Chapter 11

PIEZOELECTRICITY OF BONE AND OSTEOGENESIS BY PIEZOELECTRIC FILMS

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Piezoelectricity of Bone

IN 1953 YASUDA reported that long bone produced electric voltage when it was bent as shown in Figure 11-1.[1] The concave part was negatively polarized and the convex part positively polarized. In 1957 Fukada and Yasuda reported the piezoelectricity of bone under shear, which was the first quantitative study on piezoelectricity of bone.[2] They cut approximately cubic samples with a few millimeter dimension from the cortex of dried bovine or human femur as shown in Figure 11-2 and investigated the relationship between the direction of applied pressure or tension and the direction and magnitude of resulting polarization. The largest piezoelectric effect was observed when pressure or tension was applied at about 45 degrees to the bone axis. The same effect was also observed in the Achilles tendon.[3] Experiments confirmed that when shear stress is given to the oriented collagen fibers, either in bone or in tendon, polarization appears in the direction perpendicular to the plane of applied shear.

Rectangular coordinates were assigned to the bone: the *z*-axis was the bone axis, the *x*-axis the radial direction, and the *y*-axis the tangential direction. When the pressure (T) is applied at 45 degrees to the bone axis, which is one-half of the shear stress in the *yz* plane (T_{yz}), the electric polarization (P) is produced in the *x* direction. The piezoelectric constant is defined as the ratio of polarization to mechanical stress.

Figure 11-3 shows the linear relationship between polarization (P_x) and mechanical stress (T_{yz}) for dried bone. The slope gives the piezoelectric constant (d_{14}), which is about 0.2 pC/N.

Converse piezoelectric effect was also proved in bone, i.e. mechanical stress or strain is produced when the electric field is applied.[2] Figure 11-4 shows the linear relationship between the shear stress in the *yz* plane (T_{yz}) and the electric field applied in the *x*-axis (E_x). The slope gives another type of piezoelectric constant (e_{14}), which is the ratio of mechanical stress (T_{yz}) to the applied electric field (E_x). It was found to be 2×10^{-3} N/Vm for dried bone. The two piezoelectric constants (d_{14} and $\overset{e}{\cancel{g}}_{14}$) are related by the elastic constant (c), which is about 1×10^{10} N/m^2. The piezoelectric constant (d_{14}) calculated from the converse piezoelectric measurement agreed well with

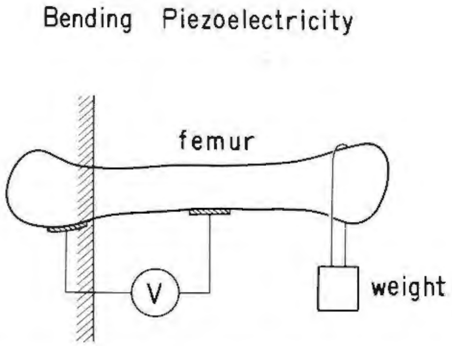

Figure 11-1. Bending piezoelectricity of bone.

that observed by direct piezoelectric measurement, as shown in Figure 11-3.

Converse piezoelectric effect in polymers has been scarcely investigated. However, the effect is important for the practical application of piezoelectric polymers such as ultrasonic transducers.

When the pressure or tension is applied in the direction of bone axis, or perpendicular to it, the electric polarization also appears in the direction of bone axis, as shown in Figure 11-5.[3] It was found that the pressure in the z direction (the bone axis) causes the polarization in the same direction, the proximal part being negative and the distal part being positive.

The piezoelectric constant d_{33}, which is the ratio of the axial polarization to the axial stress, is about one-fiftieth of d_{14}. This tensile piezoelectricity is

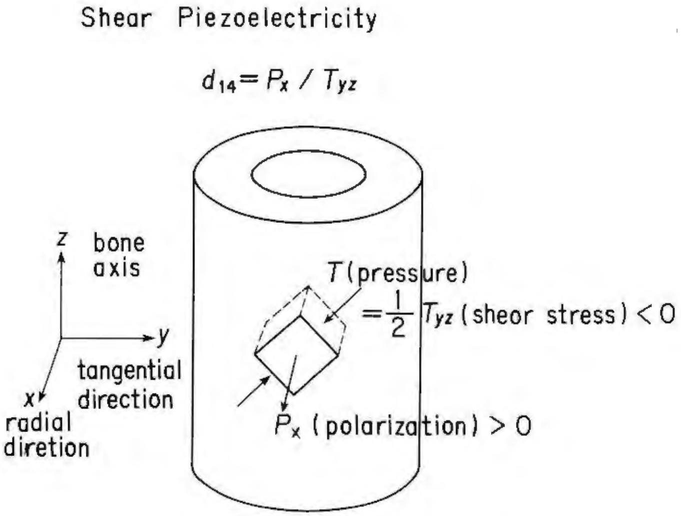

Figure 11-2. Shear piezoelectricity of bone.

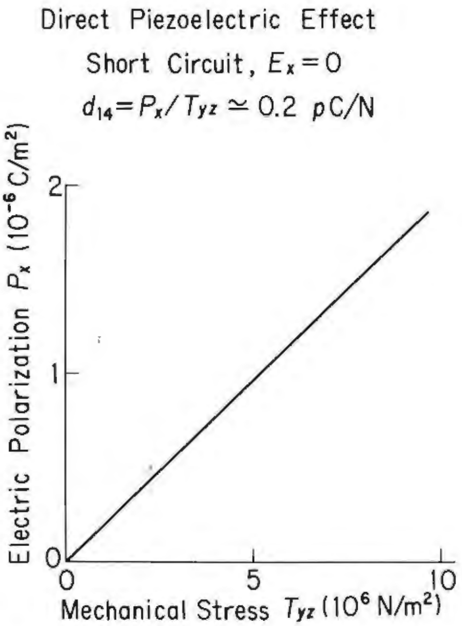

Figure 11-3. Direct piezoelectric effect in bone.

