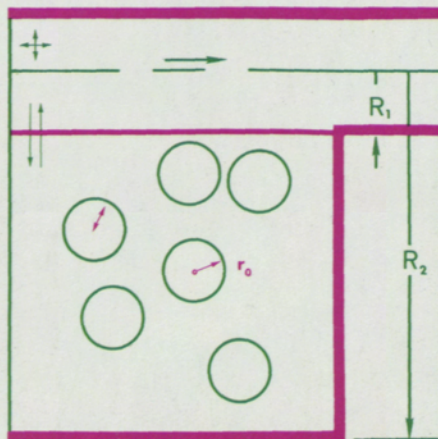
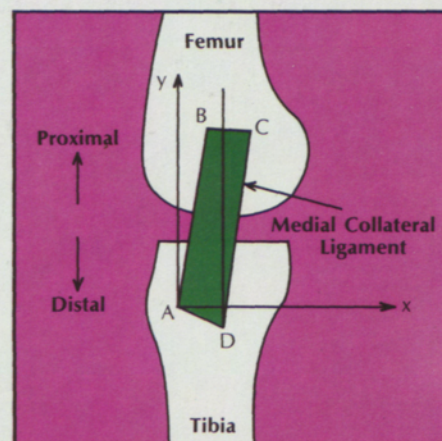
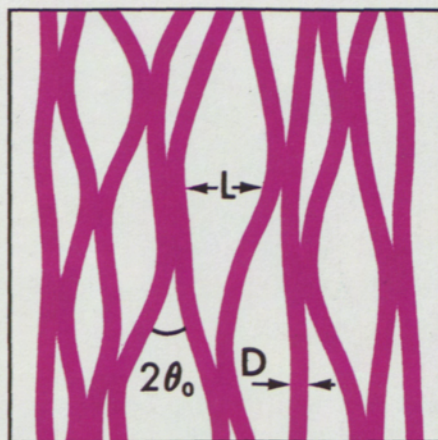
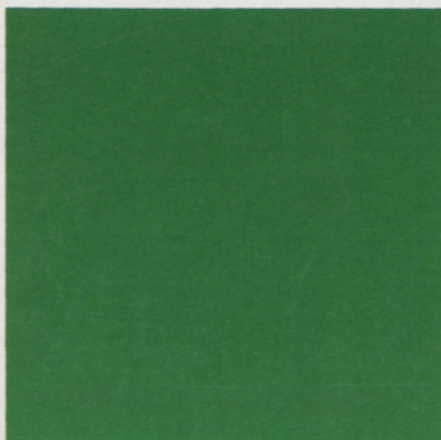


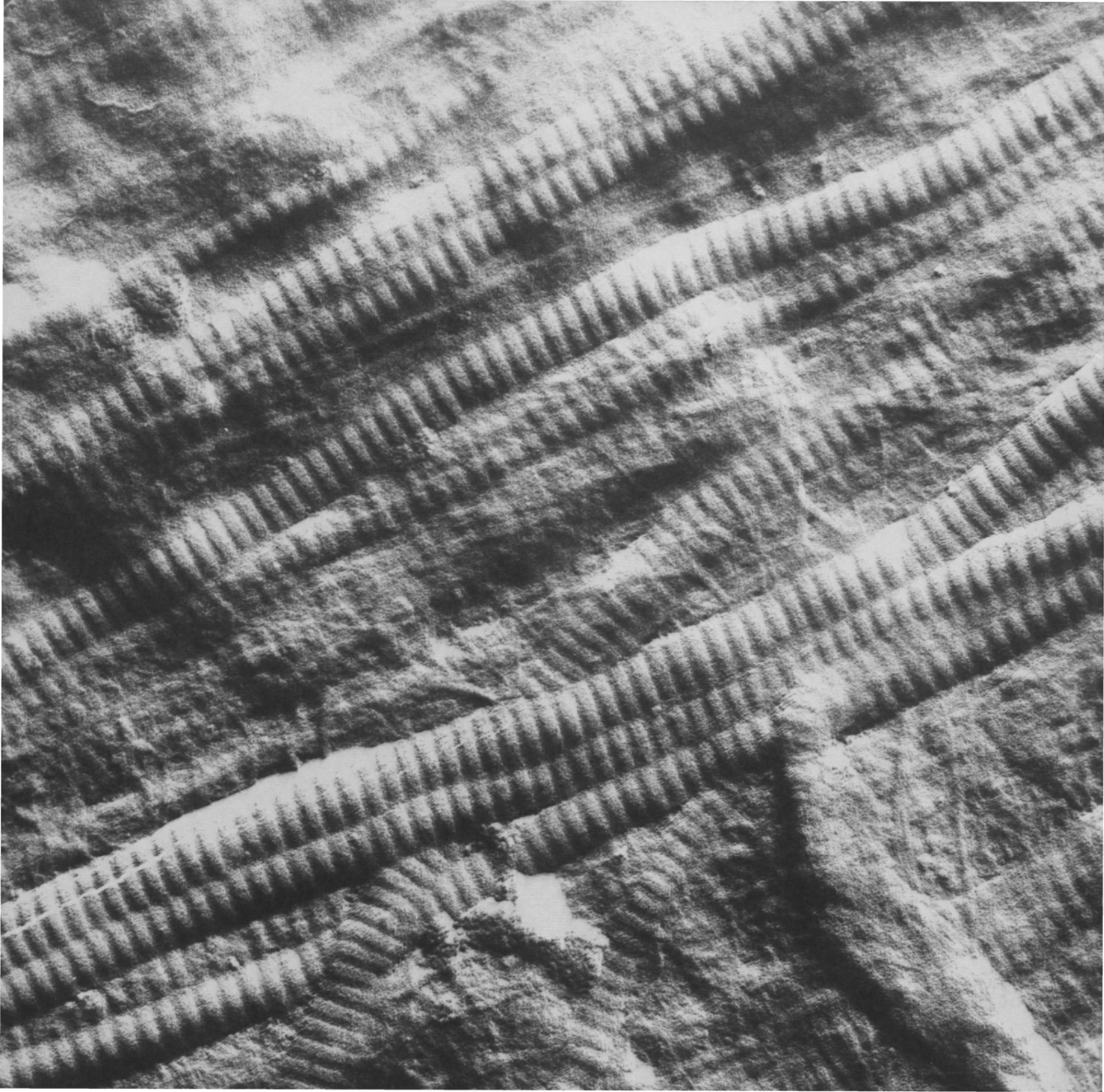
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MEDICAL USES
OF ENGINEERING
RESEARCH



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Pharmacokinetics, the mathematical description of drug distribution in the body, is one of the areas of bioengineering research that are opening up to engineers. Kenneth B. Bischoff, director of Cornell's School of Chemical Engineering, discusses his research, including work on an anti-cancer drug, conducted in collaboration with the National Institutes of Health.

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Opposite: An electron micrograph showing collagen fibers in a kidney machine membrane. The specimen is a platinum-shadowed carbon replica.



MECHANICAL ANALYSIS AND DESIGN IN ORTHOPEDICS

by Donald L. Bartel

The musculo-skeletal system is a complex mechanism which supports and positions the body; and the skeletal system, like any machine, is subject to wear and failure. In many cases, the damage may be repaired or prevented by surgical modification—and this raises a number of interesting engineering questions. How does the normal system work? What are the mechanical properties of bone, ligament, and tendon? What are the mechanisms of damage or injury? How will surgical modifications change mechanical function? What is the effect of replacing a natural joint with a simpler mechanical joint? How are joints lubricated? Can surgical modifications be identified which will optimize mechanical function?

These and many other questions have been of special interest to engineers and physicians during the past ten years. They provide at least three challenging problem areas for the engineer. First, there is the analysis of the skeletal system and components in order to achieve an understanding of the structure and function of normal,

impaired, and reconstructed systems. Second, there is the experimental determination of the mechanical properties of tissue and implants, and the experimental analysis of the system as a whole. Finally, there is the application of analysis and experiment to the design of improved implants, tissue-implant systems, and surgical procedures.

At Cornell, research in this area of biomechanics has been in progress for the past four years. At the present time, the combined efforts of Cornell engineers, physicians, and veterinarians are being directed toward three specific areas of research in orthopedics: knee mechanics, bone-implant systems, and disorders of the locomotor system.

STUDIES IN THE MECHANICS OF THE KNEE JOINT

The knee is the most frequently injured joint in the body. Consequently, the mechanical analysis of the knee is of great importance in orthopedic work. It is needed for understanding how the knee resists external loads, and for deciding what reconstructive surgical pro-

cedures would produce the best results.

The motion of the knee is constrained by the joint surfaces, by the knee cartilage, and by ligaments, which function as nonlinear springs that stiffen as they are stretched. The motion is three-dimensional, and as the knee is flexed, the axis of rotation changes. This movement of the axis is evident even when the knee is approximated as a plane mechanism, as shown in Figure 1.

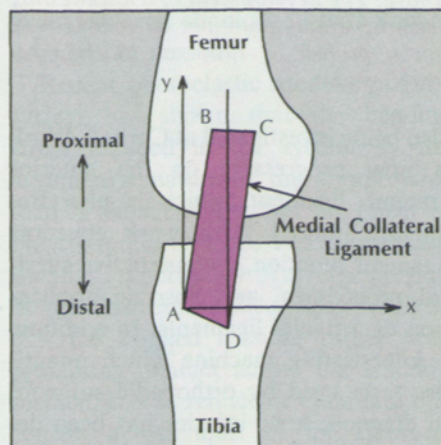
Loads applied to the knee are resisted by forces generated in the muscles, cartilage, and ligaments as the joint is distorted. Excessive loads may rupture a ligament or fracture the bone at the bone-ligament interface. In athletic injuries, for example, the medial collateral ligament (see Figure 1) is frequently damaged. Some of these injuries produce slack in the ligament and therefore looseness in the joint, a condition that can be corrected surgically by relocating the proximal attachment on the femur (BC in Figure 1) or the distal attachment on the tibia (AD in Figure 1).

