STUDIES ON THE USE OF METALS IN SURGERY*

PART II

EXPERIMENTS ON THE USE OF TICONIUM IN CRANIAL REPAIR

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IN A PREVIOUS COMMUNICATION[1] we have reported assays of cytotoxicity of certain metals in tissue cultures of chick embryo fibroblasts. Our purpose in that study, and in the present one, has been to find an alloy that conforms to the requirements of bone surgery and, hence, for the repair of cranial defects.

As was pointed out in that paper, an ideal cranioplastic substance should be nontoxic, strong and, at the same time, light enough to keep the bulk of the appliance small. In addition, it should be so malleable as to permit working and shaping during the operation. This latter characteristic is an exceedingly important one in cranial repair because casting is both time-consuming and expensive. For a cast plate to fit perfectly it is necessary to secure an impression of the defect itself. This is a cumbersome and often undesirable procedure to attempt at the time of operation. Many times the bone flap serves as a poor pattern either because it is diseased or the use of the rongeur has changed the shape of the defect after its removal. Estimation of the required plate by roentgenograms and measurement through the intact scalp is difficult. Finally, a cast plate, if found not to fit well, cannot easily be altered at the operating table.

The casting alloy Vitallium has been thoroughly studied by Venable, Stuck, and Beach.[2, 3, 4] It is light, strong and nontoxic. It has been used for cranial repair by Geib,[5] Peyton and Hall,[6] and by Beck.[7] Attention has been called to its lack of malleability as being undesirable. Its use in bone work in general, however, has been so satisfactory that we have used it as a control substance in our experiments, despite the fact that it does not completely fulfill the peculiar requirements for cranial repair.

The wrought alloy Ticonium is light and strong and, in addition, malleable. In the form of thin, perforated plates it can be cut with tin shears and molded by hand or with pliers. The perforations permit the making of slots or wedges to allow for unusual shapes, and provide many choices for screw holes.

Our previous study showed that wrought Ticonium and Vitallium and cast Ticonium (with beryllium), were not toxic to chick fibroblasts in tissue culture. The present paper reports results with these three alloys in repair of cranial defects in dogs. Some observations on electrolysis have been added.

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* Read at the Annual Meeting of the Harvey Cushing Society in New York, N. Y., May 21, 1942.

OBSERVATIONS ON DOGS

Method.—Three different alloys were used: Ticonium "wrought" (nickel 36.2%, cobalt 29.6%, chromium 28.2%, molybdenum 6%); Vitallium (cobalt 65%, chromium 30%, molybdenum 5%, manganese, silicon); and Ticonium "cast" (nickel 35.6%, cobalt 29.1%, chromium 27.7%, molybdenum 6%, beryllium 1.6%)

In Group I we used material prepared with the wrought alloy Ticonium* only. This material consisted of sheets cold-rolled, with 30 per cent cold

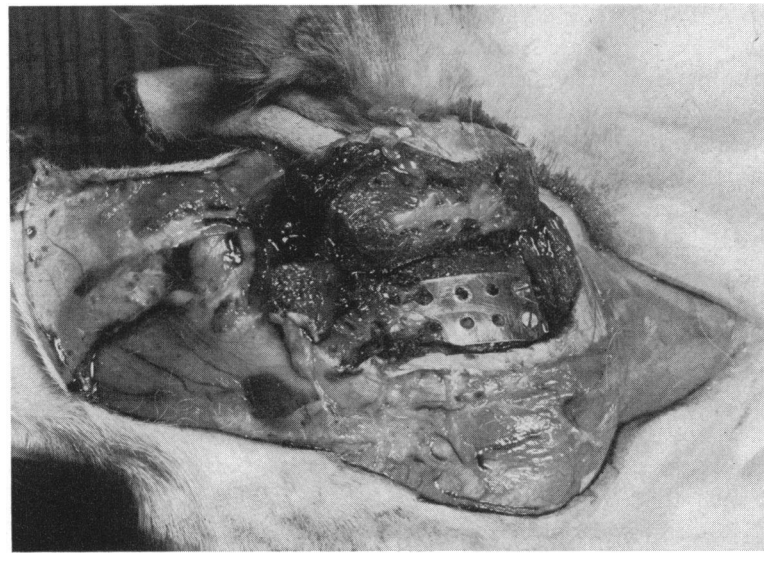

FIG. 1.—(Dog 52)—"Wrought" Ticonium: Plate over the temporoparietal region. Eleven months after operation, showing the absence of corrosion of the metal. Muscle overlying the plate and growing through the perforations has been reflected.

reduction subsequent to the final anneal. This seemed to be preferable for experimental purpose. The plates had a thickness of 0.17 cm. (27-gauge U. S. Standard). The sheets had been punched at intervals of 0.4 cm. with holes 0.3 cm. in diameter. They were then polished, thus taking the punch marks out (Fig 1). Prepared in this manner, the plates were easily cut and molded at operation.

The plates used in Groups II and III were cast in varying size and thickness, according to the shape of dogs' skulls. Each plate had three attachments for the screws. In most of the plates, four to five holes were punched. A few solid plates were used. In Group II, machine made screws of Vitallium,† and in Group III hand made screws of Ticonium "cast," were used.

* The material made of Ticonium ("wrought" and "cast") was prepared by the Research Laboratories of the "Ticonium" Co., Albany, N. Y.

