galvanized iron: Mild periosteal reaction with mild degree of thickening. Moderate degree of granulation tissue formation with a slight organization beginning to take place. Numerous degenerating bony fragments scattered through granulation tissue. Some evidence of bone regeneration present but this is not marked. General tissue reaction is of moderate degree.

NOTE: In Dogs 21 and 22 screws happened to be placed in closer approximation than in the other experiments.

Dog 22.—Operation July 28, 1936. *Brass screw* proximal and *chromium-plated screw* distal in left. Reversed on right side. Sacrificed August 17, 1936.

Roentgenologic Examination.—Union of fracture. All screws were loose and showed necrosis with excessive proliferation of new bone at all screw sites.

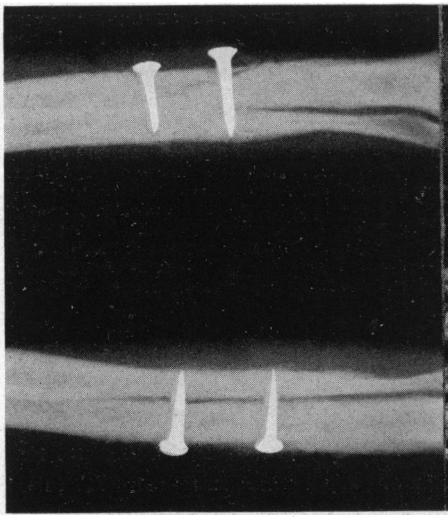


FIG. 19.—Dog 22: Chromium-plated steel and brass. Roentgenogram showing proliferation of new soft bone with necrosis at all screw sites.

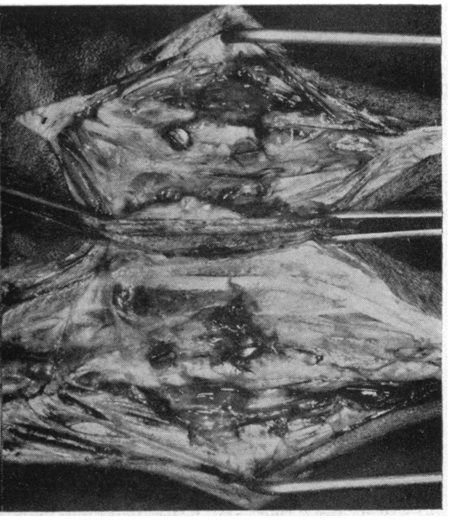


FIG. 20.—Dog 22: Chromium-plated steel and brass. Showing tissue reaction: Black stain about the chromium-plated screws. Slight reaction about all screws, which are very loose.

Autopsy.—*Macroscopic: Right:* The periosteum near the fracture was bulging with an accumulation of brownish serous exudate. The fracture was united with excessive proliferation of new bone. The brass screw was loose and free to rotate. The chromium-plated screw had new bone about it but no destruction of periosteum. The screw was loose and there was a small area of erosion at the margin where it touched the bone. The edges of the hole were black.

Left: The brass screw was tightly engaged. The tissues seemed healthy except for an area about ½ cm. around the chromium-plated screw where there was a low-grade tissue necrosis with pinkish-gray secretion. There was a proliferation of fibrous tissue about the brass screw which seemed normal. About the chromium-plated screw there was no new bone growth and there was degenerative necrosis in the screw hole.

Biochemical Analysis: Copper was deposited on chromium-plated screws and chromium on the zinc of the brass screws in both legs. (NOTE: According to the Table of E.M.F. copper should be deposited on to chromium, chromium on to zinc.) Trace of chromium in the liver.

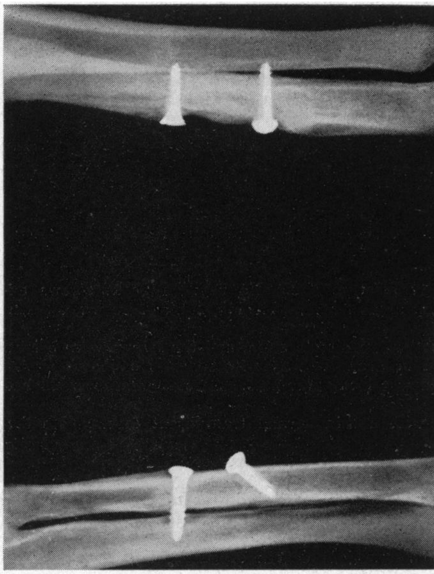
Histologic Examination.—Right proximal screw; chromium-plated steel: Moderate periosteal thickening with moderate degree of granulation tissue formation. Moderate number foreign body giant cells scattered through periosteum and granulation tissue. Marked bone regenerative changes present. General tissue reaction changes are marked.

Right distal screw; brass: Moderate periosteal thickening with moderate degree of granulation tissue formation. Moderate number foreign body giant cells scattered through periosteum and granulation tissue. Marked bone regenerative changes present. General tissue reaction changes are marked.

