PANEL DISCUSSION: TO WHAT EXTENT CAN ELECTRICAL STIMULATION BE USED IN THE TREATMENT OF HUMAN DISORDERS?

C. A. L. Bassett, R. O. Becker, C. T. Brighton, L. Lavine, and B. A. Rowley

DR. LAVINE: We are now dealing with the real world, with human beings. This subject is of special interest, because the Senate has just passed a bill to create a National Commission for the Protection of Human Subjects from or with Human Experimentation. On the panel today are the three Bs, Drs. Bassett, Becker, and Brighton; these three men are interested in bone. We have a single proponent of soft tissue, Dr. Rowley.

The purpose of today's discussion is to help formulate guidelines for the use of electrical stimulation of wound healing and human disorders. Much of the research reported during this Conference has been performed *in vitro* and *in vivo*, on animals. To what extent are we justified in transferring this work to man? We feel, and I think I am talking for the whole panel, that it is important to discuss this question, not only in scientific terms but also in terms of human and ethical values. Many of us feel that within certain constraints, clinical trials are warranted, as you have heard. Others, however, may disagree.

I would like to propose some general principles for clinical trials. First, informed consent must, of course, be given by the participants in the study. The purpose of the procedure, the potential benefits and risks, and the safeguards being employed should be revealed. Second, the results of the experimental procedure must be evaluated by being measurable and if possible quantifiable. How can this be accomplished? Three, a control group must be established against which one can compare the treatment group. Persons in the control group must be comparable in as many respects as possible to those who receive experimental treatment. This, of course, is difficult. Which type of cases should be considered? We have to obtain numbers; a sufficient amount of people must be enrolled in the control and the treatment groups to make any differences in outcome statistically meaningful. Can this be accomplished by pooling cases in several laboratories?

The panel will talk alphabetically for ten minutes each, and then we will throw the discussion open to whomever wants to make any remarks.

DR. BASSETT: We have heard a tremendous amount of information at this Conference to indicate that we are dealing with real phenomena. There is now abundant evidence to indicate, at least for bone, that there can be stimulation of bone formation or osteogenesis when electrical parameters are altered.

The mechanisms obviously are real but still obscure. That does not prevent us from asking whether they have any benefit to be applied in the clinical situation. If the hazards of application are relatively low, the benefits to be gained are relatively high, and the effect is real, I think we are justified in moving toward "limited" clinical applications. I have to stress the word limited. One of the major considerations is that we are all talking about short-term stimulation. None of the stimulation reported has been much longer than two or three weeks, except perhaps for the extremely resistant pseudarthroses, in which the period of stimulation may extend for as long as four months, which is unusual in the other systems.

I therefore think we have a reasonable degree of safety; at least we think we do at present. I tried to emphasize this when I discussed the issue of malignancy. I think that all of the evidence would seem to indicate that we are not running a sufficient risk of causing malignant transformation to dissuade us from limited application of this technique in selected cases. It is perfectly obvious to all of us that there are many, many more questions than answers, and I know that, as scientists, we will continue to deal with the fundamental issues, as limited clinical application begins. This is the great hope for the future. To deal with these factors, it is quite obvious that I, as an orthopedic surgeon, do not have the competence to examine the biophysical issues. It is just as clear that the biophysicist cannot operate in the clinic. We need to establish multidisciplinary groups throughout the country who are capable of dealing with this issue on a broad basis. I think that the kind of collaboration shown at this Conference, particularly Dr. Hambury's group, has to be developed on a much more formal basis. We have had an effective interchange at this Conference, and I would hope that it would serve as a springboard for the development of many multidisciplinary groups throughout the country to deal with these tasks. They generally will be center oriented, which brings me to one of my major points. I do not believe that we have attained enough sophistication with any of these studies to disseminate them among the clinical community. They should be kept closely guarded in centers that have the necessary depth to study them, and control should be maintained over possible hazards that may arise at any time; we are exploring the unknown. Furthermore, I can see no justification for any commercial exploitation in this area.

Finally, I would like to emphasize that I think we are standing on the threshold of a relatively new era in medicine. To go out on a limb, I would say that in 20 years, almost as much electrotherapy as chemotherapy will be used in the medical community. I think that we will be able to manipulate regeneration healing, pain control, perhaps malignancy, and a whole variety of problems. Obviously, there are many technical and scientific barriers still to be crossed. I do not believe that it is premature for the medical community to begin to prepare themselves. It is inconceivable that any medical student should not study pharmacology, because without this discipline, he cannot manipulate the chemotherapeutic modalities that he will have to use for a patient's benefit.