† The Vitallium plates and screws were furnished by the Austenal Laboratories, New York, N. Y.

Technic: Healthy, well-nourished mongrel dogs of various ages were selected. The dogs were kept in separate cages and well fed. The animals were anesthetized by intraperitoneal injection of nembutal (Abbott) (Max. dose 0.7 cc. of a 5 per cent solution per Kg. body weight). The entire head or thigh was shaved and cleaned with a brush, soap, and water for a period of five minutes. Using strict aseptic technic, a unilateral U-shaped skin flap was turned down over the frontotemporoparietal region. The "temporal" muscle was sharply dissected from the underlying bone. The periosteum was scraped off, and, in the center of the denuded area of the bone, an opening was made by use of a trephine. This opening was enlarged to an average size of 2 x 3 cm. Throughout the procedure hemostasis was secured by use of the cautery. The dura remained closed with the exception of those experiments calling for the insertion of metal pieces into the cortex. In these instances a nick was made into the dura, the cortex was incised and a piece of metal about 0.2 x 0.3 cm. was inserted vertically into the cerebrum.

In Group I a wrought Ticonium screen was used, having been previously autoclaved. From such a screen a plate was cut with tin shears to overlap the defect at all four margins by about 0.3 cm. This plate was then molded by hand to the convexity of the skull, and in each instance very satisfactory plastic repair was obtained. The plate was then fastened to the bone with 2-4 screws drilled into the bone to full length. Closure was performed in layers with the exclusive use of interrupted sutures of fine black silk. Skin closure was obtained with interrupted subcuticular sutures of the same material. A bandage dressing was applied and secured by an encasement of plaster of paris around the head and neck. The encasement remained in place for about five days.

Cast plates were used in the experiments of Group II and III. These plates, after having been autoclaved, were placed over the defect and fastened by screws drilled into the bone surrounding the defect.

Operations upon the femur were performed under the same aseptic conditions. A longitudinal incision was made over the lateral surface of the thigh. The muscles were bluntly dissected and retracted. The periosteum was removed, screw holes were drilled into the bone and the screws inserted. Closure was done in layers as above.

During the first postoperative day, fluids in the form of normal saline solution were administered subcutaneously. On the second postoperative day the dogs resumed their usual feeding. Body temperature was determined during the first postoperative days, and the dogs were reexamined at regular intervals. Roentgenograms were taken of a limited number of animals.

The dogs were sacrificed by intracardiac injection of ether or nembutal. Autopsy was performed, and the tissue fixed in 4 per cent neutral formaldehyde solution. Blocks were selected from the bone, and any grossly diseased viscera noted. These were embedded in paraffin or celloidin, and sectioned. Sections were studied with one or more of the following stains: Hematoxylin and eosin, Mallory's phosphotungstic acid hematoxylin, Masson's trichrome (Goldner's modification) and Giemsa.

GROUP I: TICONIUM "WROUGHT"

Experimental Results.—Twenty-one dogs were used for the experiments in this group. The tissues were exposed in all to a total of 115 pieces of metal: Fourteen plates, 78 screws in the skull bone, 19 screws in the femur and four pieces of metal which were embedded into the cerebral cortex. The dogs were observed from two days to 14 months; 17 animals were observed for a period of longer than 10 months. Fourteen dogs were sacrificed, and seven dogs died on account of secondary illness.

CASE REPORTS

Dog. 25.—*Operation:* July 11, 1940. Plate secured with 2 screws. 7th p.o. day dog injured flap by scratching; secondary subcutaneous infection. Healed in 3 weeks. Sacrificed August 6, 1941.

Macroscopic: Scar at operative site not unusual. Screws firmly embedded. Plate well attached, enclosed in a fibrous bursa-like sac. Metal shiny. No fluid. Bone defect filled by firm fibrous tissue

to outer surface of which muscle is attached and grows through perforations in the plate. Dura merges with this fibrous layer. Underlying cortex normal.

Microscopic: Plate bed composed of smooth layer of laminated, partially hyalinized fibrous tissue. Rare macrophage in looser connective tissue especially about blood vessels. Some marginal new bone formation.

Dog 36.—*Operation:* July 13, 1940. Plate secured with 4 screws. Flap healed *per primam.* 6th p.o. day semistuporous; drainage from eyes and nasal mucous membranes. Slight motor weakness of both hind legs. "Distemper." Died July 21, 1940.

Macroscopic: Operative site healing well. Small hematoma in superficial fascial layer. Surface of muscle overlying plate grayish-brown. Small amount of cloudy reddish fluid immediately about plate. Screws secure. Plate firmly attached. Metal bright and shiny. Dura underlying plate intact but dark red. Not adherent to cortex. Right side of heart dilated. Lungs edematous. Left kidney hydronephrotic.

Microscopic: Focal edema of lungs. Chronic pyelonephritis. Hyperemia of liver. Cranial muscle focus of organizing fibrinous exudate and regenerating muscle. Bone margin shows organizing fibrinous mat.

Dog 38.—*Operation:* July 23, 1940. Metal inserted into cortex. Plate secured with 4 screws. Flap healed *per primam.* Sacrificed September 4, 1941.