In some recent studies of ligament deformation in the flexing knee, the

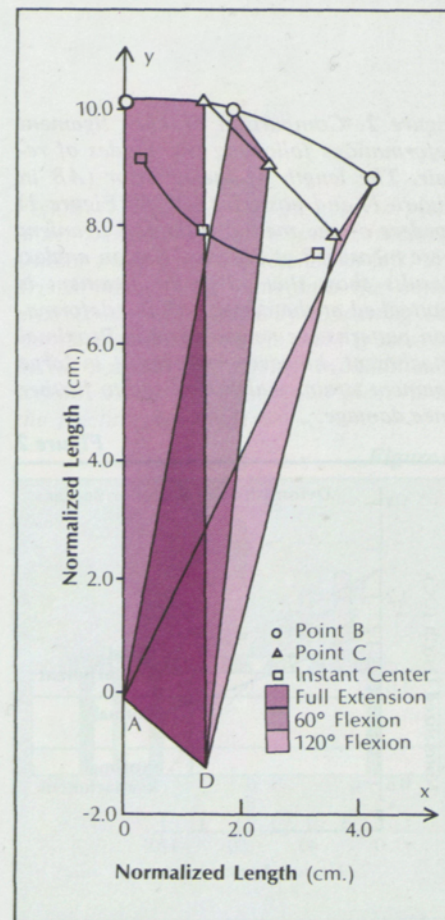
Figure 1. The medial collateral ligament of the knee (below) and its deformation (right). Looseness in this ligament, a frequent athletic injury, may be treated surgically by relocating the attachment on the tibia or the femur. Cornell studies have resulted in the reevaluation of surgical procedures.

ligaments were considered to be single fibers with specific points of attachment on the tibia and the femur. Studies by Dr. John Marshall and his colleagues at the Hospital for Special Surgery in New York City have shown, however, that changes in length of the anterior border, AB in Figure 1, and in the distance AC are quite different. The anterior border first lengthens and then shortens as the knee flexes; the distance between points A and C decreases only. As a result of this finding, an investigation was initiated by our mechanical engineering group in collaboration with Dr. Marshall, to study the behavior of the anterior and posterior borders—AB and DC, respectively. Strains in normal and relocated ligaments were analyzed, and the results of this analysis were then used to evaluate reconstructive surgical procedures.

Measurements of the ligament borders after reattachment of a slack ligament (see Figure 2) show that if the ligament is tightened by moving the distal attachment more distal, then the maximum length changes for both the



anterior and posterior borders are about the same as those that occur with a normal ligament. However, if the ligament is reattached proximally when the knee is in full flexion (a common surgical procedure), then the anterior border must stretch about four times as much as normal and the posterior border must stretch about twice as much as normal. Our study showed, therefore, that tightening of the long fibers of the medial collateral ligament should be accomplished by distal reattachment. The results imply that if the ligament



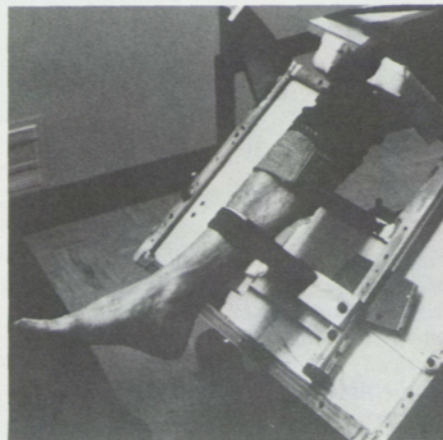
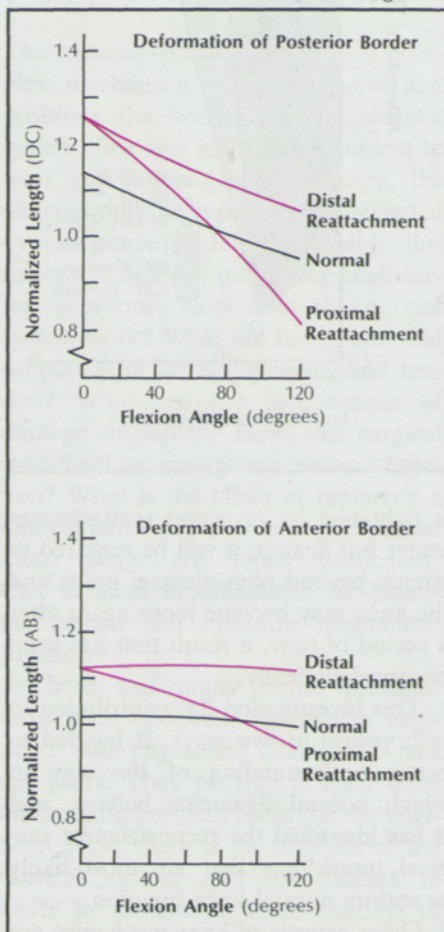
is tightened by proximal reattachment under full flexion, it will be required to stretch beyond physiological limits and the knee may become loose again after a period of time, a result that has been observed clinically.

This investigation has contributed to orthopedics in two ways. It has led to better understanding of the way in which normal ligaments behave, and it has identified the reconstructive surgical procedures that are most likely to restore normal knee function.

Other aspects of knee mechanics are

Figure 2. Comparison of knee ligament deformations following two modes of repair. The length of the anterior (AB in Figure 1) and posterior (DC in Figure 1) borders of the medial collateral ligament were measured at different flexion angles. Results show that when the ligament is reattached at the distal end, the deformation patterns are nearly normal. Proximal attachment, however, can result in large ligament strains which can lead to further knee damage.

Figure 2



Above: The development of a knee-testing machine which quantifies diagnostic tests was a project of Professor Bartel's research group.

also being investigated at Cornell. Work is now progressing on the anterior cruciate ligament, which is also frequently injured. This work concerns ligament function, reconstructive surgical procedures, and possible application of artificial ligaments. In addition, a knee-testing machine which quantifies tests used by orthopedic surgeons to diagnose knee injuries has been developed in conjunction with the Department of Physical Therapy at Ithaca College.

Force-deflection measurements made with this knee-testing machine can be used to evaluate the success of surgical procedures and to screen athletic teams in order to identify individuals who are predisposed to knee injuries. So far, data have been obtained for a number of Cornell athletes. These data, combined with information from anatomical studies, also provide estimates of the distribution of forces among the internal structures of the knee.

Figure 3. The use of implants to repair the skeletal system. Plates such as those diagrammed at left are used to provide internal fixation in the treatment of fractures. Joints are replaced by metal and plastic components cemented to the bone, as shown in the diagram of the hip joint replacement at right. This replacement includes a metal head (circular), shoulder, and stem extending into the femur. A plastic cup is adjacent to the head. Steel parts are shown in grey, plastic in light magenta, cement in dark magenta, and bone in white.

Right below: A radiograph showing the hip joint replacement.

THE DEVELOPMENT OF BONE-IMPLANT SYSTEMS

Orthopedic surgeons implant a wide range of devices for repair and replacement of bones and joints. Figure 3 shows two common applications—bone plates, used for internal fixation of fracture, and artificial joints, used to replace damaged joints.

In recent years, the internal fixation of fractured long bones has become increasingly common, particularly in cases of delayed union of the fracture. The technique, as it is currently practiced, involves the introduction of tension into the fixation plate in order to induce compression in the bone. This is based on studies which suggest that the application of mild compression may promote faster bone healing.

The basic technique is to fasten a single plate across the bone fracture under tension. After one or more screws have been driven into one of the bone segments to fasten the plate to that segment, a device such as that shown in Figure 4 is used to induce tension in the plate. The plate is then fastened to the other bone segment and the device

Figure 3

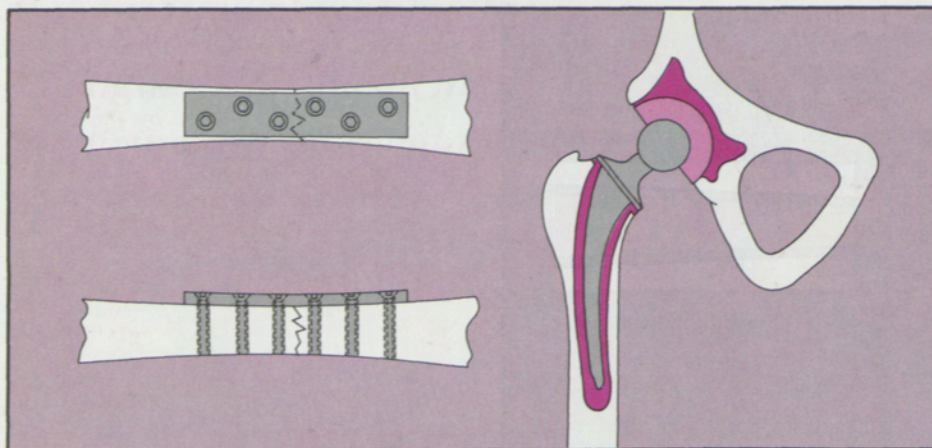
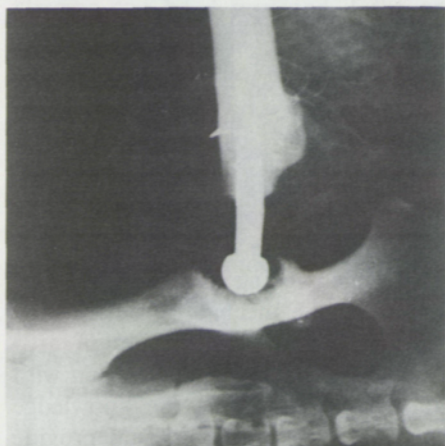


Figure 4. A device used to apply a plate under tension across a bone fracture. One or more screws (sketched at left) are driven through the plate into the bone; after tension is applied by tightening the clamping mechanism, the plate is secured in its position by driving in additional screws. The plate remains in place until the fracture has healed.

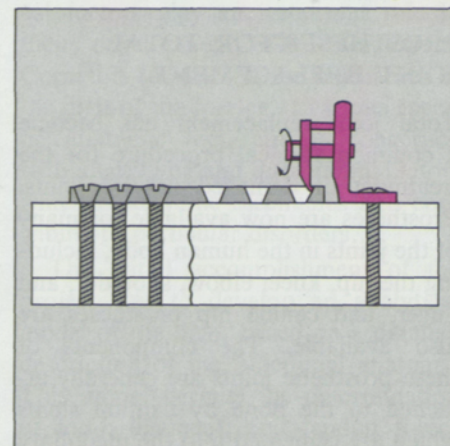
Figure 4



What material should be used? Should it be stiff or flexible?