Similarly, it is inconceivable that with this tremendous mushrooming phenomenon on the horizon, we do not make preparations for the time ahead and insist that our medical school curricula begin to incorporate the principles of biophysics, bioelectrochemistry, and electrical engineering as far as is practical at the present time. The physicians being trained today will hopefully be practicing for at least 40 years. I would hope that they would know the modality that they will have to use, at least well enough to understand the principles and to establish meaningful dialogs with team members from other disciplines.

DR. BECKER: Even though my name begins with the letter B and I am an orthopedic surgeon, my prime interest in this area is not in bone. I believe that we are dealing with a distinctly nontrivial matter for the future of medicine.

When this field began to open up, and clinical use was being postulated, and some patients were actually undergoing treatment, I raised the question of possible induction of malignant cellular changes. I did that for the following specific reasons. First, we know from a variety of reports, both ancient and modern, that tumors have a highly electronegative potential. Second, I am sure you are all aware that we really don't know the final common pathway of tumorigenesis. Third, I think there is al-

ways a possibility that the area to be treated may contain a premalignant lesion and that treatment may stimulate this premalignant lesion.

A slightly more theoretic concept is that since one can use this modality to reduce the size of a tumor, either by electrical fields or by direct injection of current, one can't induce a tumor. I don't think that this concept specifically will hold water, and I am sure that you all agree.

These are really theoretic objections; at present, there must be many thousands of animals that have been exposed to this treatment, and probably several hundred humans. Today, we have heard no report of any such harmful effects. I was well aware of this when I made the original statement, but I made it for a very specific reason. There is a historic perspective within which I think we should view the context of this Conference. Let's go back for a moment to the dawn or the predawn of scientific medicine. In the early 1880s, a report came from French physicians that the positive pole of a galvanic cell (in those days, you made your own electrical unit) when applied to a carcinoma of a human cervix, alleviated many of the symptoms, and there was some suspicion that the tumors would reduce in size. However, if the negative pole was applied, no change occurred in the clinical course.

It should be remembered that there was no effective treatment for this disease at that time. Frank Martin, then a young surgeon, published a report (*J. Amer. Med. Ass.* **6**) of four cases, two treated with the positive pole and two treated with the negative pole, in which he corroborated the French results. The following year, he reported (*J. Amer. Med. Ass.* **6**) on a much larger series of cases, which basically substantiated his conclusions of the previous year.

Martin later became one of the founders of the American College of Surgeons, the progenitor of prestigious journals. About 20 years ago, he wrote his autobiography, in which he stated that the greatest disappointment of his life was related to this situation. Following his two reports, this method fell into the hands of the quacks and charlatans of that day. Ten dollars bought a medical degree, and all you needed was a horse and wagon, and you could get the papers signed on the side. This galvanic therapy spread across the country.

Obviously, it was not effective for everything, and it totally submerged all of the possible good results that could be obtained. I think the parallel with the present situation is perfectly obvious; there is no place in this field for unsupported subjective evaluations, whether clinical or laboratory in nature. We must have impeccable experimentation, we must demand rigorous proof, and we must reject speculation that is based upon mystical or amorphous ideas no matter how seductive they may be.

DR. LAVINE: Of course, there are always two sides of a coin; if you cause cancer, possibly you can cure it. I think some people are trying to achieve that with electricity.

DR. BRIGHTON: What are the difficulties that we are encountering and that we may expect to encounter in any clinical study that involves the use of electrical current in fracture healing? As many of you may know, and physical scientists here may not know, we have a very serious problem with adequate controls. Fracture varies in its rate of healing, depending upon many factors, the age of the patient, for instance. An adolescent will heal a fracture, other elements being equal, faster than a senior citizen. The bone itself matters; some bones are more prone to heal rapidly than others. The region in the bone also is important; the midshaft area is notoriously slow healing as compared, for example, to the metaphyseal, or flared, area near the end of the bone. The type of fracture is another factor; transverse fractures, other elements being equal, will not heal as rapidly as oblique fractures, in which there is

much larger surface area. And then, of course, multiple injuries have an effect. One paper discussed spinal injury and fracture acceleration. Conversely, with multiple fractures, one fracture frequently heals at the expense of the others. Delayed healing is not uncommon with multiple fractures.