Macroscopic: Scar of operative site not unusual. Screws firmly embedded. Plate securely enclosed in bursa-like sac. Metal bright and shiny. No fluid. Bone defect bridged by firm fibrous layer, merging with dura. Cerebral cortex surface adherent to dura over an embedded piece of bright, shiny metal which is surrounded by a thin white capsule.

Microscopic: Plate bed consists of laminated fibrous tissue. At bone margin is considerable new bone almost bridging the gap. Muscle fibers are oriented perpendicular to the plate bed. No inflammation or necrosis. Rare macrophage about blood vessels of muscle.

Dog 40.—*Operation:* July 25, 1940. Plate secured with 4 screws. Following day: Fever, tachypnea, sputum (mixed bacteriae). Sulfapyridine. Died after 30 hours.

Macroscopic: Generalized adiposity. Skin flap flat and soft. Fascia sutured tightly. Plate firmly secured by 4 tightly embedded screws. Metal smooth and shiny. Between plate and dura thin layer of clotted blood. Dura smooth and not adherent. Dilatation of right side of heart. Large foci of consolidation in lungs. Uterus contains 2 small fetuses.

Microscopic: Obturation of bronchi by mucous and aspirated foreign material. Massive atelectasis. Thin layer of erythrocytes and fibrin above dura. Small fibrinous clot in screw hole. Muscle edematous, infiltrated with neutrophiles. (Period of observation too short. Findings in accord with wound healing at this stage.)

Dog 41.—*Operation:* July 26, 1940. Three screws inserted into frontoparietal region. Three screws inserted into femur. Scalp flap healed *per primam.* Lower third of leg incision healed secondarily 15th p.o. day. Sacrificed September, 1941.

Macroscopic: Operative sites show usual scarring. Screws firmly embedded. Metal shiny.

Microscopic: Skull screw hole lined by thin fibrous membrane immediately beneath which are rare macrophages containing pigment. Loose fibrous tissue covers head. Some laminated new bone beneath part of tract lining. Femur screw hole essentially similar.

Dog 42.—*Operation:* July 27, 1940. Three screws inserted into frontoparietal bone. Flap healed *per primam.* 12th p.o. day: Fever, tachypnea. Died August 13, 1940.

Macroscopic: Operative wound well healed. Screws firmly embedded, have penetrated inner table. Metal shiny. No fluid. Dura quite vascular. Underlying cortex negative. Dilatation of right chambers of heart. Massive consolidation of lungs.

Microscopic: Necrotizing bronchopneumonia. Screw holes, thin fibrous tissue lining with a few lymphocytes in vicinity. Bone undergoing remodelling.

Dog 43.—*Operation:* July 30, 1940. Metal inserted into cortex. Plate secured with 4 screws. Flap healed *per primam.* Sacrificed August, 1941.

Macroscopic: Scar of operative site not unusual. Plate firmly embedded in bursa-like sac. Screws secure. Metal smooth and shiny. Muscle has grown through perforations in plate. Firm fibrous tissue bridges the bony defect and merges with the dura. No adhesions to brain. Piece of bright metal securely embedded in cerebral cortex and invested by a thin white capsule.

Microscopic: Brain: Metal enclosed in a sac, inner lining of which is hyalinized collagen. This is separated from brain by a thin, clear space containing a few macrophages several of which enclose black iron-containing pigment. The space is bounded externally by a poorly defined thin layer of disorderly gliosis. Skull: Screw holes and plate bed show usual fibrous tissue lining without inflammation or granulation tissue. Rare pigmented macrophages in connective tissue especially about blood vessels.

Dog 44.—*Operation:* July 31, 1940. Dura thickened and roughened. Plate secured with 4 screws. Flap healed *per primam.* For 4 weeks dog continued to do well. Exact data as to further course not available. September 12th, dog was found dead.

Macroscopic: Animal emaciated, vomitus in mouth. Scar of operative site not remarkable. Plate firmly embedded in bursa-like sac. Metal smooth and shiny. No fluid. Bony defect filled by firm

fibrous tissue. Small piece of shiny metal attached to dura by few adhesions. Cortical surface not adherent. Cecal diverticulum adherent and acutely inflamed.

Microscopic: Plate bed lining thin fibrous tissue layer. No necrosis or inflammation.

Dog 45. *Operation:* August 2, 1940. Plate secured with 3 screws. Flap healed without infection. Dog did well until latter part of November: Diarrhea, vomiting. Died November 29, 1940.

Macroscopic: Plate and screws shiny. Plate embedded in bursa-like sac. Bone defect filled by fibrous tissue. Underlying brain negative. Entire sigmoid edematous, hyperemic and ulcerated. No peritonitis.

Microscopic: Colon: Acute colitis with mucosal ulceration. Skull: Plate bed thin fibrous layer in which is some new bone formation partially bridging the defect.

Dog 46.—*Operation:* August 2, 1940. Plate secured with 4 screws. 3rd p.o. day papilledema on the right. Disappeared after one week. Skin flap healed *per primam.* October 18, 1940, litter of eight puppies. Low grade fever for 2 months, evidence of fatigue and exhaustion. Impression: "Low grade infection." Recovered by January, 1941. Clinically, remained well until sacrificed September 23, 1941.