Recent photoelastic modeling of the system has shown that the bending stress induced in the system by the asymmetric nature of the compressive load is sufficient to offset the effect of the compressive load, and causes distraction (separation) of a large portion of the fracture surface. The result is that the applied tension, rather than promoting contact across the fracture surface, acts to reduce or eliminate this contact across most of the fracture, while inducing extremely large compressive stresses across the portion that remains in contact.

At Cornell, a series of computer experiments, using a two-dimensional finite element model, were performed to further investigate this bone-implant system and to answer some of the design questions posed. Our results support the basic premise that application of tension in the fixation plate induces bending moments which may lead to distraction of the fracture surface. Furthermore, the study shows that irregularities in the bone-plate system, even



very slight ones, have a significant effect. In fact, the overall stress field in the bone appears to be determined primarily by the way the plate is attached. The application of tension cannot increase either the area or the level of compression across the entire fracture site, and it may actually reduce or eliminate compression in some regions. Another finding of our study is that the use of a plate material whose elastic modulus is equal to that of bone—a procedure that has been proposed—actually exaggerates distraction.

is removed. After the fracture has healed, the plate is removed; screw holes left in the bone eventually become filled with new bone. The purpose of the procedure is to accelerate healing and permit the injured limb to return to normal function as soon as possible. A stiff joint, which may result from immobilization by an external cast, is avoided.

A number of engineering questions arise. How effective is the plate in producing compression at the fracture site?

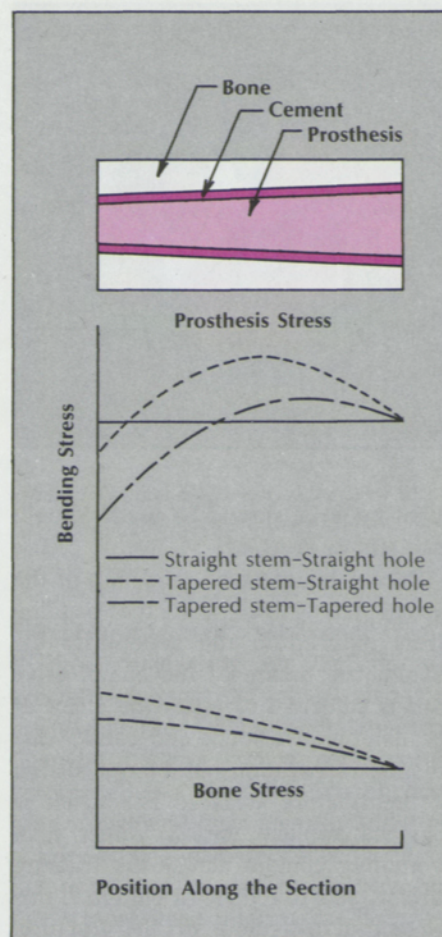
5 What should the shape of the plate be?

Figure 5. Biomechanical analysis as an aid in the design of prosthetic devices. Stresses in the bone and in an implanted prosthesis vary according to the shapes of the fixation stem and the medullary cavity. Such information is used to determine prosthesis geometry and to specify surgical procedures.

PROSTHESES FOR TOTAL JOINT REPLACEMENT

Total joint replacement has become a common surgical procedure for the treatment of damaged natural joints. Prostheses are now available for many of the joints in the human body, including the hip, knee, elbow, shoulder, and finger, and canine hip prostheses are also available. The components of these prosthetic joints are generally attached to the bone by fixation stems which are cemented into the medullary cavity. The total hip replacement shown in Figure 3 is an example of this arrangement. The loads at the joint are transmitted from the prosthesis to the bone through the cement.

Considerable attention has been given to questions of biocompatibility in the use of artificial joints, and also to problems of friction and wear. Little work has been done, however, on the mechanical compatibility of bone-cement-prosthesis systems. Prosthetic joints have been implanted mostly in older individuals, and in such cases, the risk of mechanical failure is not



high because the life expectancy is limited and because the loads applied to the system are generally less than those which might be applied by a younger person. As implants are used in younger, more vigorous patients, the question of long-term mechanical stability is becoming a serious one.

At Cornell, work in this area is proceeding on several fronts. Canine total hip replacements, designed at Cornell (see the Summer 1974 issue of this magazine), are being implanted and evaluated clinically by Dr. R. Dueland

of the Small Animal Medicine and Surgery Clinic of the Veterinary College. One purpose is to extend the working life of seeing eye dogs which develop hip dysplasia. A second goal is to verify analysis and design procedures which apply to human joints as well.

The lubrication of natural and artificial joints is being studied by John F. Booker of the mechanical engineering faculty. Since the lubrication of artificial joints is poor in comparison with that of natural joints, the knowledge gained in this research should provide guidelines for improved design of joint replacement, as well as increased understanding of the mechanisms of lubrication.

The mechanical stability of artificial joint fixation is being studied by analyzing the stresses developed in the joint components. The bone-cement-prosthesis system forms a three-material composite beam which resists bending and compressive loads. The strength of this composite system depends upon the strength of the individual components and the amount of load carried by each. In a one-material beam, the

*“... personnel and facilities
in engineering, medicine, and veterinary
medicine are all available.”*

stresses can be determined if the applied loads and the geometry of the beam are known; but in order to compute the stresses in a composite beam, the material properties of the components must be known also. A detailed stress analysis is difficult and requires the use of the finite element method; however, a simple model of the system, based on beam theory, can provide a great deal of useful information.

A sectional view of a prosthesis stem in bone (in this case, a tapered stem in a tapered hole) is shown in Figure 5. The graphs in the figure show how the bending stresses vary along the length of the section for three different stem-hole designs. These graphs show that if the stem of the prosthesis is tapered, the maximum stress in the bone will occur near the tip of the stem, and the maximum stress in the stem will occur somewhere away from the tip. These predictions are supported by clinical observations of where breaks occur in the event of system failure. A further conclusion drawn from the Figure 5 data is that if the stem is

ered to fit, for this tends to reduce the stress levels in both bone and stem.

This is an example of how a biomechanical analysis of a system and knowledge of materials properties can be valuable aids in designing a prosthetic device and in deciding on a surgical procedure. In the first case, information about the effect of tapering the stem is provided; in the second case, information concerning the preparation of the medullary cavity is obtained.

DISORDERS OF THE LOCOMOTOR SYSTEM

The horse, which is subject to many disorders of the locomotor system, is being studied in Cornell research on this aspect of orthopedics. Locomotor disorders in horses, including degenerative joint disease, fractures, tendon or ligament stress injuries, and bursitis, appear to be identical to counterpart disorders in man. The etiology of these conditions in the horse—or in man—is not known, but they are usually associated with stress due to physical activity, and most observers agree that mechani-

cal factors play an important role in their development. The research at Cornell is focused on the mechanics of the digit of the foreleg at various specific anatomic loci, and is concerned with identifying and quantifying factors which modify the mechanics and contribute to particular disorders.

The initial accomplishment of the project was to develop an analytical model of the digit, based on a detailed description of the functional anatomy. This model permits the determination of joint, ligament, and tendon forces as functions of time during the support phase of gait (heel contact to toe off). In addition, the model can be used to describe the displacements of tendons and ligaments due to configuration and load. Forces and displacements are computed from the model given (1) the kinematics of gait, (2) the external forces on the hoof, (3) the geometry of the anatomic structures of the digit, and (4) the physical properties of the tendons and ligaments involved.

The kinematic description of gait is obtained from a high-speed cinefilm of the digit of the horse during the walk,

Figure 6

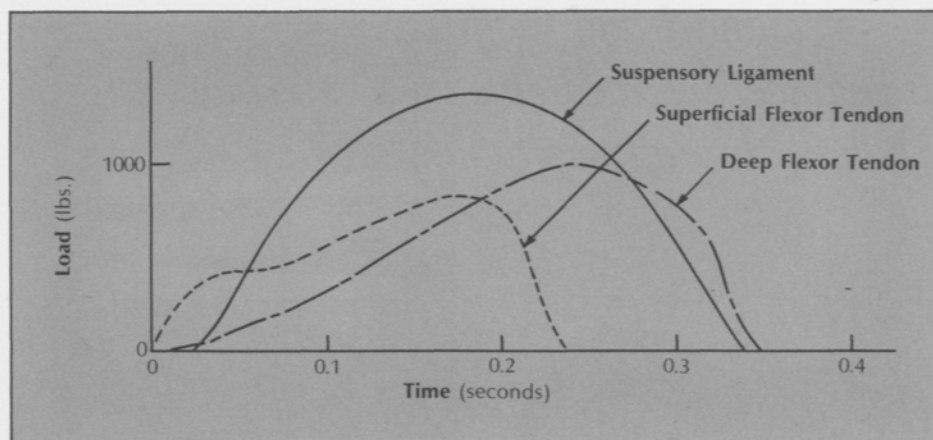
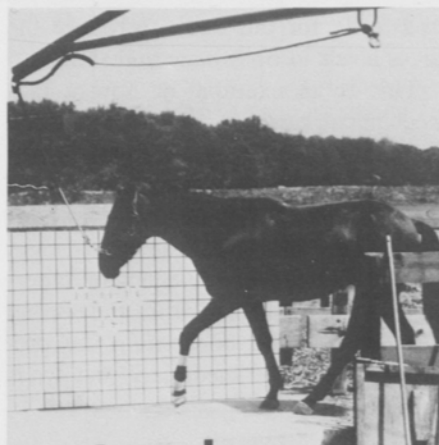
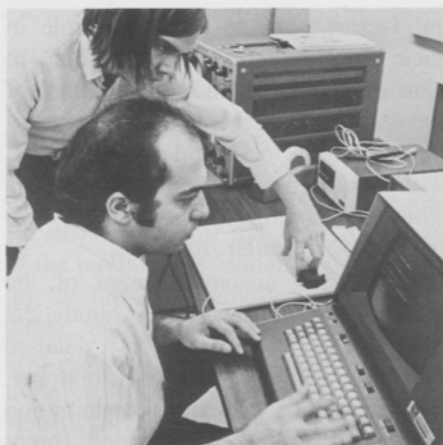


Figure 6. The use of an analytical model to determine the forces and displacements in the digit of the horse. Forces in the suspensory ligament and the extensor tendons are shown here for a walking horse. Similar measurements can be made for other gaits, and for horses with locomotor disorders.



Left: A gait analysis facility is located at Cornell's Equine Research Park.

