

# The Use of Biomedical Sensors to Monitor Capsule Formation Around Soft Tissue Implants

J. W. Bender, PhD,<sup>‡</sup> H. I. Friedman, MD, PhD,\* V. Giurgiutiu, PhD,<sup>‡</sup> C. Watson, MD,<sup>†</sup>  
M. Fitzmaurice, MD,<sup>†</sup> and M. L. Yost, PhD<sup>†</sup>

**Abstract:** Piezoelectric sensors have been shown to respond reproducibly to changes in tissue mechanical properties surrounding an implant over a 4-month period. The vibrational amplitude at a frequency corresponding to the radial resonance shows a statistically significant change over time. The initial period of inflammation is marked by a significant reduction in amplitude, which is indicative of an increase in viscous dissipation of the tissue. As collagen displaces the cellular response, the amplitude continues to decrease. Finally, as the tissue matures, the capsule becomes stiffer, and the viscous dissipation lessens. These results are consistent with qualitative assessments of explanted capsules.

Strain gauges encased in a monolithic block of silicone exhibited a greater degree of variability, yet show similar trends over time. The strain increases in the initial 4-week period and remains relatively steady over the following 4 weeks. Beyond 8 weeks, the gauges begin to extrude from the animal or suffer a loss of electrical continuity. Steps are being taken to improve the strain sensor longevity in the animals.

**Key Words:** biomedical sensors, capsule formation, soft tissue implants

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Biomedical sensing devices have had a long history in monitoring and pacing heart rate in patients and even delivering a lifesaving shock if ventricular fibrillation is detected.<sup>1–3</sup> Monitoring biochemical concentrations in vivo using implanted devices has been the subject of intense research efforts, notably in the area of glucose measurement for diabetes management.<sup>4–6</sup> Still, the majority of implanted devices are programmed as continuous drug delivery systems

(eg, Baclofen pump) or are externally located to deliver medication (insulin pump). In vivo biomechanical characterization of soft tissues has focused on cartilage and on topical wounds, in which the sensing device is external.<sup>7–12</sup> There has been limited research performed on implanted mechanical sensing devices, and those that exist focus primarily on short-term studies. For example, Park et al<sup>7</sup> implanted pressure transducers at the interface of an artificial hip joint to measure pressure distributions across the surface and validate computational models. The development of long-term in vivo stress measurement or mechanical characterization of soft tissues could have tremendous application in decubitus ulcer prevention or in early detection of capsular contraction around an implant placed during reconstructive or cosmetic surgery. The former occurs in paraplegic patients when capillary closing pressure is applied to soft tissues for too long a period of time. The latter occurs as a natural course of the later stages of wound healing and can lead to poor clinical outcomes.

The current investigation was undertaken to study the tissue response to 2 different small implantable sensing devices, piezoelectric wafer active sensors (PWAS) and strain gauge sensors (SGS). These sensors provide complementary information on the mechanical properties of tissue reactions to their presence. The piezoelectric sensor can quantify differences in local tissue viscoelasticity via the generation of high-frequency shear waves. The strain sensor deforms under static pressure. The response of the mammalian tissues to these sensors is felt to be the first step in developing devices for practical application to clinical situations. Therefore, in these experiments we have implanted these 2 types of sensors into rats and studied the sensor recordings to correlate them with the histology of the soft tissue reactions to their presence.

## Sensors

### Electromechanical Oscillation

Piezoelectric materials are those that change dimensions upon applying an electric field. When driven with an AC electric field, devices such as the PWAS are oscillated over a spectrum of frequencies. At certain frequencies, the device will resonate and have a high amplitude of motion. Because the structure of the piezomaterial can be controlled, they can be made to possess characteristic motions (resonances) at specific frequencies. Figure 1 shows 2 modes of oscillation of the PWAS sensor used in these studies. There is

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From the \*Division of Plastic Surgery and †Department of Surgery, USC School of Medicine, Columbia, SC; and ‡School of Engineering, University of South Carolina, Columbia, SC.