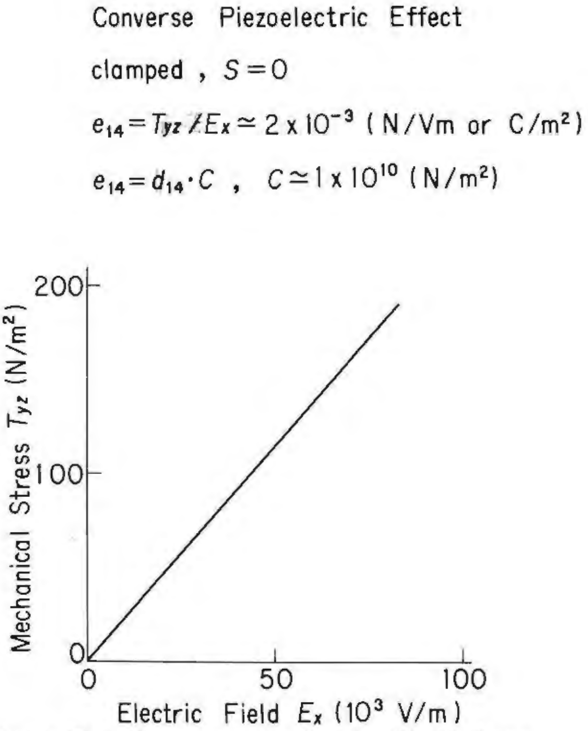

Figure 11-4. Converse piezoelectric effect in bone.

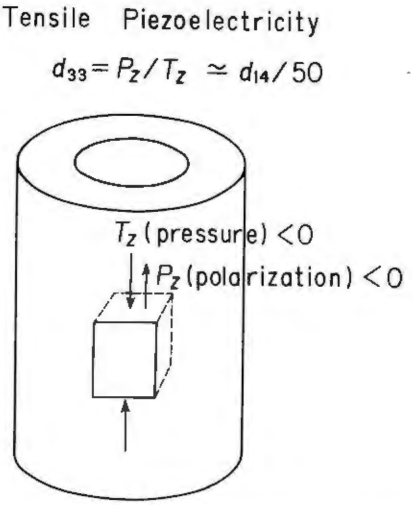

Figure 11-5. Tensile piezoelectricity of bone.

very small for bone but significant for tendon.[3] The constant d_{33} for dried tendon is larger by one order of magnitude compared to bone.

The tensile piezoelectricity is related to the pyroelectricity in the direction of bone axis. If bone or tendon is heated or cooled, the polarization is produced in the direction of bone axis.

The pyroelectric constant (p) is defined as the temperature dependence of the polarization. The experimental value of $p = 2.5 \times 10^{-9}$ C/m^{2}K was reported by Lang.[4]

The pyroelectric effect observed in bone is believed mostly due to the secondary effect through the piezoelectric effect.[5] The secondary pyroelectric constant is given by the product of d, c, and α, where d is the piezoelectric constant, c the elastic constant, and α the thermal expansion coefficient. If the sample is heated, the thermal expansion causes the elastic deformation, which then produces the electric polarization through the piezoelectric effect.

The dynamical measurements of piezoelectric constant have been carried out for various kinds of polymers.[6] The sample, in the shape of thin film or plate, is fixed between two metal clamps placed inside a cryostat. A sinusoidal vibration, typically at a frequency of 10 Hz and an amplitude of less than 10 μm, is imposed to the sample. The alternating polarization produced by the piezoelectricity is led to a charge amplifier, which is effectively short-circuited. The stress and strain of the sample are detected by a load cell and a strain gauge respectively. The ratio of polarization to stress or strain is computed as a complex quantity and both real and imaginary components of the piezoelectric constant (for instance, d' and d'') are recorded as a function of temperature on the recorder.[7] The piezoelectric constant of polymers usually depends upon temperature, frequency, and moisture content.

The temperature dependence of the d_{14} constant for bone obtained from bovine femur is shown in Figure 11-6. When the bone sample is dessicated sufficiently, the piezoelectric constant is nearly constant below about 70°C and is about 0.3 pC/N. If moisture was introduced to bone, the piezoelectric constant at a low temperature of −150°C increased, but it gradually decreased with rising temperature. The elastic constant and dielectric constant also showed relaxational changes at the corresponding temperature range. With the increase of temperature, the defreezing of bound water and free water takes place and shields the piezoelectric polarization.

The temperature and hydration dependence of the piezoelectric constant for decalcified bone is shown in Figure 11-7. The sample of bone was immersed in the buffer solution of ethylene diamine tetra-acetic acid with pH 7 for about one day. When hydroxyapatite was completely dissolved and removed, the transparent sample of decalcified bone was obtained, which was composed mainly of oriented collagen fibers. The magnitude of piezoelectric constant is about 4 pC/N, which is ten times higher than that for bone. This value is similar to the piezoelectric constant of tendon, which consists of collagen fibers. When the water content is increased, the