Far left: Noshir A. Langrana, assistant professor of engineering basic studies, and senior student Dexter Dyer (standing) digitize force plate data for calculation of the external force on the hoof.

trot, or gallop. Anatomic landmarks on the digit are labeled with paste-on markers, and the spatial coordinates of these landmarks are determined, with use of a computer and a digitizing tablet, from frame-by-frame projections of the film. The coordinates provide input to a computer program which is used to determine digit configuration (joint angles) as a function of time during the support phase of gait. The external force on the hoof is obtained from force plate measurements. Digit geometry in terms of bone lengths, joint

angles, and the location of certain tendons and ligaments is determined from radiographs. The physical properties of important tendons and ligaments are obtained at necropsy in the biomechanics laboratory in the new Veterinary College Research Tower.

The analysis procedure is to use the data obtained from gait analysis and necropsy studies as input for the computer model of the digit. So far, the method has been used to analyze the forces and displacement in a walking horse (see Figure 6) and in a galloping

horse. The primary advantage of this model is that forces in specific joint components can be computed along with the resultant force and moments at the joint. Consequently, a history of how the mechanics of the digit changes as either inherent or induced disorders progress can be constructed from the data obtained from a series of gait analyses. In our project, such a history will be used to establish a relationship between the mechanical factors and the development and progression of various disorders.



Collaborating in the project on disorders of the locomotor system in the horse are Professor Bartel (center), and John E. Lowe (left) and Herbert F. Schryver of the Equine Research Program. The laboratory is in the new Veterinary College Research Tower.

BIOMECHANICS RESEARCH AS A COOPERATIVE PROJECT

Because of the interdisciplinary nature of research in biomechanics, a strong program depends upon the development of significant relationships between mechanical engineering specialists and individuals who have access to clinical and other special facilities. It also requires support from diverse sources. Our research on locomotor disorders, for example, is being done in collaboration with Herbert F. Schryver and John E. Lowe of the Equine Research Program, which is sponsored jointly by the College of Agriculture and Life Sciences and the Veterinary College. Significant internal support has been provided by the Sibley School of Mechanical and Aerospace Engineering for the development of laboratory and gait analysis facilities, and external funding has been obtained from the National Science Foundation. The work on bone-implant systems involves cooperative relationships with Peter S. Walker, director of bioengineering at the Hospital for Special Surgery, as well as with Dr. Dueland

of the Veterinary College. The clinical aspects of this work are being supported by the Seeing Eye Foundation, and the engineering aspects by the National Science Foundation. The study of knee mechanics, developed by our group in cooperation with Dr. Marshall of the Hospital for Special Surgery, has also involved H. H. Merrifield of the Department of Physical Therapy at Ithaca College.

This work is still in its beginnings. Just within the past year, the biomechanics laboratory has been opened at the Veterinary College, the gait analysis facility has been established at Cornell's Equine Research Farm, outside funding has been obtained, and a number of studies have produced interesting and significant results.

Because personnel and facilities in engineering, medicine, and veterinary medicine are all available, Cornell offers an unusual opportunity for pursuing interdisciplinary research in biomechanics. A unique program for the study of biomechanical problems of concern in both animals and man is developing.

Donald L. Bartel has developed an active research and teaching program in biomechanics since he joined the Cornell mechanical engineering faculty in 1969 as an assistant professor. In addition to conducting and directing graduate research in biomechanics, including human and animal orthopedics, he has initiated several upperclass and graduate courses in this area.

Since 1971, Bartel has served as a consultant in biomedical engineering for the Burke Rehabilitation Center, an affiliate of the Cornell Medical School, and has established cooperative programs with members of the New York State Veterinary College at Cornell, the Hospital for Special Surgery in New York City, and the Ithaca College physical therapy group.

Bartel studied for the B.S. and M.S. degrees in mechanical engineering at the University of Illinois, Urbana, and for the Ph.D. in mechanics and hydraulics at the University of Iowa. He has served as assistant professor in engineering at Black Hawk College in Illinois, as an instructor in mechanics and hydraulics at Iowa, as a researcher and consultant for Deere and Company of Moline, Illinois, and as researcher and consultant in orthopedics at the University of Iowa hospitals.

He is a member of the Orthopaedic Research Society, the American Society of Mechanical Engineers, and Sigma Xi.

YOU CAN MAKE AN ARTIFICIAL KIDNEY OUT OF A COW'S HIDE

by James F. Stevenson

Joint medical and engineering research at Cornell is developing ways to transform a natural substance found in cattle hides into medically valuable biomaterials. Collagen, a major structural protein in the connective tissue of animals, shows promise of becoming highly useful for such applications as membranes for the artificial kidney, a controlled drug-release device for the treatment of glaucoma, corneal grafts for the eye, and wound and burn dressings.

This project requires the cooperative efforts of medical specialists and engineers. Involved in the work, which is supported by the National Science Foundation, are staff members of the Cornell Medical College in New York City, and a number of College of Engineering professors, research associates, and graduate students in the Department of Materials Science and Engineering and the School of Chemical Engineering. The project director is Albert L. Rubin, M.D., and the principal investigators are Kurt H. Stenzel, M.D., and Herbert H. Johnson, professor of materials science and engi-



neering and director of the University's Materials Science Center, who is coordinating the work on the Ithaca campus.

THE ADVANTAGES OF A NATURAL PRODUCT

For the past several years, Rubin and Stenzel and their coworkers at the Medical College have been intrigued by the potential benefits of making medical products out of collagen as an alternative to synthetic plastics, metals, or cellulose. Collagen is readily avail-

able, for it constitutes 20 to 30 percent of total animal protein, being especially prevalent in skin, hoofs, tendon, and bone. More important are the advantages for physiological applications that collagen offers: it has a normal protein structure (see Figure 1), it is biodegradable in a controlled way without release of toxic products, and it can be implanted in biologic systems without evoking severe immunologic reactions.

But how does one take a complex and sensitive biomaterial like collagen and reconstitute it on a large scale into medical products? Boiling the connective tissues of animals is an old method for preparing denatured, hot-water-soluble collagen; however, the product obtained—gelatin—is not a very exciting biomaterial, although it can be made into a tasty dessert.

A more sophisticated technique, developed during the 1960s by Drs. Tomio Nishihara and Teruo Miyata at the Japan Leather Company, is to solubilize (but not denature) the collagen found in calf skin by use of a proteolytic enzyme. After further purification, this highly viscous, enzyme-soluble col-

“... collagen can be used in new and significant ways to promote physical well-being.”

lagen can be cast into films or extruded, and then crosslinked to improve its mechanical properties. One application of extruded material, for example, is the preparation of collagen tubes of very small diameter, known as hollow fiber membranes.

The development of methods for processing and fabricating collagen opened up several new directions for research. In 1972 the interdisciplinary program of the Cornell engineering and medical colleges was initiated to consider the interrelations among (1) the

physical properties and (2) the structure of collagen; (3) methods of processing collagen; and (4) the clinical performance of collagen-based medical products. Several examples of the research conducted at the College of Engineering are described in this article.

CONNECTIONS BETWEEN STRUCTURE AND PROPERTIES

To provide a conceptual link between the structure and the physical properties of crosslinked enzyme-soluble collagen, Professor Edward J. Kramer of

the Department of Materials Science and Engineering and his research associate, Dr. R. K. Viswanadham, have devised a model (see Figure 2) which explains many of their experimental observations.

If the model is correct, one would predict that the pressure-driven flow rate of water (a very sensitive measure of pore size) across a collagen membrane would decrease rapidly as the collagen is stretched in the extrusion direction. This prediction is confirmed by the data shown in Figure 3. The

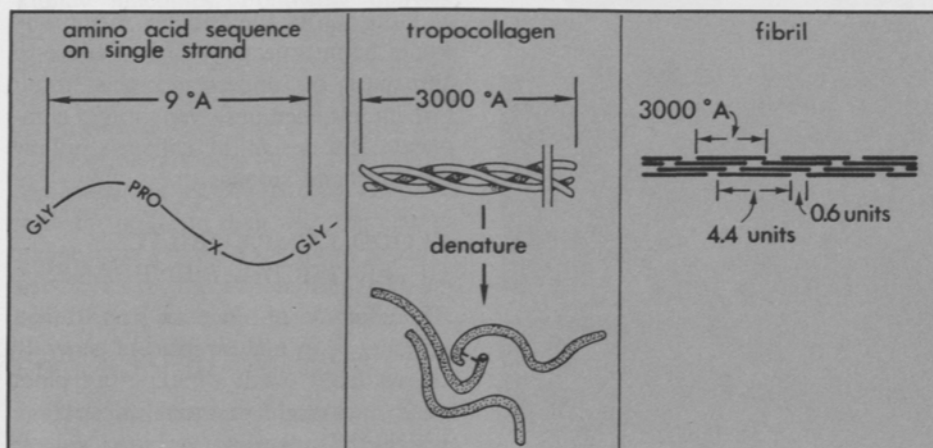


Figure 1. Schematic drawings showing the structure of collagen. Left: A single strand of collagen showing a typical amino acid sequence. Center: Three strands wound around each other to form a triple helix known as tropocollagen. Right: Tropocollagen molecules joined in a quarter stagger array to form fibrils. Staggering the tropocollagen molecules, like bricks in a wall, is evidently nature's way of increasing the tensile strength of the fibrils.