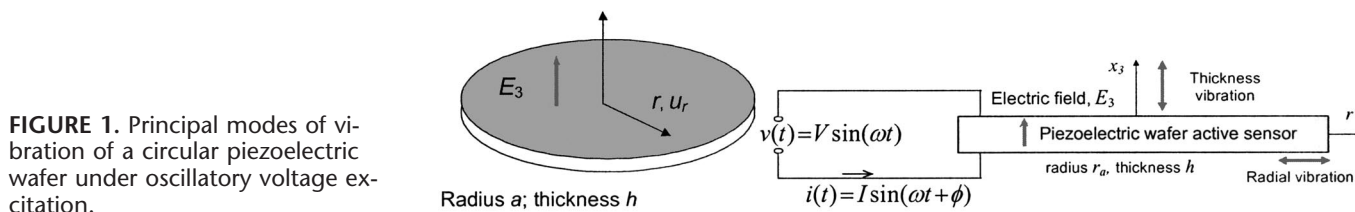
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Reprints: Harold I. Friedman, MD, PhD, Division of Plastic Surgery, Department of Surgery, USC School of Medicine, Suite 402, #2 Medical Park Rd, Columbia, SC 29203. E-mail: hfriedmandr@sc.rr.com.

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**FIGURE 1.** Principal modes of vibration of a circular piezoelectric wafer under oscillatory voltage excitation.

a lower frequency resonance in which the sensor expands and contracts radially and a higher frequency thickness vibration.

When the piezosensor is mechanically coupled with the medium, such as being attached to a rigid object or implanted in soft tissue, the amplitude of vibration changes over the frequency domain and the frequencies at which the sensor resonates change. Together, these constitute an electromechanical impedance shift that is measured by an impedance analyzer. In these experiments, the impedance will change as the mechanical properties of the tissue surrounding the sensor change. The mathematics relating the measured impedance to the mechanical impedance of the tissue is complex.<sup>13</sup> For current purposes, we focus on simply the amplitude change of the PWAS at the radial resonance, and leave a more detailed analysis for future work. As the PWAS is oscillated radially, shear waves are generated that propagate away from the surface in an exponentially decaying magnitude. The rate of decay depends on the viscosity of the medium and the frequency of oscillation. For these sensors at 100 kHz, the interaction depth is calculated to be of order 50  $\mu\text{m}$  assuming the viscosity of water. Thus, the PWAS is most sensitive to variations in mechanical properties of materials to this distance. As the viscoelasticity of the tissue surrounding the implant changes, the amplitude of the radial resonance changes as well. As the tissue becomes more viscous it dissipates more of the energy of the PWAS, leading to a damp PWAS amplitude of vibration. In this sense, the PWAS can quantify the relative viscous nature of the tissue during the process of wound healing.

### Strain Gauges

Strain gauges are complementary to the PWAS sensor in that they directly measure the contractile force generated by the surrounding tissue. The resistance of a thin metallic circuit changes as the circuit is compressed, expanded, or bent and is directly related to the compressive or bending force.

### MATERIALS AND METHODS

Twenty 250-g male Sprague-Dawley rats were each anesthetized with 75 mg/kg ketamine, 7.5 mg/kg xylazine, and 1 mg/kg acepromazine, intraperitoneal (IP). Their backs were then shaved, prepped, and draped. A ventral incision was used to create a pocket for the placement of the sensors and their connecting wires. The implants were placed beneath the platysma muscle. One of each type of sensors (PWAS and SGS) was implanted. The PWAS consists of a 7-mm diameter, 0.2-mm-thick piezoelectric wafer (APC-850) with nickel surface electrodes and connecting wires. The PWAS