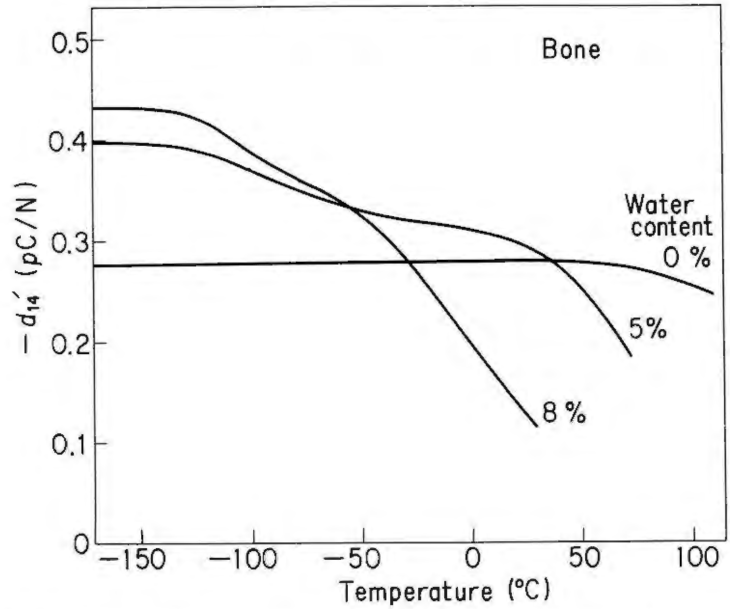

Figure 11-6. Temperature and hydration dependence of shear piezoelectric constant d_{14} for bone.

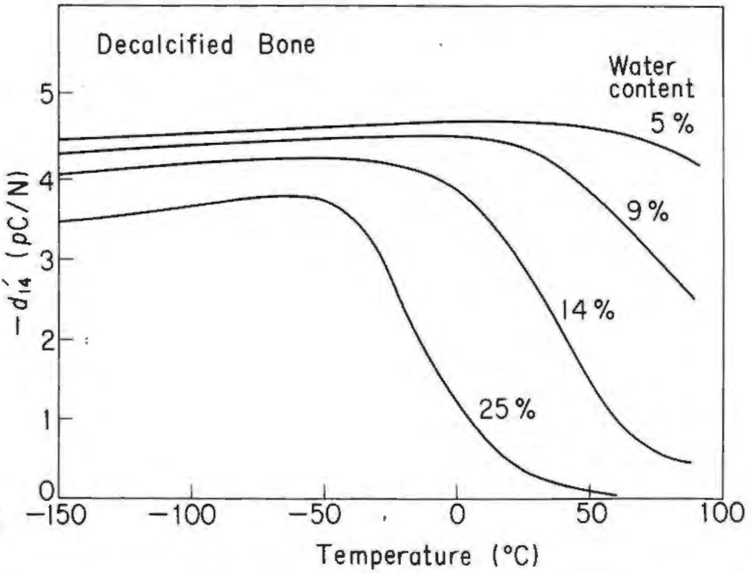

Figure 11-7. Temperature and hydration dependence of piezoelectric constant for decalcified bone.

conductivity due to water decreases the observed piezoelectric constant at higher temperatures.

Piezoelectricity of Synthetic Polymers

Starting from the study on bone and tendon, the piezoelectric activity has been found in many different kinds of proteins other than collagen. The effect has been also observed in synthetic polypeptides whose physical and chemical properties are well characterized. Poly-γ-methyl-glutamate, abbreviated PMG, is one example of the commercially available polypeptides. Its molecular structure is shown in Figure 11-8.

The PMG film oriented by stretching about twice the original length showed the piezoelectric constant (d_{14}) of about 4 pC/N, which is the same as that for decalcified bone. This film was used for proliferation of bone, which will be described later.

The origin of piezoelectricity in natural proteins and synthetic polypeptides is believed to be due to the internal rotation of peptide groups (CONH) under the action of external stress.

At present, most kinds of fibrous proteins and polypeptides are known to show piezoelectricity if they are oriented and crystallized to some extent. Two typical molecular conformations are known for the crystalline state of polypeptides: α-helix and β-form. Theoretical calculation has proved that the internal rotation of CO-NH dipoles under external stress is the origin of piezoelectric polarization.[8]

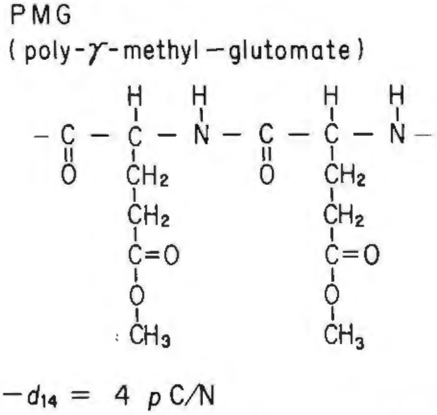

Figure 11-8. Chemical structure of poly-γ-methyl-glutamate.

As shown in Figure 11-9, the direction of dipoles in α-helix is almost in the same direction. When shear is given to the helix, each dipole changes its orientation from its neutral equilibrium state. The sum of such internal strain or polarization of dipolar groups gives rise to the observable polarization.

When the pleated sheet structure of β-form is sheared, it causes the internal rotation of CONH dipoles, which results in the observable piezoelectric polarization.[9]

Figure 11-10 shows the molecular structure of polyvinylidene fluoride (PVDF), which is a polymer with the highest piezoelectric constant at present. After the treatment of stretching and polarizing, the piezoelectric constant d_{31} is about 20 pC/N, which is about ten times greater compared to decalcified bone and one hundred times greater compared to bone. The pyroelectric constant for PVDF is about 3×10^{-5} C/M^{2}K,[10] which is greater by the order of 10^4 compared to bone. This comparison of constants indicates the extremely large piezo- and pyroelectric effect of this polymer.

