Pulsed Signal Therapy

The following is a transcription of a colloquy between Alfred Jay Bollet, MD, Professor of Medicine and Rheumatology, Yale University School of Medicine and Richard Markoll, MD, Ph.D., at a technology conference on the electrophysiology of the joint.

I have drawn on the board a picture of a joint. The key point is that the cartilage (the two surfaces that contact each other are cartilage with bone below) is made up mainly of collagen, largely arranged in arcades, so that collagen fibers near the surface run parallel to the surface . Cells, which are widely separated, make up the components of the matrix, which consists of the collagen and a complex protein-carbohydrate compound, proteoglycan, which consists in part of a protein core and radiating chains of polysaccharide-sugar molecules - which have a lot of negative charges on them. These are carboxyl groups and sulfate groups, and the negative charges tend to repel each other.

These negative charges have to be neutralized, so sodium is attracted in from the extracellular fluid, because the matrix is all extracellular - outside the cells. Thus, there is a great deal of sodium in the cartilage. This causes a very high osmotic pressure which attracts water, and that's why cartilage is 80% water- because of all these ions that are attracting water.

When you take a step, putting weight on the joint, the cartilage is compressed, the water gets displaced, and it carries with it the mobile ions, the sodium ions, leaving behind the negatively charged proteoglycan carboxyl and sulfate ions. That generates an electric current because you have unneutralized negative charges. This is called a streaming potential.

It is also how cartilage performs its function; in this case the function is to absorb compressive stresses without putting a lot of strain on the bone, and then to spring back to its former shape, to be elastic. When the sodium is displaced and these proteoglycans are squeezed closer to each other, the closer they get the more the negative charges repel each other.

They are arranged like the teeth of a comb, and as they are compressed they tend to repel each other more, the more you squeeze the more they repel, resisting compression. When the pressure is removed they push each other away, the sodium and the water are re-attracted, and the cartilage expands to its original volume. So cartilage is very good at absorbing compressive stresses in this fashion. But, each time you step down and do this to an area of the cartilage you generate a little electric current, and the thinking is that this is the main signal to the cartilage cells to make more matrix. It tells the cells "you are being used" and any tissue that you use tends to hypertrophy, to make more of the substance of that tissue. It is now well established in the laboratory that if you repetitively use an area of cartilage it thickens and if you underuse an area it thins. The thickening is from use of the

cartilage, just like your muscle gets stronger and bulkier if you use it, the cartilage gets stronger - gets thicker if you use it by making more of this matrix, more of the proteoglycan, and more of the collagen.

(You say it is the electrical current that stimulates and signals the body to reproduce?) Yes. This is called a mechanical-electrical transduction - the signal is changed from one form of energy to another. But the signal is actually caused by the movement of the water and sodium, leaving the fixed charges unneutralized.

(Its the Donnan effect, this law was introduced in 1924 and states; that fixed negative charges determine the concentration of the counterions, specifically, the fixed negative charges, the carboxyl and sulfate groups, determine the concentration of the counterions which is sodium in this case. Minus charges and plus charged electron flow produces an electrical charge.)

What Grodzinsky has done at MIT is to take a chunk of cartilage and put it in a vice-like device and then apply pressure to it intermittently; he showed that he gets a current when he squeezes the cartilage and allows the fluid (and sodium) to exude through the membrane on the surface, so that by moving the fluid you get a current - that's the streaming potential. He has shown an increased synthesis of these compounds in cartilage subjected to repetitive stresses in this fashion, so the thinking is that this is the main signaling mechanism that tells chondrocytes to take more matrix. It is the same thing that occurs in bone.

Bone is responsive to physical stresses, you get bone where you need it essentially, the mechanical- electrical transduction, again streaming potentials, occur in bone signaling the osteocytes to make more bone matrix.

Other dense connective tissues that perform mechanical functions respond to increased use with this mechanical- electrical transduction mechanism as the stimulus to make more of the tissue. What we think we are doing with this device is to generate similar currents by inducing them with magnetic fields, so that we are generating the same signal that use generates, without actual use, without putting strain and wear on the cartilage.

(In the osteoarthritis in my hip, the cartilage has worn away so there is no cartilage. Can it work if it is totally worn away?) Well, we don't know; it certainly does not work as well. If it is totally worn away there are no chondrocytes there when the cartilage is worn away which is called grade 4 disease. The grade 4 osteoarthritis cases did better in relation to the grade 4 placebo patients, but they didn't do as well as the lower grades.

(What do the grades indicate?) The grades are the severity of the X-ray changes. The more cartilage that is lost the higher the grade; so this is how the treated patients did - the grades one and two did best, grade three like this, grade four did poorest.

The grade four placebo patients did even worse and so there was more of a statistically significant difference between the grade four treated and placebo patients, but actually the grades one and two patients responded the best. But, consider the question of whether the

grade four patients need longer treatment. We are treating everybody the same way and that may not be optimal for some patients. So, I think what we should be doing is giving them a longer course of treatment, but we had to use a specific uniform protocol for the purpose of this study.

Gentlemen, the important thing here is cartilage as such is not measured in inches as people might perceive it, it's measured in millimeters or micro-millimeters, so, when a patient is told that it's all gone, it is never really all gone. If it was all gone and a bone on bone state existed, excruciating, unbearable pain would immediately occur due to the bone surfaces (the highly innervated periosteum covering of bone) touching.

What happens in osteoarthritis is a wearing away of the cartilage the matrix is gone, the substance of the cartilage is worn away; the main change, particularly early, is a loss of these matrix compounds so the cartilage is not able to perform its function normally because there is less proteoglycan in it than normal. Restoring the proteoglycan can enable the cartilage to perform its function; even if it doesn't regrow fully, what's there may still be functional.