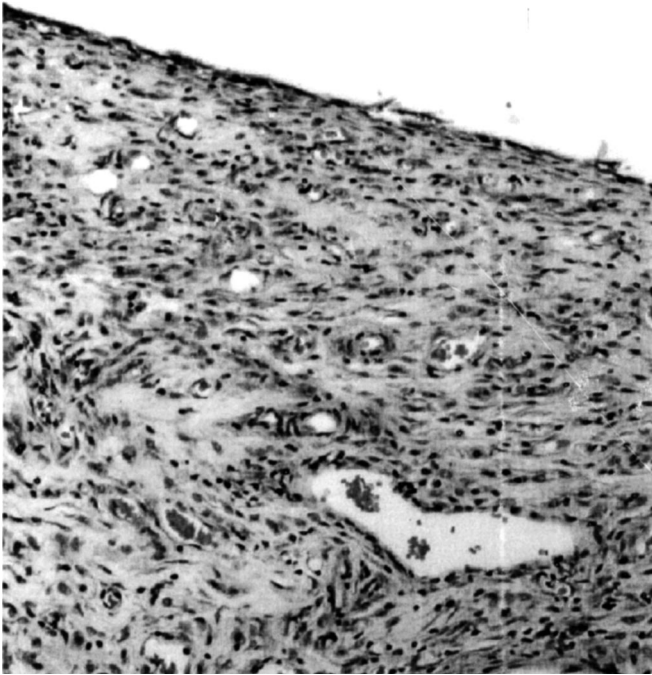
was coated with a thin layer of acrylic (Vishay Micro-Measurements, M-Coat D) to insulate the electrodes. The SGS (Vishay Micro-Measurements, CEA-13-015UW-120) were encased in a cured 2-part silicone of dimensions 10 mm by 7 mm by 4 mm using a custom mold (Silpak, Inc: R-2374 A/B RT Heat Cure Silicone). A baseline recording from each sensor was obtained prior to closing the incision with a running 4-0 Prolene suture. Subsequently, and sequentially at 2, 4, 8, 12, and 16 weeks, 4 of the animals were reanesthetized and the old incision was reopened. The wires were freed of the developed capsule and new recordings were made. For the PWAS, a Hewlett Packard 4194 Impedance Analyzer was used to measure the real and imaginary parts of the PWAS electrical impedance over a wide frequency band. The frequency band of primary interest here is the 100-900 kHz range, which covers the first and second resonance radial in-plane vibrations. For the SGS, a Wheatstone bridge (P-3500 Strain Indicator) was used to measure accumulated strain. Next, the implants and a surrounding envelope of soft tissue were dissected free and immersed in formalin. They were maintained at room temperature for several hours and then placed in the refrigerator for later preparation. The sensor was then dissected from the envelope of soft tissue, and the latter was processed for routine histopathology. The recordings obtained from the sensors were correlated with the histologic observations.

At 12 weeks, it became apparent that there was a problem with many of the connections between the wire and the sensor of the SGS devices. The wires were becoming dislocated from the sensor itself. This problem persisted with the implants placed for 16 weeks. For this reason, a modification of the sensor connection was developed, and an additional group of 4 animals was implanted with 3 SGS sensors each for 4 months. In this case, serial recordings were obtained from the same sensors at monthly intervals. That is, each animal had a sensor recording made at the time of implantation, and then the recordings were repeated each month without removal of the SGS devices. Since the material of the sensors themselves had not changed from the first set of experiments, the capsules around these sensors were not analyzed morphologically.