We therefore must compare likes with likes: we must compare patients of the same age, bone, type of fracture, and so on. This leads to enormous numbers of patients in any group before one can arrive at any statistical significance.

There are probably only two ways out of this dilemma. First, we could delegate this task to the large fracture mills that exist in the United States. Some very large hospitals, such as city hospitals, do a tremendous amount of fracture work. Maybe over many years they will obtain significant data, yet most of these busy trauma centers are not equipped to perform a carefully controlled clinical study. Or, second, we could, and I favor this alternative, have multiple units throughout the country work together, with the same research protocol, and pool their results.

The other problem with fractures, which is not easy to solve, is that of endpoint. When is a fracture healed? I am sure if anyone brought a patient and a set of x-ray films to this panel, we probably would not all agree whether the fracture is healed and whether the patient can walk or not. I'll wager that we would have four different opinions as to that patient's ability to perform physical activity. Clinical endpoint is almost useless, because after three to four weeks these fractures are no longer painful; the swelling goes down, they get sticky, and they no longer move when stressed. So the clinical endpoint is almost nonexistent.

Therefore, we are really limited. X-ray films can be taken, possibly anteroposterior lateral and oblique ones, carefully evaluated, divided into four quadrants, and used to determine whether bone or mineralized tissue crosses in each quadrant; by this technique, we can arrive at a composite figure. Perhaps, we can thus make x-ray films a little more objective.

For nonunions, there isn't any great problem with adequate controls, because we have a built-in control. These patients just have not healed after many different surgical procedures. When we talk about fresh fractures, for instance, or those that have to be operated on or those that have a tendency to heal slowly, we will encounter difficult problems evaluating our results statistically unless we make an effort such as I have suggested.

DR. ROWLEY: We have been primarily talking about the problems of human experimentation, specifically with regard to disseminating these results to the physician and then into practice, and I agree with the cautious statements that have been made. Since I am not a physician and am not as liable to have my funds cut off by some federal agency, I have a tendency to be a bit pushy. I also get regularly criticized by my colleagues.

However, I would like to first point out that human experimentation is controlled by a local committee that sets up medical standards of procedures. Whenever a human operation is performed, a physician does it, or at least he directs and controls it. Animal experimentation today is also being performed under committee auspices. And, if you think wading through the human committees to get things accomplished is a hurdle, you should see what we have to do to get through the animal committees. I very much believe in the applications research side of life and feel it is where the action really will be in the long run. I would like to utilize basic research in applications research.

It is really frustrating to wait for years and years for acceptance of results. We have to recognize that this current-voltage area also requires time. We do 14 weeks in a bone up here, which is the equivalent time necessary in soft tissue to effect a

positive change. If you are just looking for a positive change over a couple of days and you don't see it, you get very disgusted.

I should also point out that many of us working in this area, particularly in bone, are not really communicating among ourselves as to the procedures that result in success. Even in soft tissue work, if one is not very cautious and does not learn the techniques, it just does not work; for example, in tissue culture, one person will be expert in transferring the culture and another is all thumbs. We must educate everyone with respect to the techniques involved. The interdisciplinary team concept is very important. There is no way with all of the disciplines required that anyone can stand alone.

The commercial aspects of this field are rather frightening, because some ideas that have been discussed today have been clobbered here, and accepted in other places. Other proposals are slowly being advanced commercially with very careful feelers. I don't have an answer for this.

I feel that the concept of centers is the only way that we will obtain statistical numbers acceptable to anyone. One or two people working on one particular aspect simply cannot get a statistical number that has sufficient meaning with firm statistics. I also would propose that areas of rehabilitation engineering, or electrodynamics, be established.

DR. LAVINE: I would like to reemphasize that this Conference has stressed the importance of fundamental research and the interdisciplinary approach. These are still the most important aspects of this field and are necessary before we can meaningfully apply results to the human subject.

MR. F. HASLIP (*DynaWave Corporation, Staunton, Va.*): I have enjoyed this meeting very much and think it is very helpful, but I think we should have some kind of a continuing group.

DR. A. R. LIBOFF: We are exploring the possibility with the New York Academy of Sciences. They have a list of those who attended the meeting, and possibly mail will be sent to both the participants and the guests to provide a basis for a continuing group in the future. Also, there will be a mailing list available for those who would like to keep in contact with others.

I have heard suggestions that the next meeting should be six months from now, which, of course, is too soon; another person said five years from now would be a better time. Obviously, a continuing group is something we should all consider.