Let's say, it's now half the normal thickness, but if that had a normal concentration of proteoglycans it would still do pretty well. But, if only half of it is there, and that portion has half the normal concentration of proteoglycans, it's not going to do as well.

(Is there research going on around the country now on cartilage regeneration?) Yes. The main approach is using drugs that may slow the rate of breakdown of the proteoglycans in the cartilage matrix. These are called chondroprotective agents. They are inhibitors of the enzymes that cause the turnover, the loss, of the proteoglycans. There are a lot of places that have been working on this for years; I did some studies on it a long time ago. In fact, I started the studies of cartilage metabolism in osteoarthritis back in 1960. I worked out the fact that there is a loss of the proteoglycans, but there is increased synthesis going on until the very late stages of the disease; therefore, it is a reversible disease up to that point.

The term degenerative joint disease is often used and I think that it is a terrible term because it has the wrong implication as to what is going on. There is a vigorous attempt at repair going on until it's just too late, until everything is gone.

Jay also alluded to the question of what type of cartilage is the body producing. The normal joint cartilage is hyaline cartilage. Sometimes the new cartilage is fibrocartilage. There is another thing here, very fundamental in the physics of this, or the biophysics. If you take a finger, not my finger - somebody else's finger, and you take a hammer and smash it, what you will notice, biophysically, is an instant negative current of injury, which you can measure i.e., you can measure a current flow and its polarity.

The moment of trauma causes an immediate reversal of polarity and that negative current, for which there is documentation, is the trigger point or the stimulation for the reorganization process which begins with the inflammatory process, which is dilation of blood cells so it

becomes warm, or it becomes swollen. Phagocytes and monocytes and all kinds of worker cells come to the site to repair it. What we know we can do and what we are doing when you place the limb or the object under treatment into the magnetic field, you have an instant reversal of polarity and now you have a positive current as opposed to a negative. We have jumped over or shortened the reorganization process.

Sometimes, in the case of this inflamed arthritic cartilage, it might be a misguided attempt striving to bring the repair mechanism and material to the site. In fact it does not improve the complaint, it causes greater inflammatory related distress.

There is not a lot of inflammation in osteoarthritis; rheumatoid arthritis is mainly inflammatory. (Let's say in general, I didn't say osteoarthritis in general, if you damage your finger and you have an immediate repair process beginning, it's called a reorganization process. That reorganization process can take several weeks to reverse the polarity and get the reorganization healing process going.

But, one way to explain the constant pain, for example, is the primary hyperalgesic syndrome which simply says, if you have the stimulus for pain, e.g. stimulating the finger with a hammer, the pain level goes up and then drops down and you have an interruption. It goes up and it peaks and it drops down immediately; it is a very steep deteriorating angle. However, in osteoarthritis, what we know is it peaks and the level goes down slowly; this is called the secondary hyperalgesic syndrome. For example if that concept is not immediately or fully understood, another way of explaining the concept is, if you are watching television, there are 25 single still frames creating what we see as motion, i.e. 25 still pictures actually being processed by the brain per second (frequency) through the eye as a camera. The brain cannot, however, comprehend the static image and therefore, it looks like one picture. Here, we can't grasp the milliseconds between still pictures, we grasp the longer period. This is well established, and can be found in any scientific textbook. There is a hypertrophy of the nervous system, the pain detecting system that is clinically very important.

But, in terms of what we are doing, we think that we are stimulating cartilage regrowth through imitation of the basic mechanism of stimulation of cartilage, mimicking the bodies own energy signal.. (I asked that question earlier, you can't make a definitive statement as a scientist, however, we believe that the aforesaid mechanisms of action are happening).

We can, however, report what we are doing, and present the in vitro data that this device will cause bovine cartilage cells to make more collagen and proteoglycan.

In the process of rolling out this therapeutic technology, it would be valuable to be able to give everyone asking, as most do, an explanation of how it works.

Even if it were only a partial explanation of the mechanism of action, it would be valuable to say to every doctor in the United States who asks "How does that work?") If you can explain how it works, it's much more acceptable.

But between all of us at this table Jay and I are in 100% agreement, I think, that what ever mechanism of action theory we postulate now, there will be further mechanism of action theories, there will be additional ones, possibly the initial ones will be slightly wrong or completely wrong but to answer your question to say something to people now, definitive statements about mechanism of effects, perhaps to give them our short discourse on the electrophysiology of the joint and postulates of mechanism of action, would be meaningful. Grodzinsky at MIT was contacted and now Jay has established a preliminary date to visit him. He is interested in working with us, taking one of our devices and doing some of his original work as a follow-up to other work we do. There are others interested in doing collaborative laboratory work.

(If you sat with an internist now, would he understand what you are talking about?) Well, this is the talk I give to the various rheumatology groups and internal medicine groups.

They understand the basic chemistry; few have heard of streaming potentials. I didn't know about it until a couple of years ago, when I started working on this project and looked into it, so I have been learning.

This is a new field, a new aspect of rheumatology to most rheumatologists, but they understand and accept it readily once they are informed.

(So if you sat here with a dozen guys five years out of internal medicine training they will grasp this and they will understand the fact that this procedure will allow them to keep patients away from the rheumatologist and from the surgeon.) They will grasp the basic concepts as to how it may be working and when I talk, I start with those concepts. The clinical data will be what will convince them that they can keep the patients from orthopedist or rheumatologists, but they want to know, how does it work?

Statement from CEO of HMO attending conference: *"My whole life these past twelve years has been involved with and in the business of keeping people out of the special referral group. We want the prime to maintain control over the referral process as long as possible."*