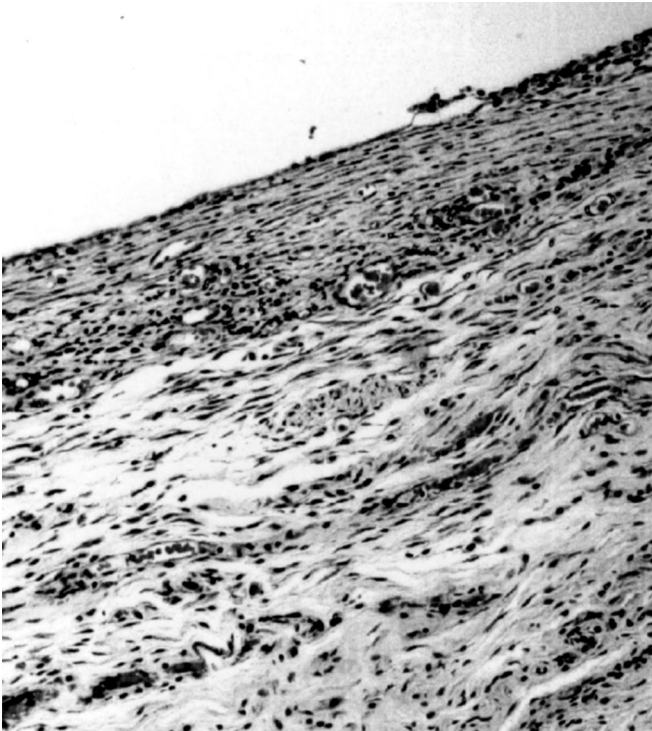
The data overall were analyzed using analysis of variance to determine statistical significance. Direct comparisons between 2 time points were analyzed using a 2-tailed Student *t* test.

### RESULTS

Of the several vibrational modes of the PWAS sensor, the radial mode at 100 kHz appears to be the most sensitive



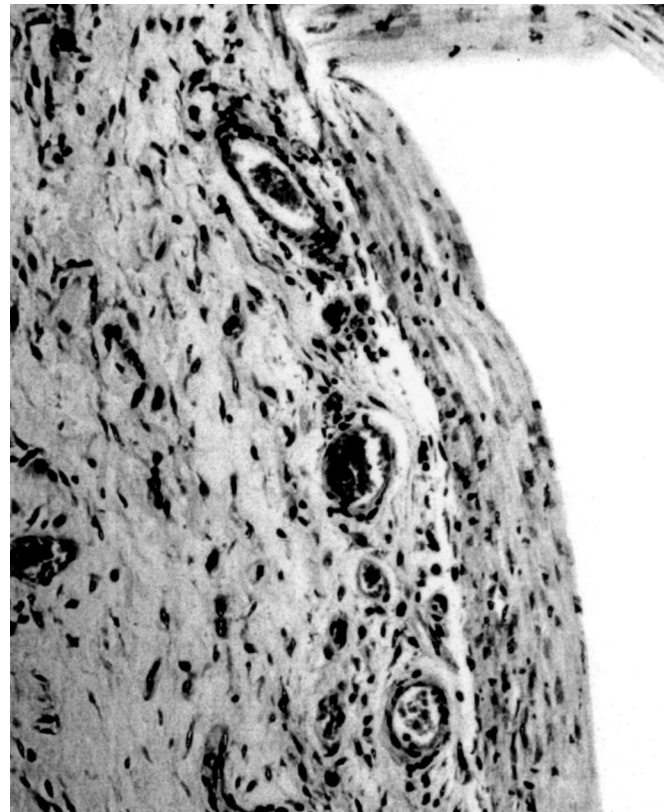
**FIGURE 2.** Light microscopic view of sensor/soft tissue interface 2 weeks after sensor implantation. Note the inflammatory response to the presence of the sensor with mononuclear cells, polymorphonuclear leukocytes and capillary proliferation; 10 $\times$ .



**FIGURE 3.** Light micrograph view of sensor/soft tissue interface 4 weeks after sensor implantation. Fibroblasts now form a layer of cells adjacent to the implant oriented parallel to the sensor surface; 10 $\times$ .

to the wound healing process. The first graph demonstrates the percent reduction in radial vibration amplitude during the study, while Figures 2 through 6 show the histology of the tissue surrounding the implant at the corresponding times. The initial reading is of the sensor amplitude immediately following implantation, which is taken as a baseline at 100%. The error bars represent the total variability in readings of 4 sensors, and analysis of variance indicates statistical differences among the mean amplitude values to a confidence of  $P < 0.001$ . Within 2 weeks, the amplitude has decreased to roughly 50% of its original value ( $P < 0.005$ ). Histologically, at this time the sensors were surrounded by a predominantly cellular response (Fig. 2) consisting of polymorphonuclear leukocytes, mononuclear lymphocytes, and an occasional multinuclear giant cell. In addition, there was a large ingrowth of capillaries in this inflammatory matrix.