Macroscopic: Skin and fascia at operative site appeared negative. Muscle overlying the plate shaggy, soft, necrotic. Cystic space between muscle and metal contained 4 cc. of yellowish-red serous fluid. The usual fibrous sac about metal incomplete. Metal smooth and shiny. Three or 4 screws loose. Bone defect replaced by firm fibrous layer with a rough surface. Underlying cortex not adherent, grossly negative.

Microscopic: Brain: Essentially negative. Skull: Plate bed composed of a thick layer of chronically inflamed granulation tissue in the inner layer of which are many neutrophils and eosinophils; acidophile necrotic masses are present in places along the lining. The bony defect is bridged by dense fibrous tissue containing foci of new bone formation. In this fibrous bridge are a number of small compact aggregates of lymphocytes and pigment bearing macrophages. Bacterial stains reveal no organism.

Dog 48.—*Operation:* August 7, 1940. Plate secured by 4 screws. Flap healed *per primam.* 20th p.o. day drainage from eyes and nasal mucous membranes. Moist râles, right lung. Despite sulfapyridine, progressive cachexia, loss of appetite, general weakness, fibrillary twitchings of muscles. "Distemper." Died September 8, 1940.

Macroscopic: Plate and screws firmly attached. Shiny and smooth. Underlying dura merges with fibrous tissue layer, filling bone defect. Focal pneumonia consolidation of lungs.

Microscopic: Lung: Necrotizing pneumonia. Skull: Plate bed and screw hole lined by thin compact fibrous tissue layer. Few pigmented macrophages.

Dog 51.—*Operation:* August 6, 1940. Plate secured by 4 screws. Post. med. screw not tight. Post. lat. screw inserted obliquely. Flap healed *per primam.* 15th p.o. day diarrhea, progressive cachexia. No clinical pulmonary findings. Died August 27, 1940.

Macroscopic: Operative site insignificant. Plate firmly embedded. Screws secure except for post. med. screw which appears movable but in place. Firm fibrous tissue bridges the defect and merges with the dura. Underlying cortex not unusual. Diffuse purulent bronchitis, with sparing of lower lobe of left lung. Diffuse pneumonitis.

Microscopic: Skull: Plate bed shows no sign of inflammation or necrosis.

Dog 52.—*Operation:* August 8, 1940. Plate secured with 4 screws. Post. lat. screw inserted obliquely. Flap healed *per primam.* Sacrificed September, 1941.

Macroscopic: Plate securely embedded in bursa-like sac. Screws firm. Metal smooth and shiny. Firm fibrous tissue bridges the defect in the bone and merges with the dura. Underlying cortex not unusual.

Microscopic: Fibrous plate bed. No inflammation or necrosis.

Dog 55.—*Operation:* August 14, 1940. Plate secured by 4 screws. Flap healed *per primam.* Sacrificed September, 1941.

Macroscopic: Plate firmly embedded in bursa-like sac. Screws tight. Metal smooth and shiny. The bony defect is bridged by firm fibrous tissue which merges with the dura. The underlying cortex does not show any gross changes.

Microscopic: Plate bed compact fibrous tissue with occasional macrophages in clefts and about blood vessels.

Dog 56.—*Operation:* August 19, 1940. Four screws inserted in parieto-occipital region. Three screws inserted into femur. Healed *per primam.* Sacrificed September 25, 1941.

Macroscopic: Operative site insignificant. All 7 screws firmly embedded. Metal shiny. No fluid.

Microscopic: Femur: Screw tract lined by thin fibrous tissue. Fine trabeculae of new bone aligned beneath part of tract lining. In intervals where bone is deficient fibrous lining lies on fatty marrow. Skull: Screw holes lining shows no inflammation or necrosis.

Dog 57.—*Operation:* August 23, 1940. Four screws inserted into frontoparietal region. Four screws inserted into femur. Healed *per primam.* Sacrificed September 24, 1941.

Macroscopic: Operative scars grossly negative. Eight screws firmly embedded. Metal smooth and shiny.

Microscopic: Screw tracts in both bones show no inflammation or necrosis. Thin fibrous layer

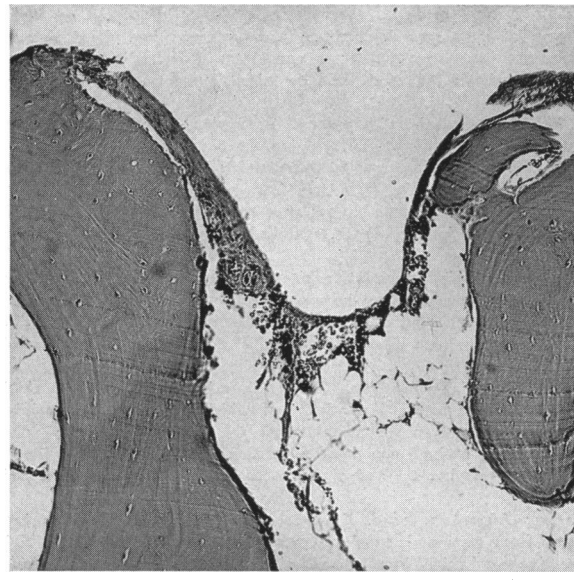

FIG. 2.—(Dog 57)—"Wrought" Ticonium: Screw hole in skull. Eleven months after operation. (H. and E., ×170)