DR. S. D. SMITH: As a basic scientist, I appreciate the value of a statistical approach to the data that we are collecting, but I also believe we should keep our eyes open for the nonstatistical evidence; for example, my work is just not statistical. If you take a frog and cut off his arm, he will never grow it back. If this ever occurs, however, it will be highly significant, even if it is only one in 10 million times. There are times when statistics are important, though, and they lend support.

DR. BECKER: I think Dr. Smith's paper perhaps went over the heads of many in the audience, and I think it is a highly significant contribution to biology and also to this specific field. We hear so much talk about bones, which is where I make my money. Bone, however, does not exist *in vacuo;* it is part of the human organism. In these past few days, we have discussed a technique that could well open the door to applying what Dr. Smith demonstrated in the frog to humans. Don't downgrade the frog; it is our relative, although a far removed one. I am not proposing that we attempt to induce the regeneration of amputated extremities, but rather that we work toward effective control over growth by the practicing physician. If we could restore regenerative growth to the human, transplant surgery and prosthetic surgery would be relegated to the past. Those in the audience who are orthopedic surgeons might

not like that, but I would if I were a patient. I think that this is the biologic approach that must be emphasized over all the others. Engineering, physics, and bioelectrical chemistry are fine in themselves, but we are dealing with the biologic world.

DR. P. N. SAWYER (*Downstate Medical Center, Brooklyn, N.Y.*): We were the first, in 1961–63, to produce hemostasis in hemophiliacs. We delivered hundreds of miliamperes to these patients for periods of months until their flaps healed and their psuedotumors disappeared. The first of these patients died last year, without ever developing the manifestations or evidence of malignancy in those areas or, in fact, anywhere that one would suspect either local or long-term effects to produce neoplasms.

You are talking about microamperes, and we were talking about currents two to five orders of magnitude higher. I therefore suspect that the human is considerably more tough in terms of survival, in a radiation atmosphere, than any of us realize, unless we consider that we are constantly being bombarded with radiation and that genetic mutations have made us fairly resistant. What keeps going through my mind is the basis for my laboratory work, which is that there are biochemical analogs of all physicochemical phenomena and that it is interesting to look at the enzymology of the phenomena we are kinetically transforming or accelerating.

DR. LAVINE: It is reassuring that you did not find malignancies.

DR. BECKER: Dr. Sawyer, I appreciate your remarks and am familiar with your work; you certainly have been a pioneer in this field. I would say only that biologic systems are the specific controls; one of the pertinent variations is electrical. This does not mean that to produce a result, such as increased growth in bone or restimulation of the fracture healing sequence, just because 100 nA is good, 1000 nA will be 10 times better. The higher value may be totally ineffective. The literature has reported on eliciting a specific measurable, morphologic and biochemical response from a cell. This occurs within a very narrow range of current densities. If you exceed the range, the cell will just sit and do nothing.

Your patients had a preexisting disease condition, so your results are pertinent to that disease condition. However, when you have a freshly incurred bone fracture, you have pulled the trigger on a control system that will induce a response. I feel that this control system is electronic in nature. I would be very hesitant to superimpose on a preexisting system already in operation, in a human, an additional amount of signal. I could not predict what would happen, and I don't think anyone can predict.

This is a good example of experimentation that should be conducted in animals before it is performed with humans. If in a normal subject an electronic system is already in operation, you better be confident of no harmful effects before superimposing an additional electronic signal.

The other side of the coin is the nonunion, where for one reason or another the healing process fails. The control system is triggered, it works for a period of time, and then it stops. When this happens, you can keep the patient in a plaster cast forever, but the bone will not heal.

When you insert a wire or electrode and induce current by a field or pulses, that is, when you induce an appropriate electrical environment that simulates the control system, you can restart this process. I believe that this procedure is perfectly justifiable and feasible and well within the theoretic and practical realms to use in clinical medicine today.

DR. BRIGHTON: There have been reports that in fresh fractures, with animals, an electric current superimposed has enhanced or increased the fracture healing rate.

DR. ROWLEY: We have observed with decubitus ulcer healing that after a period

of time, some of the resistant ulcers will exhibit a plateauing of the rate of granulation in the wound. Also, at that particular time, a simple switch occurs in the polarity of the wound for a 24-hr period, and then the granulation is triggered off again. I therefore agree with Dr. Becker that this is a clinically usable feature.