In PVDF, the ferroelectric behavior was also observed. When the applied electric field is cyclically changed with a large amplitude such as 100 MV/m, the electric displacement D showed a remarkable hysteresis loop, as shown in Figure 11-11. This hysteresis loop strongly suggests that the dipoles CF_2 and CH_2 are cooperatively oriented by the action of electric field and that the remnant polarization exists when the field is removed, which should be produced by the residual orientation of dipoles.[11]

As shown in the right side of Figure 11-11, the piezoelectric constant e_{31} also showed hysteresis when the biasing electric field was cyclically changed. These hysteresis behaviors are very similar to those observed in ferroelectric crystals. It is believed now that PVDF is the first ferroelectric polymer ever discovered.

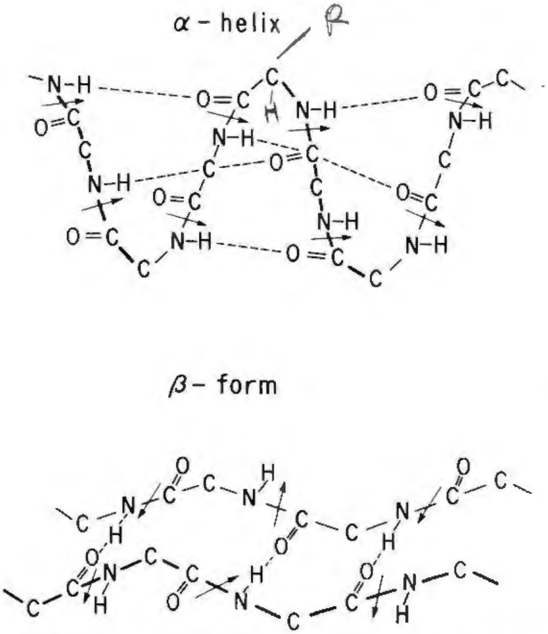

Figure 11-9. Two molecular conformations of polypeptides.

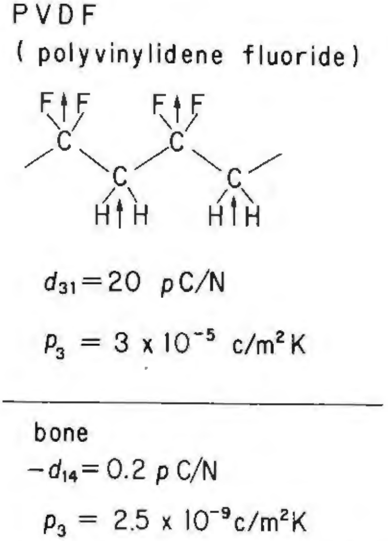

Figure 11-10. Chemical structure of polyvinylidene fluoride.

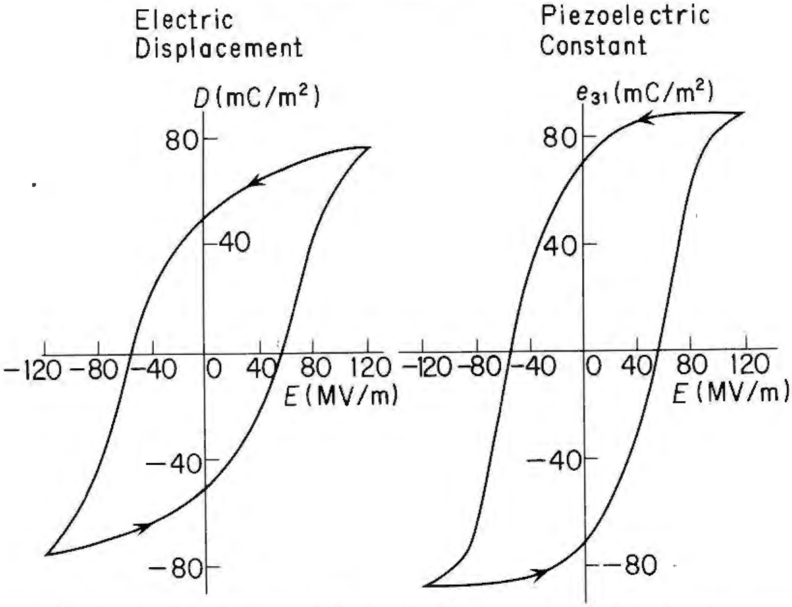

Figure 11-11. Hysteresis loops of electric displacement and piezoelectric constant for polyvinylidene fluoride.

Osteogenesis by Piezoelectric Films

It has been recently found that the piezoelectric polymer films can be used to induce osteogenesis. A small piece of piezoelectric film or electret film was applied onto the femur of living animals and the formation of callus surrounding the polymer films was observed.

In initial experiments,[12, 13] the authors used Teflon® film, whose chemical structure is shown in Figure 11-12. This polymer is known to have a good biocompatibility.

In order to make electret films of Teflon, the authors used the technique of corona discharge. The thin polymer film was placed on a grounded metal plate and a needle electrode was put about 1 cm above the film and a high potential (5-10 kV) was applied. Corona discharge then took place in the air gap and polarized the Teflon film by injecting the electric charges onto the surface of the film. The corona-polarized Teflon film shows the bending piezoelectricity but no tensile piezoelectricity.

The Teflon electret film was wrapped around the femur of a rabbit as shown in Figure 11-13 and maintained for a few weeks.

Figure 11-14 shows the x-ray photograph taken at four weeks after operation showing the growth of callus surrounding Teflon film.[12] The callus started to grow at both sides of the film, made a bridgelike callus, and finally formed rigid bone.

Inoue et al. used an oriented film of poly-γ-methyl-L-glutamate (PMLG), which is piezoelectric but not an electret film, to induce bone in

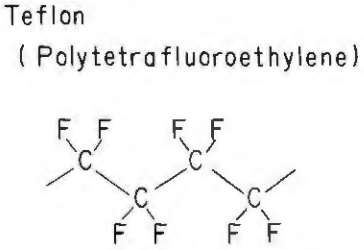

Figure 11-12. Chemical structure of Teflon®.