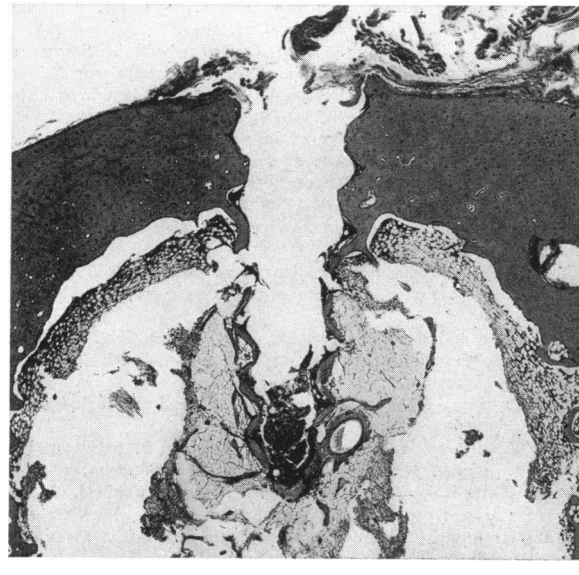

FIG. 3.—(Dog 56)—"Wrought" Ticonium: Screw hole in femur. Eleven months after operation. (H. and E., ×14)

over head of screws in skull and a spur of new bone is prescnt in thickened periosteum of same region.

Dog 58.—*Operation:* August 22, 1940. Four screws inserted into frontoparietal region. Three screws inserted into femur. Healed *per primam.* Sacrificed September, 1941.

Macroscopic: Operation scars not remarkable. Screws firmly embedded. Metal shiny.

Microscopic: Screw tracts lined by thin fibrous layer with rare pigmented macrophages nearby.

Dog 64.—*Operation:* August 28, 1940. Plate secured with 4 screws. Post. lat. screw not inserted in full length. Flap healed *per primam.* Sacrificed September 23, 1941.

Macroscopic: Operative scar not unusual. Plate firmly enclosed in bursa-like sac. Screws tight. Metal smooth and shiny. Bony defect filled by fibrous layer. Dura not adherent.

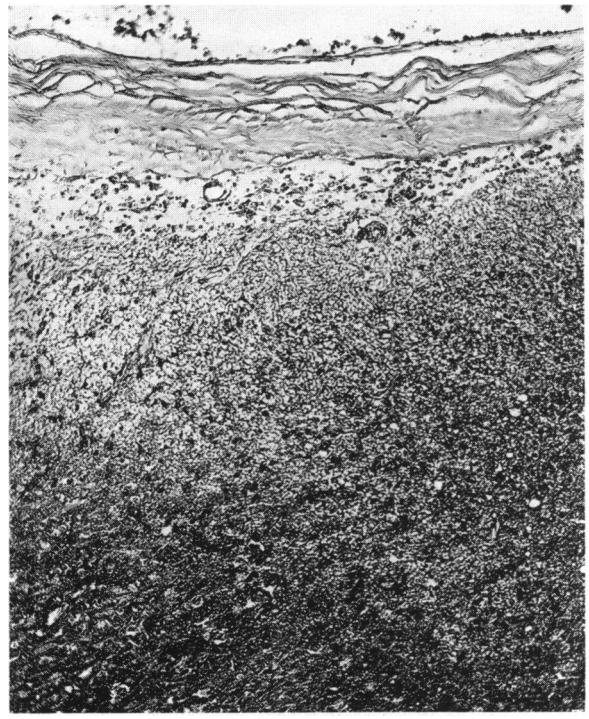

FIG. 4.—(Dog 43)—"Wrought" Ticonium: Brain showing the tissue immediately adjacent to the embedded piece of metal. Eleven months after operation. (PTAH, ×170)

Microscopic: Plate bed consists of usual 3 layers of thin partly hyalinized collagen with rare pigment bearing macrophages in clefts about blood vessels. No inflammation or necrosis.

Dog 67.—*Operation:* August 20, 1940. Four screws inserted into frontoparietal region. Three screws inserted into femur. Healed *per primam.* Sacrificed September 24, 1941.

Macroscopic: Operative scars not unusual. Seven screws firmly embedded. Metal smooth and shiny.

Microscopic: Screw tracts in both sites lined by thin fibrous tissue layer. No inflammation. No necrosis.

Dog 68.—*Operation:* August 20, 1940. Dura vascular. Dura opened. Plate secured with 3 screws. Flap healed *per primam.* Sacrificed September 25, 1941.

Macroscopic: Operative site not unusual. Plate firmly embedded into usual bursa-like sac. Screws tight. Dura merges with fibrous tissue filling bone defect. Underlying cortex negative.

Microscopic: Plate bed smooth thin compact fibrous layer with slight new bone formation in bony defect. Rare pigmented macrophage.

Dog. 70.—*Operation:* August 31, 1940. Four screws inserted into frontoparietal region. Three screws inserted into femur. Flap healed *per primam.* Sacrificed September, 1941.

Macroscopic: Operative scars not significant. All screws firmly imbedded; shiny.

Microscopic: Screw tracts in both bones have thin fibrous linings resting on fatty marrow or spicules of newly formed bone. Some periosteal new bone also formed around screw point in skull where it has passed through internal table.

COMMENT: All screws and plates in this series were securely fixed and showed no corrosion.