DR. BASSETT: I agree with everything that Dr. Becker has said with respect to the great care needed when superimposing external control signals on a normally operating control mechanism. This should be investigated very extensively in experimental animals before we can be justified in proceeding to routine treatment of fresh fractures. We will have had to prove that the benefit/risk ratio is in the patient's favor. One of the key issues here is whether one can materially reduce the disability time. The total cost of fracture care, fracture and disability payments, and third party coverage in the United States every year runs into billions of dollars. If you can reduce the time to return to work by 40 or 50%, you will make a major impact on human suffering and economics. If we can therefore work toward having a practical, safe, and efficacious method for improving the tempo of fracture healing, I think it is a goal well worth striving for.

DR. LAVINE: This is a rare moment—we all agree. We cannot close on such a unanimous vote.

DR. S. A. BROWN (*Dartmouth Medical School, Hanover, N.H.*): One of the major problems with interdisciplinary activity is to produce effective communication. This can be accomplished in two ways. One approach is to get a physician who has some engineering background and an engineer who has some medical background; it is possible to water down the sophistication of each discipline somewhat to produce some beneficial interaction.

The other approach is to have a medical specialist, an engineering specialist, and a third person who can speak to both individuals and can interpret the problems of combining sophisticated engineering design and the concepts of current, voltage, and field density and the difference between a probe and an electrode and who then can talk to the physician and understand the clinical setting.

In light of these problems of interdisciplinary studies and avoiding industrial price and profit incentive problems, how do we obtain funding for such studies? How should a proposal be written—as an engineer, or as a clinician? Should both specialties be watered down—should we write a proposal that no one man can understand?

DR. BASSETT: It is a big problem, Dr. Brown. First, we must broaden the base of common understanding in the populus, which involves education. Earlier I tried to emphasize the need for broadening our medical education in this area.

Second, we have a serious problem of educating federal funding agencies that there is a desperate need to begin to focus on this issue and to set up and support multidisciplinary groups in these areas. I think all of us in our individual spheres of influence should make an effort to correct this situation.

DR. D. M. STREET (*University of California at Los Angeles, Los Angeles, Calif.*): My interest in this subject goes back to experiments in medical school days 40 years ago; I have kept up my interest in it since. I think it is fair to say that electrotherapy in the succeeding years has gradually waned. Currently, there seems to be a little negative bias among the profession toward this type of treatment.

However, I have seen no instance of malignancy over a 40-year period that was attributable to high-frequency radiation, in contrast to the ionizing radiation, of course. On the other hand, I thoroughly agree that we should examine all of these factors. Some of the orthopedists will remember that 12 years ago, I made a movie

that almost destroyed whatever reputation I had in the profession. This film involved treating patients with diapulse.

We obtained definite effects from diapulse therapy, but we didn't know why. For example, we found a 20–30% increase in plasma cortisol in rheumatoid arthritics. It was a very definite change, but why? I wonder whether we have come much further in the last 10 years in identifying the reasons for these results. Nevertheless, I feel that we all should really work at it, even if only because of its fascinating aspects.

DR. D. H. WILSON: As an overseas visitor, this meeting has been a very valuable experience. I thought I was coming to attend a Conference on Electrically Mediated Growth Mechanisms in Living Systems. I think the title perhaps should have instead been Electrically Mediated Growth Mechanisms in Bone and Other Tissues, because we have concentrated our efforts on bone. There is a saying current among orthopedic surgeons on my side of the Atlantic that there is no such thing as bone per se; bones, yes, but bone as a concept is too difficult and complex. I feel that we should devote more effort toward other tissues. I reported on studies in peripheral nerve, and I am sure that this tissue is much more amenable to study and precise measurement. I think we have been investigating the most difficult system first.

DR. LAVINE: As you can see we are well represented by the soft tissue people at this time.

DR. SMITH: With regard to malignancy, in looking at neural tissue, I can tell you, and can prove, that one can take neural tissue containing neurons that have stopped dividing, electrify it, and find that they start dividing again. This is obviously something to think about.

Conversely, and this is much more subjective and not provable, anyone familiar with frog biology knows that many of them, especially those that I get from Minnesota, have renal carcinomas. None of the frogs I have treated electrically has ever died of this disease.

DR. H. J. HAMBURY: I would like to again emphasize and agree with Dr. Bassett's attempt to educate the federal funding authorities. When he has made good progress, perhaps he would let me know. A very fine spare interdisciplinary team is waiting on the other side of the ocean. To Dr. Becker, I would also like to say that we do have a live biologist, a pathologist, and a medical physicist and we will return as soon as you have succeeded.

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