Figure 2

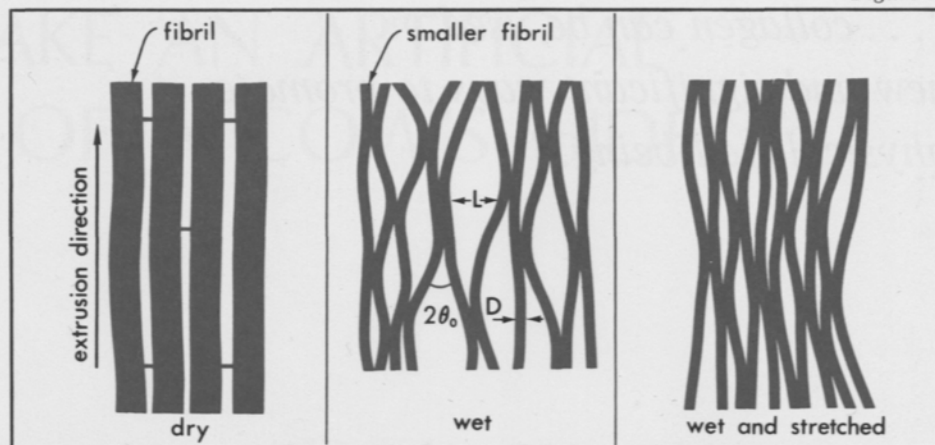


Figure 3

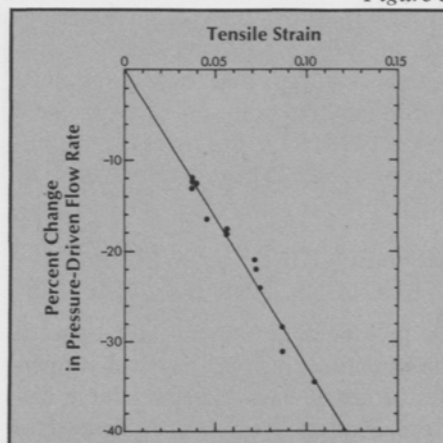


Figure 2. Model of an enzyme-soluble collagen membrane. Left: X-ray scattering measurements on dry collagen show that fibrils (bundles of tropocollagen molecules) are oriented in the extrusion direction. Center: Upon wetting, collagen swells to four times its dry volume but contracts slightly in the extrusion direction. X-ray scattering measurements show that new pores open up and have the approximate dimensions, as labeled in the schematic, of $L = 160 \text{ \AA}$, $D = 60 \text{ \AA}$, and $\phi_0 = 17\text{--}18^\circ$. Right: Stretching the wet collagen in the extrusion direction decreases the effective radius of the pores.

Figure 3. The effect of tensile strain on the pressure-driven flow rate of water across a collagen membrane. These measurements, made in Professor Kramer's laboratory, substantiate the model shown in Figure 2: Pore size in the collagen membrane would be expected to diminish as the fibrils are stretched, so that under conditions such that the pressure difference is constant, there would be a decrease in flow rate as tensile strain increased.

Right: Dr. R. K. Vaswanadham, research associate working with Professor Kramer, uses the Statton camera to measure small angle x-ray scattering from collagen hollow fibers.



model is also consistent with the observed shape of the stress-strain curve for collagen at various values of the relative humidity.

Once the model is shown to be reliable, it can be used to predict the performance of collagen membranes under a variety of conditions. For example, the pressure exerted by flowing blood on a tubular collagen membrane in the artificial kidney would tend to cause the membrane to contract instead of stretch. This contraction of the membrane would increase the effective pore size, and the pressure-driven flow rate of fluid across the tubular membrane would be unexpectedly high. Failure to anticipate or understand this result (which has been observed) might complicate the design of collagen hollow fiber artificial kidneys.

BLOOD COMPATIBILITY OF ARTIFICIAL MEMBRANES

The adhesion of blood cells to artificial surfaces is an undesirable but generally unavoidable result of exposing blood to a man-made material. A study in which the adhesion of blood cells is

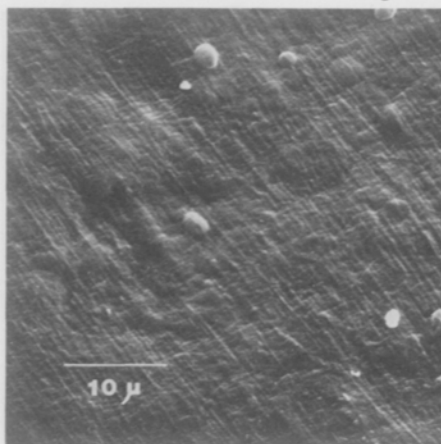
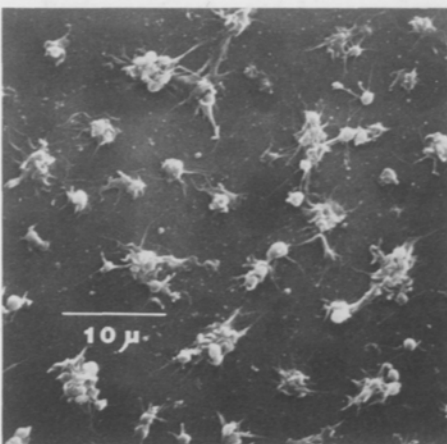


Figure 4

Figure 4. Scanning electron micrographs of flat membranes following a thirty-minute exposure to flowing dog blood. Left: Cuprophane membrane with adhering platelets (small particles) and leucocytes (large particles). Red blood cells do not adhere to any significant extent. Right: Collagen membrane showing less adhesion of blood cells. This membrane contains both enzyme-soluble collagen and collagen fiber dispersion. (Specimens prepared by Janice Z. Clark.)

used as an index of the blood compatibility of various membrane materials is being conducted at Cornell by Professor Dieter Ast of the Department of Materials Science and Engineering and his research associate, Dr. Abraham Schwartz, in collaboration with several investigators at the Medical College.

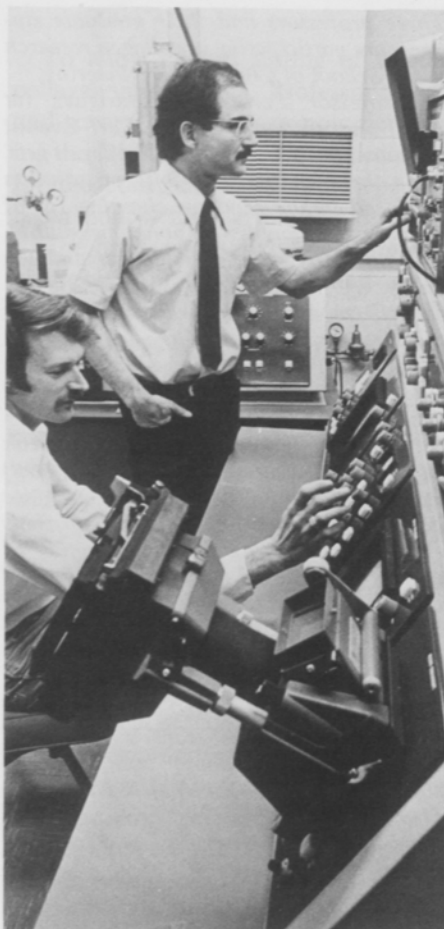
For example, in one experiment at the Cornell Medical Center, large dogs were connected to artificial kidneys containing flat membranes of either collagen or commercial Cuprophane, the material now used in most artificial kidney machines. Following dialysis, sections of the membranes were removed and studied under a scanning electron microscope at the College of Engineering. A comparison of the two kinds of membranes showed that much less adhesion of blood cells occurred with the collagen than with the Cuprophane (see Figure 4). Future research will focus on the explanation and significance of these observed differences.

COLLAGEN IN THE BODY

In the fabrication of artificial blood vessels, corneal grafts, and burn dress-

ings, the tear strength (for suturing) and elastic properties of collagen are extremely important. Professors Ferdinand Rodriguez and George Cocks and graduate students Gary Hamed, Carl Zvanut, and Richard Weissman in the School of Chemical Engineering have been studying the effects of the cross-linking agent, exposure time, composition, pH, and temperature on the elastic properties of collagen gels.

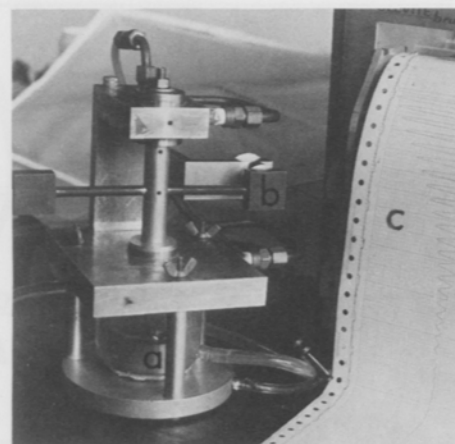
In a typical experiment, a viscous collagen solution is placed in a combination reaction chamber and "gel jiggle," known as a torsional pendulum (see the photograph). In this device, the elastic properties of collagen gels are monitored continuously while the collagen is crosslinked by ultraviolet or gamma radiation or by a chemical reaction with glutaraldehyde. By this process, the collagen is transformed from a viscous liquid into an elastic gel. Since overexposure of collagen gels to radiation causes chain scission and loss of elasticity, one useful result of this work is the determination of optimum radiation time for producing maximum elastic properties.



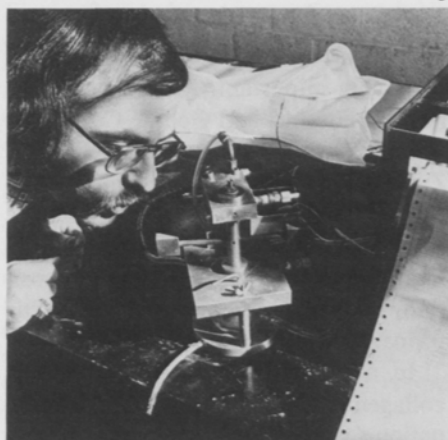
Left below: Dr. Abraham Schwartz (seated) and Professor Dieter Ast use the scanning electron microscope.



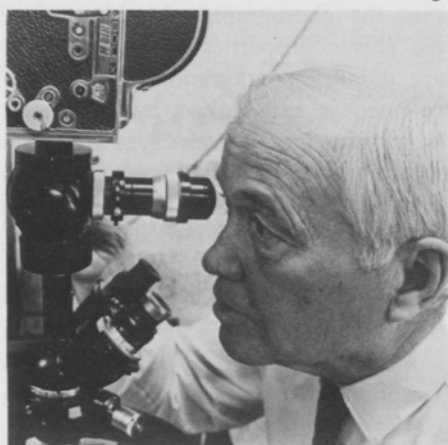
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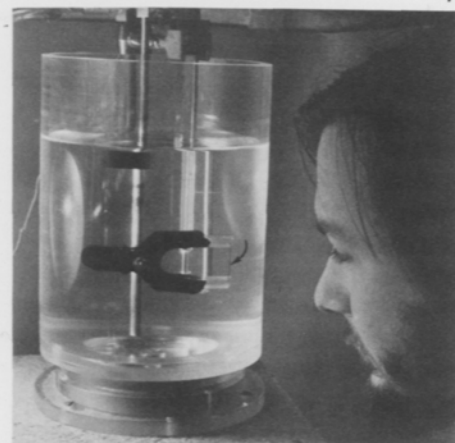
Three professors and their graduate students are participating in collagen research at the School of Chemical Engineering.