In the presence of a wrought Ticonium plate, skull defects underwent uncomplicated repair. Two layers of parallel hyalinized fibers were laid down continuous with the pericranium and dura, respectively, the pericranial layer being somewhat thicker. Between these two layers was a third, the new fibers of which were deposited parallel to the surface but at right angles to those of the other two. The larger blood vessels coursed in this middle layer. A limited amount of periosteal new bone was formed which failed to fill the gap. The bone margins underwent remodelling so that they were smooth and tapered in cross-section. Small tufts of muscle filled the plate perforations. Screw holes were lined by a thin layer of fibrous tissue with fibrils again parallel to the metal surface. This lining lay on a base composed of either new bone spicules or fatty marrow (Figs. 2 and 3).

The tissue about metal implants in the brain showed only a thin layer of fibrous tissue beneath which were a few macrophages. The brain substance proper showed a narrow zone of gliosis. The vessels appeared negative (Fig. 4).

A single exception to the otherwise uniform results was found in Dog 46. Necrosis and polymorphonuclear cell exudate characterized the tissue response. This was unique in this group, which included 21 dogs and 115 pieces of metal. The reaction in this case could be differentiated, histologically, from the toxic response seen in Group III. We could not, however, differentiate between Dog 46 and one infected case in Group III. The clinical history and the pathologic findings, as noted in the protocol, suggested infection.

In many cases, a dark brownish or black pigment containing iron was present in macrophages. These were found in clefts between the fibrous tissue of the skull defects, just beneath the fibrous lining of screw holes and in the muscle about the screw heads. The macrophages were most numerous about blood vessels but could not be found immediately adjacent to the metal. The amount of pigment was small, never constituting granulomata. It appeared to be identical with the pigment seen about Vitallium plates and screws.

It may be concluded, therefore, that wrought Ticonium is essentially inert, as is Vitallium.

GROUP II: VITALLIUM

This alloy was examined in seven dogs. The tissues were exposed in all to a total of 34 pieces of metals; three plates and 31 screws. The animals were observed from 24 days to 15 months. Five dogs were sacrificed, and two died on account of secondary illness.

CASE REPORTS

Dog 6.—*Operation:* December 1, 1939. Plate secured with 3 screws. Secondary subcutaneous infection in area about medial flap margin. Healed 26th p.o. day. Sacrificed September 3, 1940.

Macroscopic: Skin scar sound. Muscle tufts have grown through perforations in plate. Screws tight. Plate firm. Metal smooth, and shiny. Dura thickened but not adherent to cortex.

Microscopic: Plate base consists of hyalinized fibrous tissue merging with bone. At the margin

of the two tissues are a few spicules of new bone arising from periosteum. Very rare macrophage in fibrous tissue clefts contains iron pigment.

Dog. 13.—*Operation:* December 29, 1939. Plate secured with 3 screws. Healed *per primam.* Sacrificed September 3, 1940.

Macroscopic: Skin scar negative. Plate and screws tight. Muscle has grown through plate perforations. Metal smooth and shiny. Dura thickened beneath the defect but not adherent to cortex.

Microscopic: Defect filled with bridge of hyalinized fibrous tissue merging with bone. In clefts of fibrous tissue iron-containing pigment in macrophages. Muscle attached to plate bed appears negative. Some foreign body response to bone wax.

Dog 16.—*Operation:* February 15, 1940. Solid plate secured with 3 screws. Posterior screw not tight. Flap healed *per primam.* Sacrificed September 3, 1940.

Macroscopic: Skin scar sound. Screws firm. Plate shiny and well fixed. Underlying dura thickened but not adherent to cortex.

Microscopic: Defect bridged by laminated, partly hyalinized fibrous tissue. Between a few fibers, especially near vessels, are occasionally pigment bearing macrophages. Slight new bone formation.

Dog. 30.—*Operation:* June 29, 1940. Six screws inserted into frontoparietal region. Due to injury, flap broke open. Secondary subcutaneous purulent infection. Healed 20th p.o. day. Sacrificed September 23, 1941.

Macroscopic: Scar and musculature negative. All 6 screws firmly embedded, smooth and shiny.

Microscopic: Screw tract lined by thin fibrous layer, with fibers parallel to screw surface. This rests on spicules of new bone or on fatty marrow. Considerable periosteal new bone at dural end of tract, where screw has evidently penetrated inner table pushing periosteum before it. Few pigment-laden macrophages in looser connective tissue just beneath fibrous lining. Same type of macrophages in connective tissue about head of screw. Here they seem chiefly perivascular.

Dog 31.—*Operation:* June 30, 1940. Six screws inserted into frontoparietal region. All screw holes somewhat too large. Flap healed *per primam.* 26th p.o. day, drainage from eyes and nasal mucous membranes. Slow and incomplete recovery. Two months later flaccid paralysis of both hind legs. Epileptic seizures. "Distemper." Died December 19, 1940.

Macroscopic: Operative scar negative. Six screws firm.

Microscopic: Screw tract lined with thin laminated fibrous tissue. Occasional pigment-laden macrophage in looser tissue immediately adjacent.

Dog 32.—*Operation:* July 6, 1940. Six screws inserted into frontoparietal region. Flap healed *per primam.* 5th p.o. day, drainage from eyes and nasal mucous membranes, fever, dyspnea. "Distemper." Died August 1, 1940.