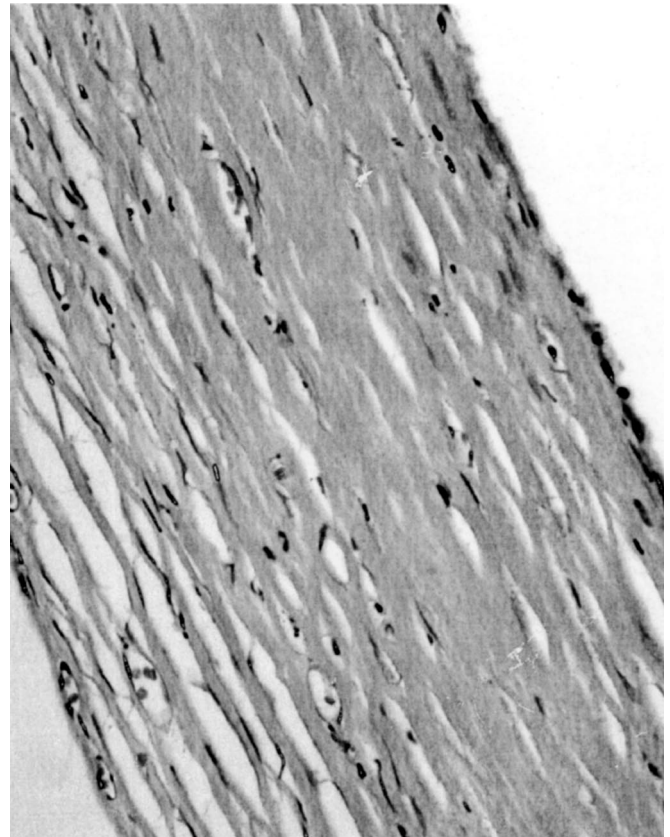
At 4 weeks, little change has occurred in the PWAS radial amplitude compared with the 2-week period (graph 1). During this time, the cellular response had matured somewhat with the presence of more fibroblasts and the early application of collagen fibers around the implant (Fig. 3). The collagen bundles and cells are oriented parallel to the surface of the implant. As shown in graph 2, the increase in compressive strain generated by the tissue surrounding the SGS



**FIGURE 4.** Light micrograph view of sensor/soft tissue interface 8 weeks after sensor implantation. There are fewer fibroblasts present at the surface of the sensor, while collagen deposition has increased. There are still many capillaries present; 10 $\times$ .



**FIGURE 5.** Light micrograph view of the sensor/soft tissue interface 12 weeks after sensor implantation. The tissue adjacent to the sensor is now predominantly collagen with very few mononuclear cells compared with the appearance of the capsule earlier; 10×.



**FIGURE 6.** Light micrograph view of the sensor/soft tissue interface 16 weeks after sensor implantation. At this time the capsule has further matured and is almost all collagen with scattered cells and small capillaries; 10×.

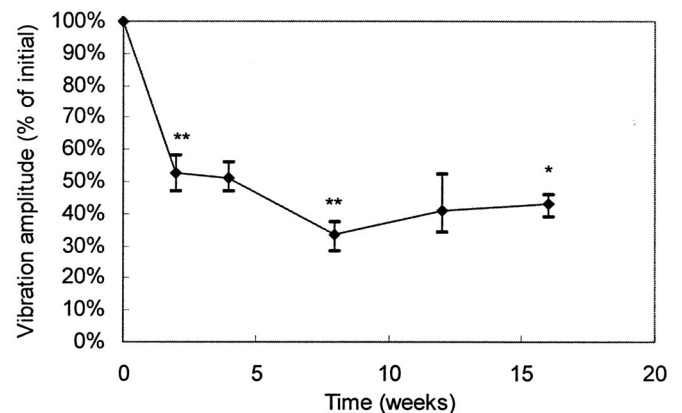
implant during the initial 4-week period was statistically significant ( $P < 0.05$ ), although the results are considerably more scattered. Overall, analysis of variance of the SGS data indicates a significant change in the mean value of the sensors that survived to 8 weeks ( $P < 0.005$ ).