1. Professor Ferdinand Rodriguez (at right) and graduate student Carl Zvanut measure elastic properties of collagen gels.

2. In these studies, the collagen solution is placed in the reaction chamber (a) of a nearly frictionless torsional pendulum. The arms (b) are set in motion and the decay of the oscillatory motion is recorded (c). The decay rate decreases as the elastic properties of the gel increase.

3. Richard Weissman, a graduate student, is about to start an experiment by puffing gently on the arms of the pendulum.

4. Graduate student Mike Von Deak checks the alignment of a (simulated) stationary hollow fiber membrane (see arrow) in a rotating cylindrical bath. This experiment is part of an investigation of tubular collagen as a membrane material for the artificial kidney.



4

Figure 5



Professor Cocks and his associates are also looking for relations between the mechanical properties and the microstructure of collagen gels and membranes. In this work, freeze-etching techniques are used to prepare radiation crosslinked gels for study under the electron microscope.

THE HOLLOW FIBER ARTIFICIAL KIDNEY

Other projects at the School of Chemical Engineering are concerned with the possible use of extruded tubular collagen in the preparation of artificial kidney membranes. The material is prepared at the Japan Leather Company by extruding and crosslinking collagen to form continuous lengths of tubular membranes less than one millimeter in outside diameter. Thousands of these tubes can be arranged in parallel to form a membrane unit.

To determine whether collagen membranes have the appropriate permeability properties for use in the artificial kidney, graduate students Mark Weinberg and Mike Von Deak have worked with me in the development of a transient diffusion experiment to measure membrane permeabilities. In a typical experiment, a sealed tubular membrane is first equilibrated with a radioactive solute such as urea, and then the sealed membrane is immersed in a rotating solute-free bath for a predetermined time (see photographs). Other things being equal, the more permeable the membrane, the greater the amount of solute that will diffuse out of the sealed membrane tube in a given time. These experiments showed that collagen membranes are at least three times as permeable as commercial cellulose acetate membranes.



Michihiko Takahashi of the Japan Leather Company takes a collagen break. In working with collagen, one has the consolation that an unsuccessful experiment can be eaten for lunch.

To allow clinical testing of tubular collagen membranes, Professor Cocks and several students are now developing the fabrication techniques necessary for the construction of prototype collagen hollow fiber artificial kidneys.

The projects described here are only a sampling of the ongoing and anticipated research on collagen at Cornell. Various ways are being explored to increase the strength and endurance of films and gels; two possibilities under consideration are reinforcing collagen with latex and combining collagen with synthetic polymers by co-irradiation. At the Medical College, numerous studies on the biocompatibility of collagen are continuing. During the next year, a major effort will be made to develop and clinically test collagen capsules for the controlled release of a drug to treat glaucoma.

Engineers and medical specialists at Cornell are demonstrating that collagen can be used in new and significant ways to promote physical well-being. This familiar protein has a more promising future than as gelatin desserts.

The application of chemical engineering to biomedical problems is a major research interest of James F. Stevenson, who has been an assistant professor of chemical engineering at Cornell since 1971. He is a specialist also in polymer rheology.

Stevenson received his undergraduate education at Rensselaer Polytechnic Institute, earning the B.Ch.E. degree in 1965. He did his graduate work at the University of Wisconsin, Madison, completing the Ph.D. in 1970, and then spent a year as an NIH postdoctoral fellow in the Artificial Organ Research Laboratory at Columbia University.

At Cornell, one aspect of his research has been the characterization of hollow fiber membranes, as described in this article. He has also offered a freshman mini-course, Fluid Flow and Mass Transfer in the Artificial Kidney.

He is a member of the American Institute of Chemical Engineers, the Society of Rheology, the Society of Plastics Engineers, and the American Society for Artificial Internal Organs.

THE DEVELOPMENT OF AN ISOTOPIC CARDIAC PACER

by David L. Purdy

A long-lasting cardiac pacemaker, the first in the world to be powered by a nuclear battery, became available for implantation in human patients not quite three years ago. For the past few months, a second generation radioisotopic pacer has also been in production. Half the size of any other known pacer, this advanced unit can be expected to serve as a permanent implantation for most patients.

The story of the isotopic pacemaker began in the summer of 1965, when Dr. Victor Parsonnet, director of surgery at Beth Israel Hospital in Newark, New Jersey, requested the Atomic Energy Commission (AEC) to consider the development of a long-life nuclear battery for pacemakers. This started a chain of events which eventually resulted in a development contract with the Nuclear Materials and Equipment Corporation (NUMEC).

The development of implantable pacemakers is a field in which Cornell engineers have participated from the beginning. The first model, which contained a transistorized battery, was designed by Wilson Greatbatch, who

graduated from Cornell with a degree in electrical engineering in 1950. This device was implanted in a patient for the first time in 1960. My work on the radioisotopic pacer resulted in a patent issued in 1972.

In an implanted pacemaker, a device placed beneath the skin of the patient stimulates the heart with an electrical pulse which passes through a lead or catheter in contact with the heart tissue. The normal contraction of the human heart is caused by an electrochemical pulse which starts in the sinus node near the top of the heart and spreads downward across the heart to the ventricles. In many individuals, particularly the elderly, this progression does not occur; the heart does not beat in synchronism with the sinus node impulse, and therefore may beat at a very low rate or not at all. This condition, known as heart block, can result from disease, injury, birth defects, or complications following surgery.

The first pacers to be developed stimulated the heart through an electrode attached to the outside of the patient's chest. In later models, the electrode was

attached to the outside of the heart, and finally the electrode was positioned at the end of a catheter wire implanted in the heart.

In the early 1960s, the pacers were all fixed-rate, usually beating at 70 to 72 beats a minute, and were used in patients who had total heart block. Improvements in electronic circuitry and better understanding of the pacemaking requirements of the heart led to the introduction a few years later of demand pacers. When the heart pulses normally, a demand pacer either remains quiescent or provides a harmless pulse in synchronism with the heart's own pulse; but when the heart pulse ceases or pulses abnormally—conditions which can occur intermittently and unpredictably—the pacer takes over at a fixed rate until the heart again returns to its normal pulsing.

THE NEED FOR A LONGER LASTING DEVICE

In 1965, the only source of energy to drive the electronic circuitry of the pacemaker was the mercuric oxide-zinc cell or "mercury battery," and the

“... most patients will never need another implant if they are provided with a nuclear powered model.”

life expectancy of a pacemaker was approximately two years. It was this short life expectancy that prompted Dr. Parsonnet to make his appeal for a long-lived nuclear source to power the electronics. The AEC accepted the challenge and went to industry with a request for proposals.

At that time, the AEC had reason to believe that such a development was possible, for a number of nuclear-powered electrical generators had been developed for aerospace or oceanographic use. These generators utilized an isotope as the heat source and converted the thermal energy to electrical power by the use of the “Seebeck” or “thermocouple” effect. Whether an electrical generator using the plutonium isotope Pu-238 could be constructed sufficiently small in size for implantation in the human body had to be determined, however. Most generators at that time were large by comparison and had electrical outputs ranging from one to a thousand electrical watts. Examination of the power requirements of a fixed-rate electronic circuit then being used in pacers indicated that 160 micro-

watts of electrical power would be required to drive the electronic circuitry of the pacemaker.

THE DEVELOPMENT OF ISOTOPE PACER MODELS

The contract awarded to NUMEC by the AEC was for development of a cardiac pacemaker based on a concept I had proposed. The device was to use Pu-238 as a fuel, to convert the isotopic decay heat to electricity by means of thermocouples, and to supply an electronically controlled electric impulse to the heart. The first model is shown in Figure 1.

The selection of materials was an important aspect of the development. Titanium was used for the external case because of its inertness to body fluids and its high strength-to-weight ratio. The thermoelectric material chosen was Tophel-Cupron, which has the highest efficiency in converting heat to electricity of all metallic thermocouple materials. A number of semiconducting materials with superior conversion properties were available, but they were not used because of other properties

undesirable for this application. A very large number of thermocouples are needed to produce the required output of six volts, and brittle, ceramic-like semiconductor materials are difficult to assemble in electrical series in large numbers because they cannot be made in small diameter and are mechanically weak. Although the Tophel-Cupron provides a very small output voltage per couple, this is compensated for by the fact that large numbers can be used. This material also has the advantage of superior shock resistance.

BIOLOGICAL TESTING OF THE PACEMAKER

Between 1965 and 1968, when the first radioisotope powered cardiac pacemaker was implanted in a dog at the National Heart and Lung Institute in Bethesda, Maryland, the design had evolved to the model diagrammed in Figure 2. A total of eight of the pacemakers were implanted in dogs, but unfortunately, all eight failed, four because of battery failure, and four because of electronics failure. An analysis conducted in 1970 indicated that the

Figure 1

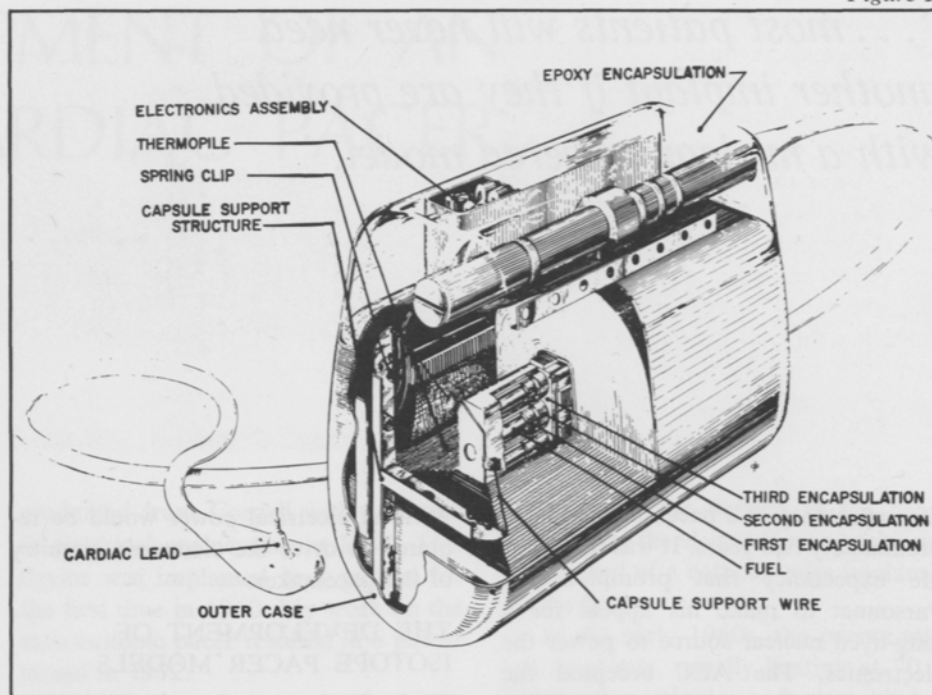


Figure 1. The first model of a radioisotope powered cardiac pacemaker. The plutonium-238 fuel is at the center of the generator. Six Tophel-Cupron thermocouple assemblies, composed of 212 thermocouple wires each, are wrapped spirally around the isotope capsule. The thermocouples are attached to the capsule at one end and to the heat-rejecting surface at the other. A portion of the isotopic decay heat passes through the thermocouples, and approximately 0.1% of the heat is converted to electric power at 6 volts. The case is hermetically sealed and a ceramic-to-metal feedthrough penetrates through the case to carry electricity to the electronics assembly. The electronics are encapsulated in a sealed container with a feedthrough which penetrates a second container. The external case is of titanium. A connector installed by the surgeon carries the electric pulse to the heart.