Macroscopic: Operative scar insignificant. Muscle grossly negative. Six screws firm and shiny. All 6 screws have passed through the inner table. Appear as firm smooth nodules on dural sides. Not adherent to cortex. Right atrium and ventricle of heart dilated. Lungs consolidated.

Microscopic: Screw tract lined with thin fibrous tissue layer. Considerable periosteal new bone formed at dural end of tract. Rare pigment bearing macrophage.

Dog. 34.—*Operation:* July 10, 1940. Four screws inserted into frontoparietal region. Flap healed *per primam.* Sacrificed September 23, 1940.

Macroscopic: Muscle and skin of operative site negative. Four screws firm. Metal smooth and shiny. Dura smooth.

Microscopic: Slight new bone formation between dura and inner table near point of screw. No reaction in tract.

COMMENT.—The original purpose of using Vitallium in these experiments was chiefly to supply a control series. These results are reported merely to confirm the histologic studies of Venable, Stuck, and Beech.[2, 3] They are of particular interest only in that a longer observation and survival period is covered than yet recorded.

In brief, no evidence of toxicity was found. The screws were tight, the plates firmly fixed, and the metal shiny. Cranial defects healed normally, and the tissues on which the plate rested showed no necrosis nor inflammation. The screw holes were lined by a thin layer of fibrous tissue overlying newly formed trabeculae of bone or fatty marrow (Fig. 5).

In every case an occasional pigment-bearing macrophage in the vicinity of the metal was observed. These cells were located in spaces between collagen fibers in the skull defects and about blood vessels. In screw hole tracts they were usually seen beneath the thin fibrous inner lining, and here, too,

were often clustered about vessels. They were not noted immediately adjacent to the metal. This pigment contained iron, and it is presumed to be the same as that reported by Wise[9] about a Vitallium Smith-Petersen nail. It is worthy of note that this pigment occurred in very small amounts, that it did not give rise to granulomata, and in our opinion, does not constitute a sign of toxicity. As was noted above, this pigment was also found in

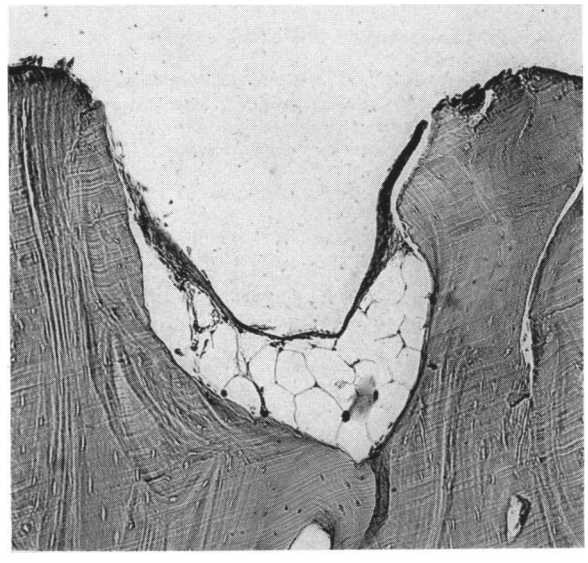

FIG. 5.—(Dog 30)—Vitallium: Screw hole in skull. Fourteen months after operation. (H. and E., ×170)

animals in which Ticonium "wrought" was buried. Since both Vitallium and wrought Ticonium are nonferrous alloys, the iron cannot have been derived from these metals. Our data do not permit us to assign its source. We are inclined to agree with Wise that it is of hematogenous origin.

GROUP III: TICONIUM "CAST" WITH BERYLLIUM

This alloy was tested in 14 animals. The tissues were exposed to a total of 55 pieces of metals: Nine plates, 35 screws in the skull bone, 10 screws in the femur, and one piece of metal which was embedded into the cerebral cortex. The dogs were observed from 50 days to 22 months. Eight animals were observed for a period longer than 10 months. Eleven dogs were sacrificed, three died on account of secondary illness.

COMMENT.—The findings in this group may be summarized without giving the individual case reports of the 14 animals observed.

In dogs which were killed before six months, plates were firmly fixed, screws were tight and the metal was bright and shiny. In dogs which survived longer, however, screws were usually loose and the tissues about the plates were discolored. Occasionally, fluid was found about the metal.

Histologically, the screw holes and plate beds were lined by chronically inflamed granulation tissue containing many macrophages. In the vicinity of the screw holes there was extensive fibrosis of the marrow and some

new bone formation. In general, the amount of lymphocytic and macrophagic exudate was greater in long term experiments. In one dog which survived three months the plate bed consisted of dense fibrous tissue in which were a few focal collections of lymphocytes and macrophages especially numerous about the plate edge. In another dog which survived 22 months, the lining of the space filled by the plate consisted of macrophages with their long axis perpendicular to the plate surface so that these formed a palisade-like layer. The tissue beneath them was highly vascularized and great numbers of swollen macrophages and lymphocytes were enmeshed in a loose fibrillar network. There was a thick layer of fibrous tissue, partly hyalinized beneath the granulations. In the interstices of this were foci of lymphocytic infiltration. Similar changes were seen in the brain where a thick fibrous capsule was surrounded by degenerated brain substance markedly infiltrated with lymphocytes. Perivascular lyphocytic collars were present at some distance from the metal. In spite of the extensive exudative reaction, fibroplasia and osteoplasia were not significantly impaired. In the skull periosteal new bone formed near the bony margin of the defects. In femurs the usual fine trabeculae of the marrow were replaced, in the vicinity of the screws, by dense bone having well developed haversian systems.

