Evaluation of Electrical Techniques for Stimulation of Hard Tissue Growth
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Over the past 12 months work has continued on the following projects:

**Electrically Injected Silver Ions as a Local Bactericidal Agent**

1. The use of electrically injected silver ions as a local bactericidal agent has been under continuing investigation, both at the basic and the clinical level. At the basic level, we have re-evaluated the electrical parameters necessary for the bactericidal effect, using a more sophisticated electrode measuring system. We have found that the voltage on the silver electrode must be a minimum of 250 mV positive for the effect to occur. We have also found that the effect, in vitro, can be produced with the application of as short a time as 2 minutes. Presumably, the amount of silver ions ejected in this time is sufficient to inhibit completely the bacteria in the target zone. While this may not be possible in vivo, the information may prove useful in our future studies on the mechanisms of the silver bactericidal effect.

We continue to attempt to develop techniques enabling us to expand the diameter of the zone of inhibition, but have not been successful thus far.

The clinical evaluation of the electrically injected silver ion as a bactericidal agent has passed from the experimental to the application phase. We are now using this treatment against all of our osteomyelitis cases that require treatment. In the past 6 months, we have treated four additional patients (two with co-existing non-unions) and all have been successful. Two more patients are presently under study, and we are receiving referrals from other VA Hospitals specifically for the infected non-unions of long bones.

A complete report on our clinical usage of this technique has been accepted for publication in the Journal of Bone and Joint Surgery.

We are attempting to expand the clinical situations in which the technique is used, to include such cases as bladder infection in paraplegics, burns, and the recalcitrant skin ulcerations such as severe decubiti, etc.
Silver Compounds as Additives to Bone Cement

2. In a related study, we are determining the local bactericidal efficiency of various silver compounds as additives to methylmethacrylate bone cement. Total joint replacement necessitates the use of such a cementing agent which, in its setting phase, is exothermic to the extent of producing a narrow zone of bone necrosis surrounding the cement. This, coupled with the large mass of foreign material (cement plus prosthetic device), makes any local post-operative infection a clinical disaster. Various techniques have been employed to reduce the incidence of such infections ("clean room" operating techniques, intravenous antibiotics, addition of antibiotics to the cement, etc.). All have been less than totally effective since various studies list the present incidence of post-operative infections in total joint replacement to between 1 and 5 percent.

We theorized that the addition of silver compounds to the cement may be locally bactericidal by a diffusion process alone. Such a technique would be superior to the addition of antibiotics to the cement, since the exothermic reaction temperature that occurs with setting inactivates these complex organic molecules, but would have no effect upon inorganic silver salts. We have evaluated both the ability of silver ions to diffuse out of the cement (in sufficient numbers to be locally bactericidal) and the mechanical properties of the silver compound and methylmethacrylate mix. Silver salts that have been evaluated (in concentrations ranging from 0.05 to 1 percent) are: chloride, oxide, sulfate, and phosphate. We found that silver sulfate exhibited the maximum bactericidal effect for the longest period of time following implantation, and that this compound had no effect upon the mechanical properties of the methylmethacrylate. Antibacterial effects of Ag$_2$SO$_4$ methacrylate produced a visible, measurable, zone of inhibition in culture plates against both gram positive and gram negative organisms (Fig. 10). Some antibacterial activity was still obtainable after 49 days of soaking the silver methacrylate in warm normal saline, indicating a prolonged activity period.

At this point the concept of adding silver salts to methylmethacrylate bone cement as a local antibacterial agent appears to be both effective and without effect upon the mechanical properties of the cement. Biocompatibility studies will be started in the near future: should these indicate that there are no severe local toxic effects resulting from the added silver (as compared to the methylmethacrylate alone) we hope to arrange actual testing using total joint replacements in dogs (in cooperation with Cornell Veterinary College).
Figure 10.—Bacterial culture plates showing inhibition of: (A) Staphylococcus aureus; (B) E. Coli, and (C) Pseudomonas aeruginosa, by silver antibacterial bone cement (SABC). In these tablets, Ag$_2$SO$_4$ was added to Simplex-P Radiopaque Bone Cement in concentrations of 0, 0.05, 0.1, 0.5, and 1 percent, reading clockwise from the top tablet in each dish.

The entire concept of silver ions as effective broad-spectrum local antibacterial agents leads to a number of possible clinical applications of interest beyond those presently under study. These would include the use of silver coatings on prosthetic attachment devices designed to provide bony anchors for attachment by penetrating the skin barrier. The silver would appear to obviate the problem of local bacterial infections at this site, and its ability to be attached to a variety of fabric materials may provide for dermal ingrowth directly into the attachment.
Electrical Stimulation of Bone Growth

3. The electrical stimulation of bone growth in the human by low-intensity direct current continues to be evaluated. A full report was published (Clinical Experience with Low Intensity Direct Current Stimulation of Bone Growth. Clin. Orthop. & Rel. Res. 124: 75-83, 1977. Becker, R. O., J. A. Spadaro, and A. A. Marino) last year and a number of additional cases have been carried to completion since then.

An international meeting with the theme of “The Mechanisms Involved in the Stimulation and Control of Regenerative Growth and Their Clinical Application” is being planned for the Fall of 1979. This will bring together a number of lines of inquiry in basic research, such as stimulation by electrical factors, chemical growth stimulation, and inductive substrate stimulation, and will relate them to ongoing clinical research such as the electrical stimulation of bone growth. It is expected that such a meeting will hasten the clinical application of additional techniques and increase the scope of such applications to include tissues other than bone.