Figure 2

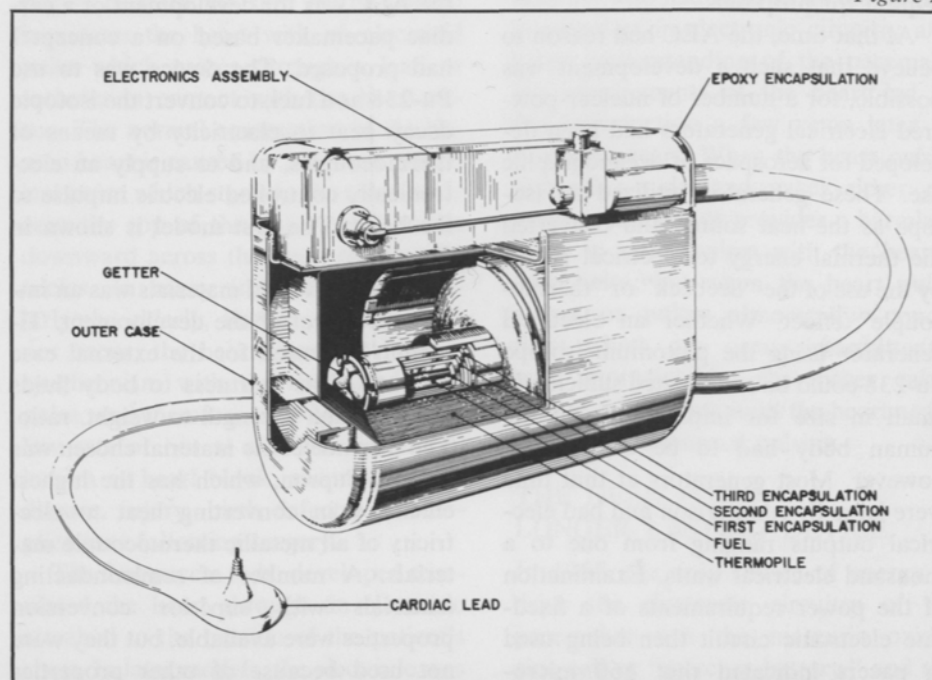


Figure 2. The first radioisotope powered cardiac pacemaker model to be implanted experimentally. The general design concept is the same as that of the original model in Figure 1. Modifications include elimination of the tapered case, which had been found to be difficult to weld. Also, the three different fuel cells have been replaced by one central capsule, and the capsule support wire has been eliminated. The overall size is larger because of the larger fuel capsule diameter, the addition of insulating material, and increased thickness of wire in the thermopile wrap.

Figure 3



mechanical shock levels experienced by the pacemakers within the dogs were substantially greater than had been anticipated, and that the reliability of the electronic components was substantially lower than had been hoped. The AEC, in conjunction with NUMEC, therefore undertook a modification of the pacer, and after another discouraging series of failures, finally shock-hardened the unit sufficiently to succeed with dog implantation. Thirty of the pacers were implanted in the fall of 1972, and with one exception, these are still operating.

The first human implant of this pacer was accomplished in April of 1973 by Dr. Parsonnet, the physician who had initiated the idea for the research. A second generation pacer, the Coratomic C-100, was implanted in humans on October 3, 1974, at Washington Hospital Center in Washington, D.C., by Dr. Nicholas P. D. Smyth; on October 11 by Dr. George Magovern at Allegheny General Hospital in Pittsburgh; and on November 2 by Dr. Parsonnet. By December 1, fourteen of the advanced units had been successfully implanted in humans.

The Coratomic C-100, produced by Coratomic, Inc., in Indiana, Pennsylvania, utilizes much of the technology developed in the AEC program, but also incorporates some new advances. It is a demand rather than a fixed-rate pacer, and is very much smaller in size and weight than the AEC first generation pacer, as well as being contoured for maximum anatomical acceptability. A photograph of this unit is shown in Figure 3.

One of the most valuable features of the AEC program was the establish-

ment of test criteria which were used as a quantitative basis for design by research and development engineers. An example is a qualification test for mechanical shock; if a pacer passes this test, it is known to be safe for human use with regard to shock.

LIFE EXPECTANCY OF THE MODERN PACERS

The power output of an isotopic battery is a function of the thermal power supplied by the isotopic fuel. This thermal power gradually diminishes with time, so that it has only 85.4% of its original value after twenty years, and 78.9% after thirty years. The result is a reduction in battery performance with time.

In production, nuclear batteries and electronic sub-assemblies are combined into completed pacers, and their calculated or projected lives determined. The calculated life of twenty-five nuclear pacers that have been produced for human implantation ranges from twenty-nine to fifty-nine years, with a median and an average of forty-four years. Since the median age of pacemaker patients is sixty-nine years, most patients

Figure 3. The second generation Coratomic C-100 pacer. This model is 6 centimeters long, 4.7 centimeters high, and 1.9 centimeters wide. It weighs 61 grams and occupies a volume of 33 cubic centimeters. A hermetically sealed and welded case surrounds both the nuclear batteries and the electronics, a difference from earlier models in which these two units had separate cases. Also, since this is a demand pacer, electromagnetic shielding is provided to protect the pacer electronics unit from spurious signals or electromagnetic interferences.

will never need another implant if they are provided with a nuclear powered model.

TESTING THE PACERS FOR RADIATION SAFETY

Since the nuclear pacer has as its thermal source the isotope Pu-238, which is radioactive and hazardous if ingested in its metallic or metal vapor form, the AEC is justifiably concerned about any accidental release into the biosphere. All kinds of accidents and possible breeches to the fuel capsule were studied under the AEC development program, and the AEC Pacer was designed to meet extremely severe constraints on the possible breach of the capsule. Then, during the period between 1966 and 1974, the device was tested under a large number of credible accident situations. The Division of Materials Licensing of the AEC worked independently on this program, and also had input from the AEC development program, from other AEC studies, and from other countries through the International Nuclear Energy Agency. The set of criteria which evolved is presently



Figure 4. Test pacers after exposure to extreme conditions designed to simulate possible accidents that could conceivably release the radioactive fuel to the biosphere. Left: A pacer after a fire and water quench designed to simulate the conditions of a large-scale fire. Right: A pacer after removal from a crematorium furnace. Although extreme damage occurred to the outer cases, in neither of these pacers was there any breach of the fuel capsule.

The nuclear pacers are also tested for such contingencies as a fall from an aircraft or loss at sea. The radiation dose from normal use is considered negligible.



used for the design of radioisotope powered cardiac pacemakers; both the AEC Pacer and the Coratomic C-100 meet these standards. The following examples illustrate the types of accidents that were considered.

Since a high-temperature industrial, hospital, or storage fire engulfing a pacer is conceivable, criteria were established to assure that the fuel capsule would not release fuel in the event of such a fire. The test consists of subjecting the pacer to an 800° oxidizing environment for 30 minutes, followed by a water quench to simulate the use of fire hoses, and then applying a 1,000-kilogram load to simulate the crushing effect of a collapsing building. Although the case is destroyed in the test (see Figure 4) and ductile deformation of the capsule occurs, there is no breach of containment, and all of the encapsulated layers of metal surrounding the fuel remain completely intact. The conclusion is that the fuel would not be released in a fire or severe crushing accident.

Another accident that can be hypothesized is the fall of a pacer from an

aircraft or other high altitude with subsequent impact on an unyielding object such as a sidewalk or concrete structure. It can be hypothesized also that in the explosion of an aircraft, the fuel capsule might be blown from the interior of the pacer, although this is very improbable. To guarantee environmental safety in such contingencies, the AEC guideline requires that a fuel cell be able to withstand impact at a velocity of 50 meters per second or greater, assumed to be the terminal velocity of an object falling freely from a high altitude. Test capsules were placed in three different attitudes to simulate any probable impact situation, and were impacted against granite at 63, 66, and 67 meters per second. Mild deformation occurred, but no breach of the encapsulating materials could be detected with a highly sensitive helium leak detector.

The most severe test simulates a possible accident which could occur if a pacer were accidentally left in a body to be cremated. This test requires that a pacer be placed in a furnace at a temperature greater than 1300°C for 90

minutes. A C-100 was tested in the oxidizing atmosphere of a crematorium furnace at 1380°C for 90 minutes. As shown in a photograph (Figure 4), there was severe damage to the external structure, but the fuel capsule was undamaged. The external sheath of the capsule is made of an oxidation-resistant alloy of platinum and rhodium, and is protected internally by a number of metallic and oxide layers.

The fuel capsule must also be able to withstand internal pressure increases with time, for as Pu-238 decays, pressure within the fuel capsule gradually increases. This is because Pu-238 decays by alpha emission, which results in a slow accumulation of helium gas within the capsule, a phenomenon that was studied in great detail in the NUMEC program. The work included the derivation by Harold Garber of an empirical equation expressing the pressure-volume-temperature relationship for helium which can be used to calculate the wall stress of the fuel capsule at given temperatures.