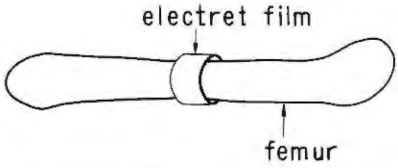

Figure 11-13. Teflon® electret film wrapped around the femur of rabbit.

the femur of Donryu rat.[14] The ends of the film were fixed to muscle of quadriceps and to muscle of biceps, as shown in Figure 11-15. The cross section of the bone and PMLG film is shown in the right side of the figure. By the motion of the rat, the PMLG film is always deformed dynamically and produces the piezoelectric polarization.

Figure 11-16 shows the x-ray picture indicating the formation of callus. The PMLG film was wrapped around the femur on the right side. At sixteen days after operation, a slight growth of bone is observed at the quadriceps side. At thirty-eight days after operation, the formation of new bone is quite obvious.

For the purpose of comparison, the Teflon electret film was wrapped around the femur in the right side of the figure. It is observed that new

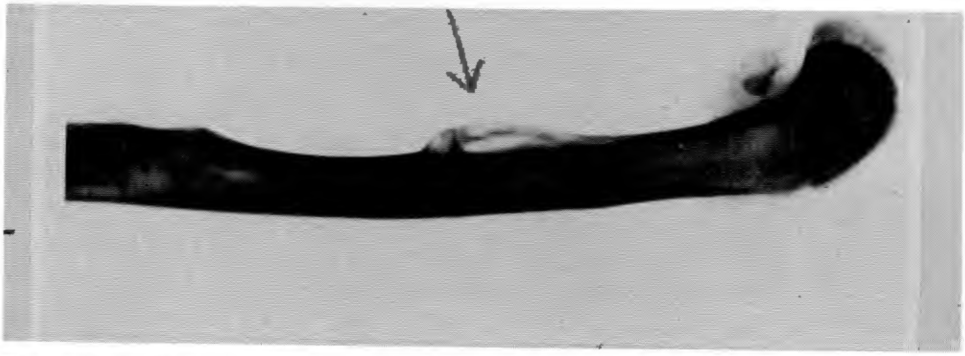

Figure 11-14. X-ray photograph of the femur of rabbit with Teflon electret film taken four weeks after operation.

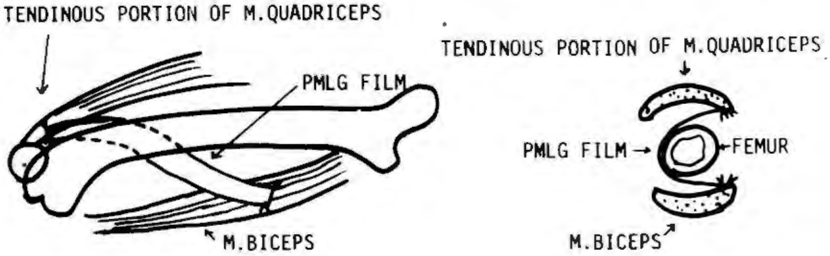

Figure 11-15: A film of poly-γ-methyl-L-glutamate fixed around the femur of rat.

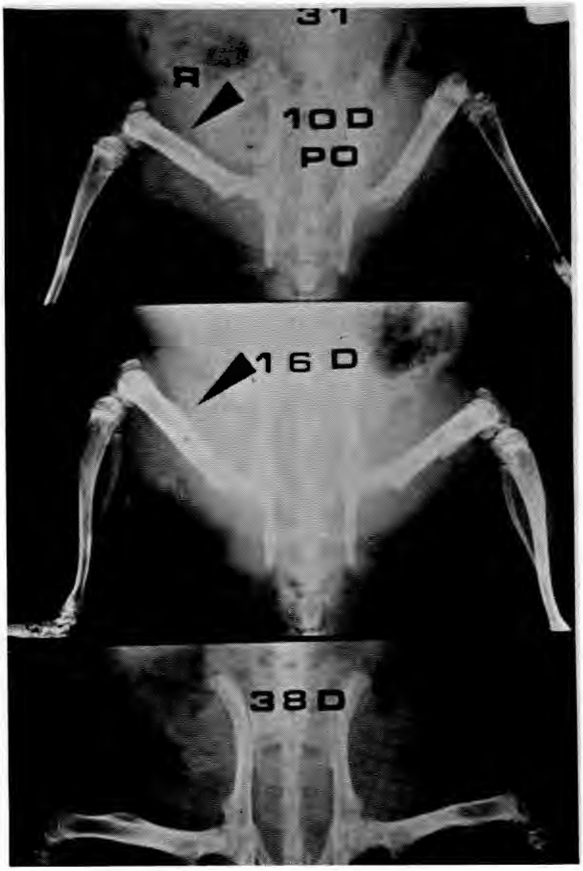

Figure 11-16. X-ray photograph of the femur of rat with a piezoelectric film of poly-γ-methyl-L-glutamate on right side and with an electret film of Teflon at left side, observed ten, sixteen, and thirty-eight days after operation.