These observations are at variance with the results obtained in fibroblast cultures. Two explanations suggest themselves. The first is that the time during which a metal may be studied in any one generation of fibroblasts *in vitro*, is insufficient. Against this explanation is the unimpaired fibroplasia in the long term *in vivo* experiments. The second is that a factor of *selective cytotoxicity* complicates the picture. By this it is meant that some metals may not be toxic to fibroblasts although they may be toxic to other types of cells.

Whatever the explanation, Ménégaux's[8] belief that fibroblast cultures are a valid medium for testing all metals may be questioned.

OBSERVATIONS ON ELECTROLYSIS

Venable, Stuck, and coworkers[2, 3, 4] maintain that electrolysis is the controlling factor in osteosynthesis with metals, and that "metals which are nonelectrolytic in body fluids cause no pathologic reaction in the tissue." This has been a point of controversy. Murray, Martin[10] (Fracture Committee of the American College of Surgeons, New York, 1938), and Key[11] do not feel that electrolysis has an essential bearing on the problem. Bothe, Beaton, and Davenport [12, 13] concluded that "electrolysis is an accompaniment of unfavorable bone reaction rather than the direct cause of it."

Using Venable's[3] method, we have checked the electrolytic activity of the two Ticonium alloys and compared them with that of Vitallium and Vanadium. Silver and copper were used as anodes. Ringer's solution served as electrolyte. A micro-ammeter with an internal resistance of 50 ohms was used. Full-scale deflection amounted to 120 micro-amps. The results are given in Table I.

It is of interest to note that the final reading for Ticonium "wrought" and Vitallium approximates zero, while Ticonium "cast" shows only a minimum current. Ticonium "cast" did not prove to be toxic to fibroblast cultures but did give a local toxic response in dogs which was out of all proportion to the minimal galvanic current produced.

It is common knowledge that pure copper is toxic by chemical action even though it cannot be accused of being electrolytic. This may be taken to indicate that electrolysis may be an accompanying factor of unfavorable bone reaction but it cannot be its only cause. Key has presented good evidence as to its lack of importance clinically.

TABLE I

ELECTROLYTIC DETERMINATIONS

Cells in Ringer's Solution	Initial Deflection in Micro-amperes	Immediate Drop in Micro-amperes to	Deflection after 3 Minutes in Micro-amperes	Deflection after 90 Minutes in Micro-amperes
Ticonium "wrought"-copper	24	3	0	0
Ticonium "wrought"-silver	24	3	0	0
Vitallium-copper	35	2½	0	0
Vitallium-silver	35	2½	0	0
Ticonium "cast"-copper	100	24	13	0
Ticonium "cast"-silver	100	24	13	0
Vanadium-copper	"off scale"	—	—	"off scale"
Vanadium-silver	"off scale"	—	—	"off scale"

The data recorded in this table were compiled by Mr. E. Griffith, Chief-Metallurgist, Research Laboratories. "Ticonium" Co., Albany, N. Y.

Discussion.—Our observations, as expressed in the present communication, establish the inertness in tissues of wrought Ticonium and Vitallium.

Contrary to our previous conception, the cast alloy Ticonium (containing beryllium) proved to be toxic *in vivo*.* It did not, however, interfere with fibroplasia or osteoplasia in any of the animals observed. Therefore, it seems unlikely that the short duration of the tissue culture experiment is the explanation for the lack of "fibroblast cytotoxicity." The evidence is in favor of a *selective cytotoxicity* of the toxic agent, which presumably in this case is beryllium.

Our experiments to date lead us to believe that fibroblast cultures and electrolytic measurements are inferior to histologic studies as tests for the toxicity of metals.

In the alloy Ticonium "wrought" (*without* beryllium), it is believed that a material has been found which conforms to the requirements set forth for the use of metals in the repair of cranial defects. Accordingly, we have commenced to use this alloy as cranioplastic material in patients and will report our observations at a later date.

* Ticonium is made in several forms, "wrought" Ticonium for surgical purposes, and a cast form with beryllium for dental restorations. As employed in the dental alloy, beryllium, we are informed, improves the casting qualities of Ticonium and assists the production of appliances of extreme dimensional accuracy. It has been used successfully in dentistry for some years. Surgical appliances are not made of cast Ticonium with beryllium. While this alloy is toxic *in vivo*, no inference can be drawn from our experience and information on its behavior in such external appliances as dental restorations.

SUMMARY

1. The alloys Ticonium "wrought," Vitallium, and Ticonium "cast," have been studied *in vivo* with special reference to their usage as cranioplastic material.

2. Ticonium "wrought" and Vitallium have been found inert. Ticonium "cast" (with beryllium) has been found cytotoxic. It is suggested that this toxicity is "selective."

3. Fibroblast cultures and electrolytic measurements have been found inferior to histologic studies as tests for the toxicity of metals.

4. The importance of carrying out *in vivo* studies for periods longer than six months is indicated by the late toxic reaction in the Ticonium "cast" material.

5. The wrought alloy Ticonium appears worthy of trial as a cranioplastic material in man.

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