At 8 weeks, the PWAS radial amplitude decreased significantly compared with that at 4 weeks ( $P < 0.005$ ). At this same time, the remaining fibroblasts are gradually replaced by a diffusely organized layer of collagen (Fig. 4). In contrast, the SGS sensors showed no significant change over the same time period. There are few inflammatory cells in the layer of the capsule beneath the collagen envelope; however, a large number of capillaries persist.

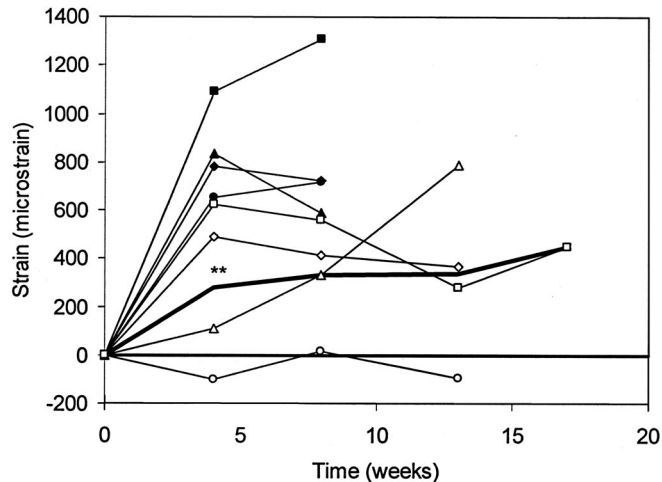
At 12 weeks, there is an apparent *increase* in radial amplitude as measured by the PWAS sensors. Dense bundles of collagen fibers with scattered fibroblasts surround the implant (Fig. 5). Fewer capillaries are observed in the layer beneath the collagen envelope. Half of the SGS sensors failed to generate data at this time point, and resistance changes in those that survived are not statistically distinguishable. This finding was attributable to continued challenges with both maintaining electrical continuity at the wire-sensor junction and preventing extrusion of this more prominent sensor through the skin.

Finally, at 16 weeks, there is a further rise in amplitude of the PWAS sensor, which is statistically distinguishable

from the readings at 8 weeks ( $P < 0.05$ ). Histologically, this is commensurate with the formation of an increasingly dense and structurally aligned collagen layer (Fig. 6). Unfortu-



**GRAPH 1.** PWAS vibration amplitude as a percentage of the initial for the duration of the experiment. The double asterisk indicates a  $P$  value less than 0.005, whereas a single asterisk indicates a  $P$  value less than 0.05 compared with the values at 8 weeks. The error bars indicate the total variation in the data.



**GRAPH 2.** Strain accumulation for the SGS over time. The bold line is the average of the readings. The double asterisk indicates a *P* value less than 0.005.

nately, at this point, only 1 SGS remained operational, and it was associated with a very significant capsular contracture almost to the point of extrusion. Interestingly, the SGS recording from that sensor showed an increase in amplitude from the previous month.