Left proximal screw; brass: Marked periosteal thickening with small amount of granulation tissue formation. Numerous foreign body giant cells in periosteum. Mild degree of bone degeneration present near margin of screw hole. Irritative tissue reaction moderate.

Left distal screw; chromium-plated steel: Marked degree of periosteal thickening with moderate degree of granulation tissue formation. Moderate degree of new bone formation along line of fracture with marked callus formation. General tissue reaction moderate to marked.

Dog 23.—Operation July 23, 1936. *Steel screw* proximal and *silver-plated copper screw* distal on left. Reversed on right. Sacrificed September 3, 1936.



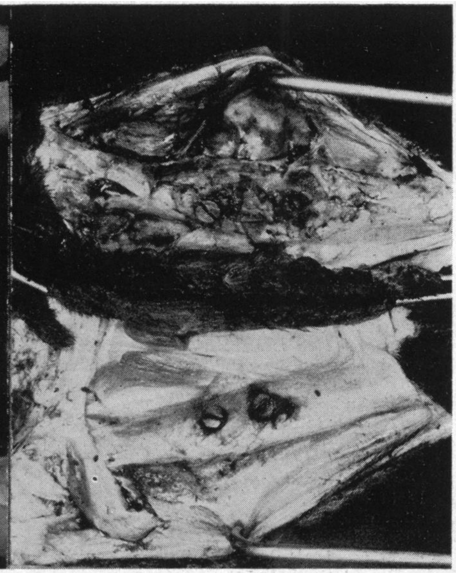
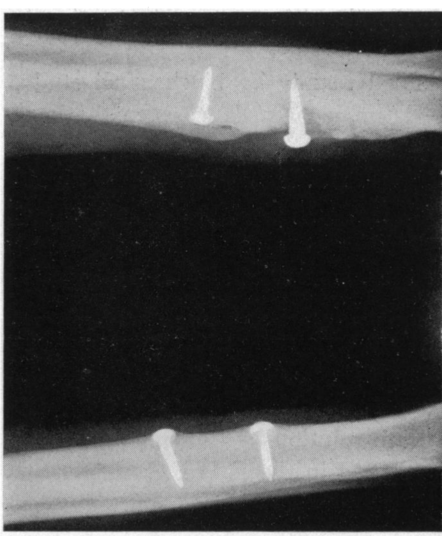


FIG. 21.—Dog 23: Silver-plated copper and steel. Roentgenogram showing proliferation of new bone at fracture site. Necrosis at all screw sites.

FIG. 22.—Dog 23: Silver-plated copper and brass. Showing tissue reaction: Gray exudation about the copper screws with brown discoloration about the brass screws. All screws loose.



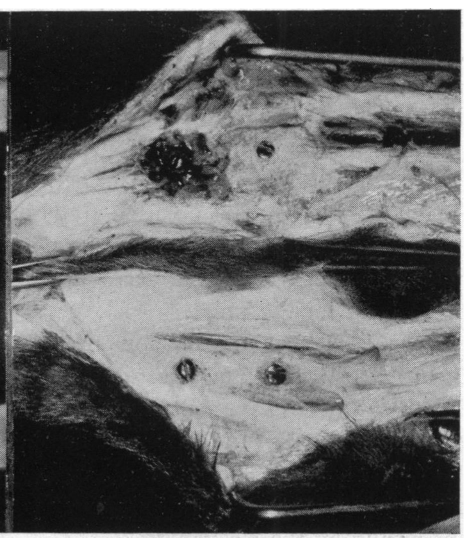


FIG. 23.—Dog 24: Vitalium throughout. Roentgenogram showing no change around screws except one in fracture site, about which there is new bone growth.

FIG. 24.—Dog 24: Vitalium throughout. Showing tissue reaction: Granulation around the one screw in fracture site; none about the remaining screws, all of which were very tight.

Roentgenologic Examination.—Union of fracture. All screws loose with slight necrosis and much new bone.

Autopsy.—*Macroscopic: Right:* There was a small amount of grayish secretion on the proximal side of the distal steel screw. The head of the screw was completely covered with new bone. The silver-plated copper screw was loose two plus. There was a small amount of callus and some brownish fluid about the edges of the screw.

Left: There was an excess of brown tissue about the steel screw and the screw was loose two plus. The silver-plated copper screw was tightly engaged. Both screw heads were encapsulated and there was a small amount of tannish tissue about the head of each. There was some formation of new bone about the steel screw but the screw itself was loose in the hole.

Biochemical Analysis: Trace of copper about the steel on the left. Trace of copper in the liver.

Histologic Examination.—Right proximal screw; silver-plated copper: Slight to moderate degree of periosteal thickening. Granulation tissue formation slight to moderate with low grade inflammatory reaction. Numerous eosinophiles scattered throughout granulation tissue. General tissue reaction appears to be of moderate degree.