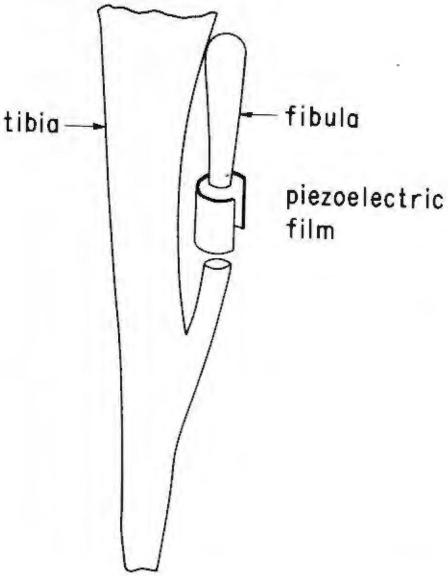

Figure 11-17. Cylindrical piezoelectric film is placed between the gap made by cutting the fibula.

bone was formed at the biceps side. If the films of PMLG and Teflon were placed surrounding the femur of the rat for about eleven months, the newly formed bone near the Teflon film almost disappeared, but the bone formed near the PMLG film continued to grow. The reason should be that the charge in Teflon electret decays with time, but the piezoelectric activity in PMLG film never decays.

Hayashi and Yabuki used oriented films of poly-γ-methyl-L-glutamate and collagen, cut 45° to the direction of orientation. They cut the fibula of rabbit about 5 mm long and placed a cylindrical piezoelectric film in the gap, as shown in Figure 11-17. They observed the formation of callus surrounding piezoelectric films.

Figure 11-18 shows the x-ray picture taken three weeks after operation. PMLG film was placed in the gap of the right fibula. It is seen that new bone is formed surrounding the PMLG film. The left fibula is a control. Even without the piezoelectric film, the callus is formed in the gap, but the amount of the callus formed is much smaller.

Figure 11-19 shows the x-ray picture three weeks after the collagen film was placed in the gap between amputated ends in right side fibula. The fibula on the left was the control. The callus is more formed with the presence of collagen piezoelectric film.[16] The advantage of the use of collagen films is the possibility that the film might be degradated after a long period of time.

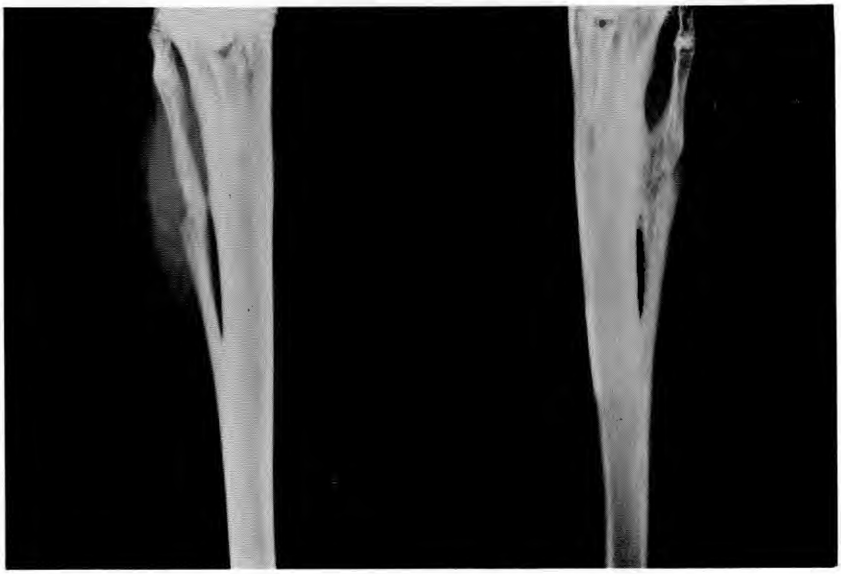

Figure 11-18. X-ray photograph taken three weeks after a PMLG film was placed in the gap on right side fibula of rabbit.

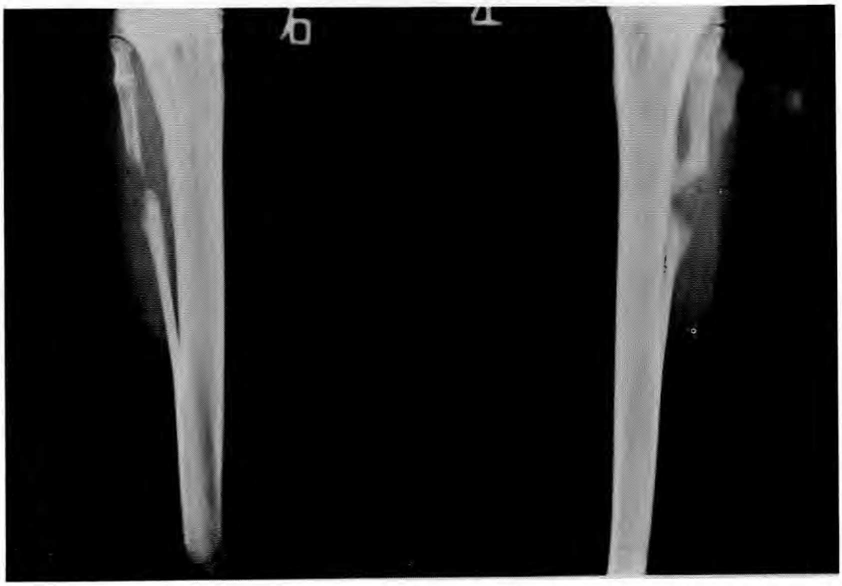

Figure 11-19. X-ray photograph taken three weeks after a collagen film was placed in the gap of right side fibula of rabbit.

Figure 11-20. Histogram of callus formed on the collagen film.

Figure 11-20 shows the micrograph of new callus formed adjacent to the collagen film. The white part at the upper left side shows the collagen film. The callus is formed just on the wall of piezoelectric film. The orientation of new callus is observed, which is directed in parallel towards the surface of film.