## DISCUSSION

Introduction of a foreign substance into the human body results in a cascade of events culminating in the complete encasement of the substance in a dense connective tissue envelope.<sup>14–22</sup> This process affects all devices, including breast implants, pacemakers, plates and screws used for bony union, and even catheters used for intravenous access. The initial response to the material is identical to what is observed in normal response to the creation of a wound. Within hours, there is adherence and activation of platelets in the areas of injury,<sup>23,24</sup> and the release of growth factors and chemotactic agents contained in the platelet granules.<sup>25</sup> Granulocytes and mononuclear phagocytes migrate into the wound. Subsequently, the site is infiltrated by fibroblasts. Products released by both platelets and mononuclear phagocytes stimulate the migration and proliferation of these cells. Platelet-derived growth factor (PDGF),<sup>26,27</sup> as well as other factors, plays a crucial role in up-regulating fibroblasts to reproduce and lay down collagen.<sup>28–30</sup> These findings were clearly mirrored in the current investigation as an inflammatory response to the SGS and PWAS sensors eventually was replaced by the migration of fibroblasts into the wound and the production of collagen at the sensor surface. Thus, at 2 weeks after implantation of the sensors the predominant morphologic response is one of inflammation. By 1 month, fibroblasts and early collagen production has replaced the highly cellular inflammation. At 8 weeks, collagen production appears to have increased. The numbers of cells decrease as the collagen becomes more predominant, as was seen in this investigation at 3 and 4 months after sensor implantation.<sup>31</sup> Thus, the response of the soft tissues to the

placement of the sensors was identical to what is observed with other foreign materials, including silicone.

The recordings obtained from the PWAS sensors directly reflected many of the findings observed morphologically. At the time of PWAS implantation, an initial reading of radial amplitude was obtained. Two weeks later, as edema and cell inflammation occur, the amplitude is significantly dampened by approximately 50%, and this continues for the first month. The decrease in amplitude actually reflects an increase in surrounding tissue viscosity caused by the edema and cell infiltration. The dampening effect significantly increased during the period of early collagen formation out to 8 weeks, at which time the amplitude decreased to approximately 35% of the initial value. One may surmise that early collagen production around the sensor further increases viscosity of the tissue surrounding it, thereby impeding its radial motion. What was interesting was that at 12 and 16 weeks, the dampening lessened, and the radial motion amplitude of the sensor returned to approximately 45% of the initial reading. One possible explanation is that as the collagen bundles surrounding the implant mature—and the number of inter- and intramolecular bonds increases—edema within the collagen bundles decreases. In this fashion, there is less impedance or inertial dampening (ie, viscosity) to the vibratory motion of the sensor. Thus, one can envision the sensor more freely vibrating within the collagen envelope.

The SGS sensors were implanted to yield different physical data regarding contractile forces against the sensor. As with the PWAS sensor, there was an initial statistically significant increase in strain gauge readings 4 weeks after implantation. These persisted to 8 and 12 weeks from those sensors that remained functional. Unfortunately, loss of contact between the sensor and connecting wires prevented readings from half the sensors at 12 weeks. In addition, these sensors had a rectangular shape with a high profile that led to extrusion during the course of the study. The trend, although not significant, was for a gradual rise in strain units over time as the collagen bundles around the sensor increased. Large increases in strain will only occur when the gauge itself is deformed by bending or unequal axial compression. If contractile forces are applied to the SGS in equal force around the sensor (isotropic compression) so that it is minimally deformed or not deformed at all, then the magnitude of recorded change will be less. At the current time, we have improved the connection between the wire and the sensor, and we have made design changes in the sensor and its silicone coating to hopefully yield more consistent data that we can correlate with the histologic observations.

The observations recorded in this investigation have opened a new avenue for the study of soft tissue responses to implanted materials and for the application of implanted sensors to study a number of biologic and clinical processes. In the future, we hope to study the effects of inhibition of capsule formation by blocking the process at different levels (eg, COX inhibitors, lathyrisms, etc). We also are developing sensors that can be accessed remotely without connecting wires. Sensors such as these could be used to monitor pressure phenomena in paraplegics over sensitive points with

warning signals emitted when capillary closing pressures over bone have been exceeded for too long a period of time. Sensors could be incorporated into tissue implants to detect early capsule contracture so that early intervention might be feasible.

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