Right distal screw; steel: Marked thickening of periosteum which appears dense and fibrous. Moderate granulation tissue formation with a low grade chronic inflammatory process. Some hemorrhage and fibrinous exudation in deeper tissues. General irritative tissue reaction may be classed as moderate.

Left proximal screw; steel: Periosteum shows a slight to moderate degree of thickening with only a small amount of granulation present. No giant cells observed. General tissue reaction appears to be slight.

Dog 24.—Operation July 23, 1936. *Vitalium screws* used throughout. Sacrificed September 8, 1936.

Roentgenologic Examination.—There was union at fracture site. No reaction about screws except one in the fracture site, which showed proliferation of new bone. No inhibition of bone growth in fracture site.

Autopsy.—*Macroscopic: Right:* There was no infection, no discoloration, and the screws were bright. The proximal screw was embedded under 2 or 3 Mm. of dense healthy new bone. No fibrous tissue, no fluid. The distal screw was in the fracture site and was loose four plus. Serosanguineous fluid had collected in an area about 1/3 by 1½ cm.

Left: Both screws were tight and were covered with a thin normal transparent fascia. No discoloration. No destruction of the tissue.

Biochemical Analysis: No evidence of metal in soft tissue of the leg, liver or kidney.

Histologic Examination.—Vitalium throughout.

Right distal: Marked periosteal thickening with moderate to marked degree of granulation tissue formation which is undergoing organization. Marked bone regeneration along line of fracture. General tissue reaction is marked.

Right proximal: Moderate periosteal thickening. Very slight degree of granulation tissue formation. General tissue reaction slight.

CONCLUSIONS

(1) That it is impossible from macroscopic, microscopic and roentgenologic studies alone, to differentiate accurately the different reactions of soft tissue and bone to metals.

(2) That such reactions can be explained readily by biochemical study, based upon the behavior of metals ad seriatim in accordance with the laws of the electromotive force of metals.

(3) That electrical force is generated when different metals are placed in the tissues, by the creation of a battery, and the amount of current is proportionate to the difference in potential of metals at the two poles, the degree in which they are acted upon by the given electrolyte, and the distance between the poles.

(4) That pure metals alone are inert. Any action which takes place about them is a chemical reaction to body acids and has no electrolytic significance. Example—a battery containing two zinc plates only, cannot be "charged" electrically though the zinc may be taken into solution by the sulphuric acid.

(5) That those metals most widely separated in the E.M.F. series create the greatest potentials, although only one of the pair may be acted upon chemically by the electrolyte.

(6) That when different metals are connected or coupled directly, there is a galvanic action between the poles which is increased in direct ratio with the resistance of the couple, and the rate of corrosion on the more electropositive metal is accelerated. This is exactly analogous to a "short" in an ordinary wet cell.

(7) That any single metallic appliance made of galvanized iron, plated steel, or of metallic alloy containing a metal subject to the action of body fluids will cause some galvanic action.

(8) That it is this electrolytic action which causes the formation of irritating metallic salt solutions in the local fluids. The reaction against it leads to the excessive proliferation of cellular and fibrous tissue which is protective, and the inhibition of growth of bone which is destructive.

(9) That no different metals should be placed in a given patient and only pure metals, least subject to the action of the body fluids, should be used as far as possible. This explains why pure silver wire has been fairly well tolerated. However, when rigidity and tensile strength are necessary as in plates, screws, and nails, pure metals are too soft and alloys of the more resistant metals have to be used.

(10) That in the selection of alloys to be used the relative position of metals selected in the E.M.F. series is not essential as the properties of the alloy may be different from any of its components.

(11) That in our opinion such alloys should not contain iron because iron is so subject to the action of the physiologic body salts. In all of our experiments those metals which contained iron showed large amounts of iron in the tissues adjacent and an excess of iron in the livers.

(12) The alloy of least reaction that we have found is one called vitalium, which contains no iron and consists of cobalt, chromium and tungsten. There was no tissue reaction or bone change at the site of any vitalium screw though it was checked in many experiments with several different combinations of metals.

(13) That any appliance that is plated with chromium is dangerous because chromium salts, which are extremely poisonous, are promptly liberated and readily concentrated in the liver. Once the plating is chipped or broken, a battery is immediately created. For this reason, unless chromium in an alloy can be shown to have had its potential completely lost in the new potential of the alloy in its changed position in the E.M.F. series it might have the same effect as when used in plating.

(14) That for this reason we suggest an alloy for bone work that is similar to vitalium in which vanadium may be substituted for the chromium, if such an alloy should confer the same degree of corrosion resistance and not be too brittle. However, following our experiments with the alloy vitalium, the constituents of its components seem to have lost their potential, as there was no trace of chromium liberated in any instance.

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