Suzuki and Takahashi investigated the effect of highly piezoelectric and pyroelectric film of polyvinylidene fluoride on osteogenesis.[17, 18]

They applied a PVDF film to the femur and mandible of monkey *(Macaca irus)*. As shown in Figure 11-21, the half portion of the femur

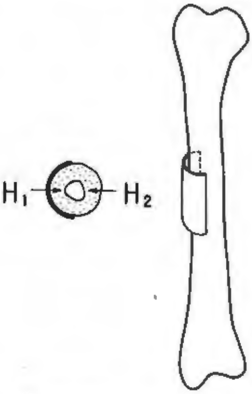

Figure 11-21. A film of polyvinylidene piezoelectric film covers a half circumference of femur of monkey. Courtesy of Dr. H. Suzuki.

(denoted by H_1) was covered by the PVDF film and the other half (denoted by H_2) was uncovered.

Figure 11-22 shows a large amount of callus formed surrounding the PVDF film at six weeks after operation.[17, 18] The effect of PVDF film appears to be remarkable, owing to its very large piezoelectric effect.

They also investigated the effect of PVDF film on the metabolic activity in the cortex bone. The remodelling of cortical bone is performed by the resorption by osteoblasts followed by the formation of secondary osteons by osteoblasts. These activities were detected by tetrachrome staining method.

Figure 11-23 shows the number of resorption cavities at six weeks after applying PVDF film. The number for the portion covered by PVDF (H_1) is larger than that for uncovered (H_2). The number for the portion covered by non-electret film of Teflon (PTFE) is very small, which is a control experiment. Similar effects are observed for the mandible.

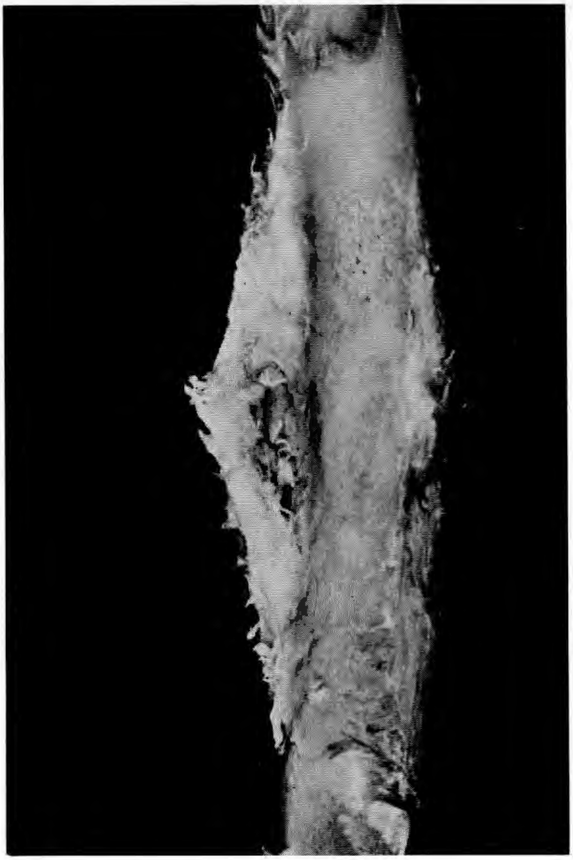

Figure 11-22. Photographs taken six weeks after PVDF film was placed on the femur of monkey. Courtesy of Dr. H. Suzuki.

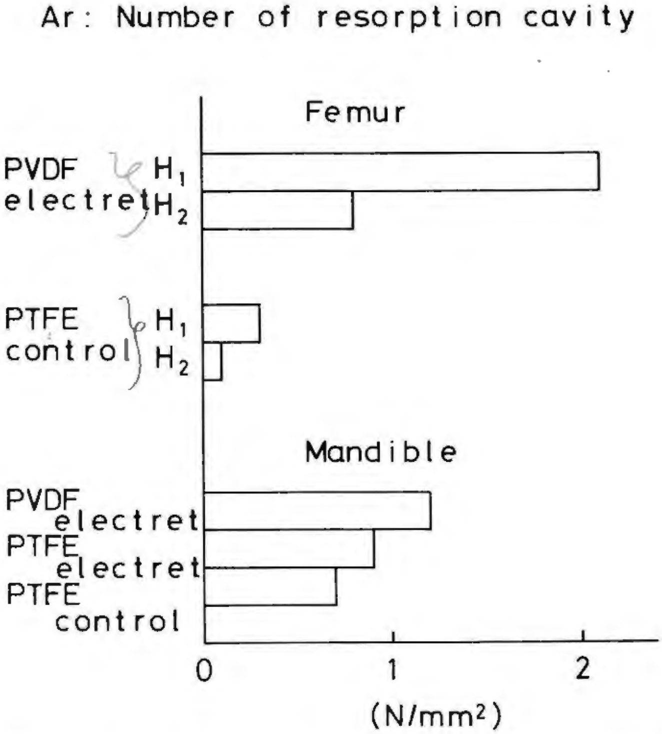

Figure 11-23. The number of resorption cavities six weeks after applying PVDF film on femur and mandible of monkey. Courtesy of Dr. H. Suzuki.

Figure 11-24 shows the number of secondary osteons. For the femur, the number with PVDF film is larger than that with non-electret Teflon film. For the mandible, PVDF and Teflon electrets also show larger effects than the control Teflon film.

Summarizing these experimental observations, we may conclude that the application of piezoelectric films onto bone has an effect to induce osteogenesis without producing any injury to bone. Since osteogenesis can be produced frequently by the foreign body reaction, one must be careful to make decisive conclusions. However, the comparison of the results with control experiments showed a significant difference.

Since the piezoelectric film is implanted in the body of the animal, the film must be surrounded by the tissue fluid, which is electrically conductive. Therefore the static surface potential of the electret film must be shielded by the adsorbed ions. However, when the piezoelectric film is mechanically deformed by the movement of animal, the piezoelectric polarization should be produced and this should cause the flow of ionic current surrounding the film. We assume that this ionic current may provide the stimulus to accelerate the proliferation of bone cells and their

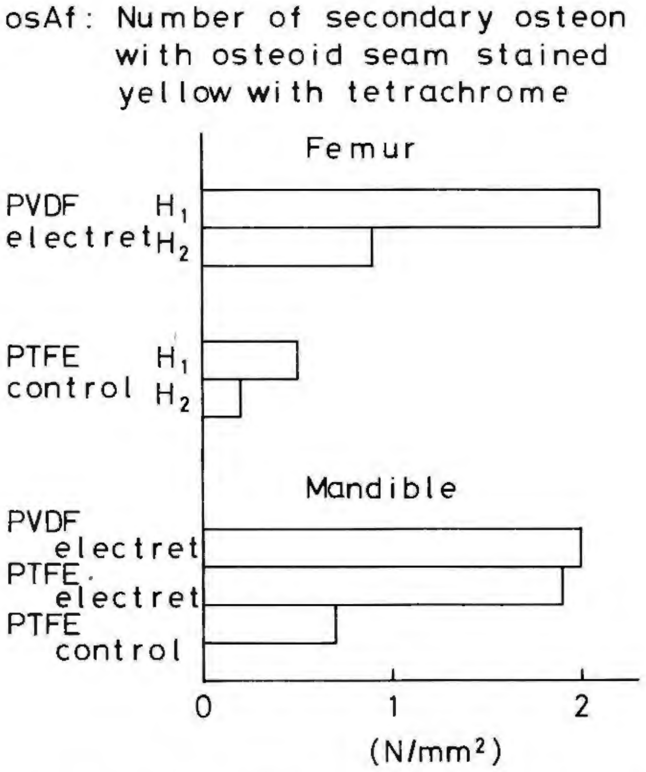

Figure 11-24. The number of secondary osteons six weeks after applying PVDF film on femur and mandible of monkey. Courtesy of Dr. H. Suzuki.

metabolic activity. The deformation of the film should be dynamic and the induced current should be fluctuating with irregular amplitudes. Such very small fluctuation of electric current or electric field appears to influence the activity of bone cells.

Figure 11-25 compares the magnitude of the piezoelectric activity of various substances. The vertical axis is electric polarization and the horizontal axis is the applied mechanical stress. The slope of the lines gives the piezoelectric constant. PMG and tendon have piezoelectric constants about ten times larger than that of bone, and PVDF film about one hundred times larger than that of bone. If the piezoelectric effect in bone is effective in controlling the growth of bone, it may be expected that the application of synthetic or natural polymer films with such large piezoelectric constants should also have an effect on the growth of bone.

A rough estimation can be made for alternating currents in body tissues. Tbe piezoelectric g-constant for PVDF film is about 300 mV/gram. The electrical capacity of the PVDF film may be assumed as about 1000 pF. The

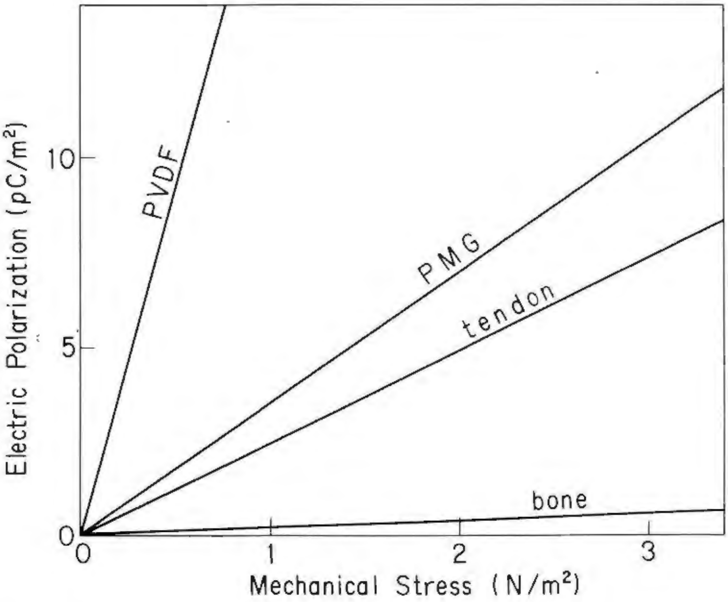

Figure 11-25. Comparison of the piezoelectric effect in bone, tendon, PMG, and PVDF.

film is short-circuited by resistance of tissues, which is roughly assumed to be 1 Megohm.

The equivalent circuit is given in Figure 11-26. The critical frequency of the circuit 1/RC is 1 kHz. If the angular frequency ω is low, the impedance of the circuit is mainly determined by the capacity. At an angular frequency of 100 Hz, the current I is calculated to be 0.03 μA/gram.

On the other hand, if the angular frequency is higher than the critical frequency, about 1 kHz, the impedance of the circuit is mainly determined by the resistance R. Then the current I is about 0.3 μA/gram.

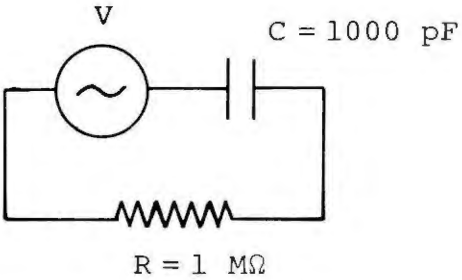

Figure 11-26. An equivalent circuit of PVDF film implanted in body tissues.

If the motion of animals causes a force of 10 grams, the current of 3 μA can be expected in angular frequencies higher than about 1 kHz. It is anticipated that the dynamic force acting on PVDF films may easily produce several microamperes at the high frequency range.

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