Figure 5 shows curves for calculated capsule wall stress as a function of time

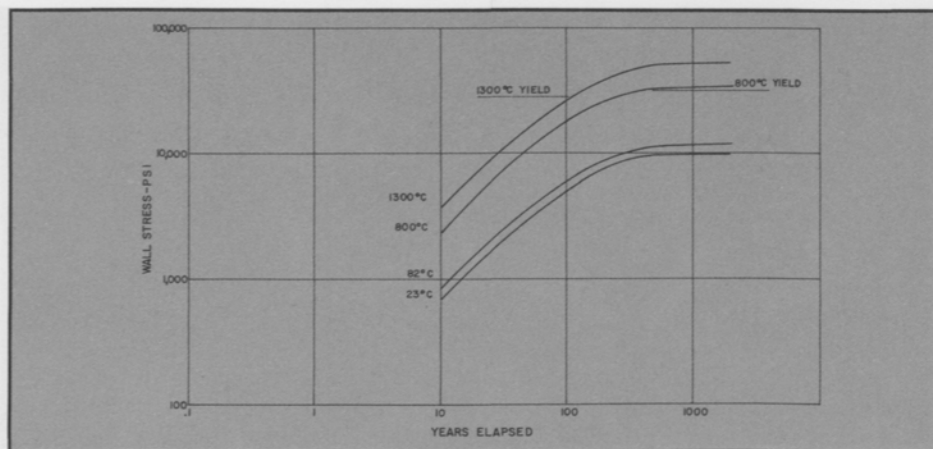


Figure 5. Calculated wall stress of the fuel capsule as a function of time at various temperatures. This analysis was made to investigate the ability of the capsule to withstand gradually rising pressure due to the production of helium as the plutonium isotope decays. The temperatures correspond to the condition of normal room temperature (23°C), normal operating temperature (82°C), the temperature of an industrial fire (800°C), and the temperature of a crematorium furnace (1300°C). In all cases, the calculated yield stress of the material is reached after a length of time sufficient to provide a large margin of safety.

at various temperatures. It can be seen that the yield stress is not exceeded at 1300°C (cremation temperature) until after one hundred years has elapsed; this provides a substantial margin of safety, since the anticipated length of use of a pacer is around twenty years. At 800°C (industrial fire condition), the yield point occurs at about four hundred years, thereby providing a safety factor of almost 80.

Another hypothetical accident is the loss of a pacer in an ocean, possibly as a result of a patient drowning, a burial at sea, the accidental crash of an aircraft, or the sinking of a vessel carrying the pacer to foreign countries. It must be certain that the pacer fuel would not be released as a result of corrosion of the fuel capsule by seawater. In both the AEC and the Coratomic C-100 Pacers, an alloy of platinum with 10% rhodium is used as a corrosion-resistant barrier, and tests of the corrosive effect of seawater on this material under aerobic and anaerobic conditions over a period of fifteen months showed a weight loss rate well below the tolerance established by AEC standards. A

further indication of the stability of the material is that spectrographic analysis of residues after evaporation of the water samples showed no measurable quantities of platinum or rhodium.

These various tests show that no fuel release can occur as a result of any credible accident to either the AEC Pacer or the Coratomic C-100 Pacer. As an additional safeguard, the AEC has stipulated that industrial suppliers use the most insoluble and inert form of plutonium, the oxide. This oxide is so inert and prepared in such a manner that even if it were ingested by an individual, it would pass through the alimentary tract with no effect on the host.

RADIATION DOSE RATE FROM THE ISOTOPIC PACER

Pu-238 is an alpha and gamma emitter. In addition, an alpha-n reaction occurs with light elements near the plutonium atom as it decays, and neutrons are created. Thus, a small amount of radiation, from neutrons as well as gamma rays, exists around the pacer. This amounts to a yearly dose rate to the patient's trunk of approximately 350

millirem per year, which is comparable to the excess dose of 400 millirem per year that is received by an airline stewardess or a pilot flying at jet altitudes. It is lower by a factor of 14 than the whole-body occupational exposure limit of 5,000 millirem per year that has been established by the National Council on Radiation Protection.

Radiation reaching the gonads from a chest implant 40 centimeters away would amount to a dose of approximately 100 millirem per year: this is lower by a factor of 150 than the limit for critical organs (15,000 millirem per year) that is recommended by the national council. The dose to the gonads of the spouse of a patient has also been calculated. Assuming a separation distance of 50 centimeters in air and an exposure time of 3,000 hours a year, the dose is approximately 20 millirem per year, or less than 1/25 of the maximum permissible dose of 500 millirem per year that has been established for non-occupational personnel.

The radiation hazard to the patient—or to a spouse or the general public—is therefore considered negligible.

THE HISTORY AND FUTURE OF THE NUCLEAR PACER

The development of the nuclear pacer would not have been possible without the financial and technical support of the United States Atomic Energy Commission. The first model, developed under an AEC contract, provided a large base of technology in the public domain for the evolution of the second generation nuclear pacer system, as well as the establishment of design and test standards.

The Coratomic C-100 is the smallest, lightest, and longest-lived pacer known to be available for implantation in humans. Its size and weight are roughly half that of any other known pacer, and its calculated average life of forty-four years is almost four times longer than the calculated life of the longest-lived battery pacers, which use lithium batteries in place of the mercury batteries of earlier models.

Although the \$5,000 cost of a nuclear pacemaker is high compared to the \$1,000 cost of a battery powered model, when the repeated number of operations and additional pacemakers required for the short-lived systems are taken into consideration, the nuclear pacer is less expensive. The cumulative costs to the patient after three implants of a battery pacer, for example, exceed the cost of the single implant required for a nuclear pacer.

The future of the nuclear pacer remains to be determined in the marketplace, but the obvious advantages of the system are sufficient to cause it to be a very viable alternative to all other implantable battery powered pacer systems available at this time.



David L. Purdy, a Cornell engineering graduate and president of Coratomic, Inc., was granted a patent in 1972 for the nuclear powered cardiac pacer he discusses in this article. His corporation is now developing an implantable, nuclear powered artificial heart.

Purdy, who received the Cornell degree of Bachelor of Mechanical Engineering in 1951, recalls his five-year program as "extensive training in the fundamentals of engineering and mathematics that have remained relatively timeless," even though much of the technology he is applying today was nonexistent in the 1940's. "The training in creative and analytical thinking, and the hours spent over the drafting board on the third floor of Sibley, have assisted me greatly in attacking many of the complex problems encountered in the development and manufacture of new products and devices," he comments.

Purdy founded Coratomic, Inc. in 1972 to develop and produce the pacer and related medical products. His work with the pacer began when he headed the design team as manager of the Energy Conversion Division of the Nuclear Materials and Equipment Corporation (NUMEC), which was awarded the initial development contract from the AEC. Subsequently, he

continued this work as manager of the Energy Conversion Technical Center of the Atlantic Richfield Company (ARCO).

During his years with NUMEC and ARCO, Purdy's accomplishments included being the first to use vacuum insulation for radioisotopic thermoelectric generators, leading the team which developed a nuclear powered artificial human diaphragm stimulator for breathing, leading the team which developed the first nuclear powered under-sea pinger system (a sound device to locate objects under water), and designing for the AEC an aerospace radioisotope fueled generator capable of re-entering the earth's atmosphere after missions to the distant planets.

Before joining NUMEC in 1964, Purdy spent fifteen years with the General Electric Company participating in aerospace and energy conversion research and development, and had a variety of work experience in sales, manufacturing, and engineering organizations.

He is the author of numerous papers in the fields of biomedical engineering, atomic technology, direct conversion of heat to electricity, and creative engineering problem solving. He holds five patents and has made application for a number of others, including one for the artificial heart. He is a member of the American Society of Mechanical Engineers, the American Institute of Aeronautics and Astronautics, and the Association for the Advancement of Medical Instrumentation.

HOW DRUGS WORK IN THE BODY

A New Problem for Chemical Engineers

by Kenneth B. Bischoff

The reliable prediction of drug effects in the body is a goal long sought by pharmaceutical and medical specialists. The use of anti-cancer drugs, for example, depends on assessments of what happens when they are introduced under various conditions. In designing drug therapy procedures, pharmacologists and clinicians must be concerned with such problems as what the dosage regimen should be and what the concomitant biochemical events will be.

The prediction of drug effects involves two basic steps: (1) predicting the drug distribution, or pharmacokinetics, throughout the body, including the local concentration at the site of action; and (2) relating the local concentration levels to actual drug action. Although both steps are important, only the first will be considered here.

Experimental and analytical difficulties are involved in each phase, and there may be some doubt that definitive *predictions* are feasible. The potential benefits, however, justify every reasonable effort that could help to simplify and reduce the typically extensive and

somewhat risky clinical experimentation that is the alternative.

THE CONTRIBUTIONS OF CHEMICAL ENGINEERS

What can chemical engineers do in this area? The answer lies in the fact that many methods and techniques that have been developed for predicting events in complicated networks of interacting chemical processing units can be adapted to the problems of pharmacokinetics. The operation of an oil refinery or a chemical plant, for example, can be compared with that of the body, which also contains filtering devices (kidneys), chemical reactors (liver and other organs), and pump (heart), all connected by the pipes (arteries and veins) of the circulatory system.

Of course, biological systems are usually much more complex than those made of steel and plastic, and existing chemical engineering methods really only provide a useful starting point for studying drug distribution. The qualitative aspects of the problem—those usually studied by biologists—must also

be grasped in order for engineers to do anything meaningful in work with physiological systems.

Actually, methods devised independently by biologists and engineers have some similarities in spite of differences in approach, and I believe that the most significant advances in pharmacokinetics will be made by utilizing the best parts of both. Pharmacokinetics is one of many areas in which there can be fruitful collaboration among engineers, biologists, and physicians.

MATHEMATICAL MODELING OF DRUG DISTRIBUTION

The approach is to mathematically account for the amount of drug entering and leaving a particular region of the body—the so-called mass balance. The analysis is based on the conceptual diagram, shown in Figure 1, of the flow and diffusion of drug molecules in tissue regions. For further simplification, the representation is usually “lumped” into a few “compartments,” as in Figure 2, that are most important or most easily sampled by experimental biopsy techniques. These compartments are

Figure 1

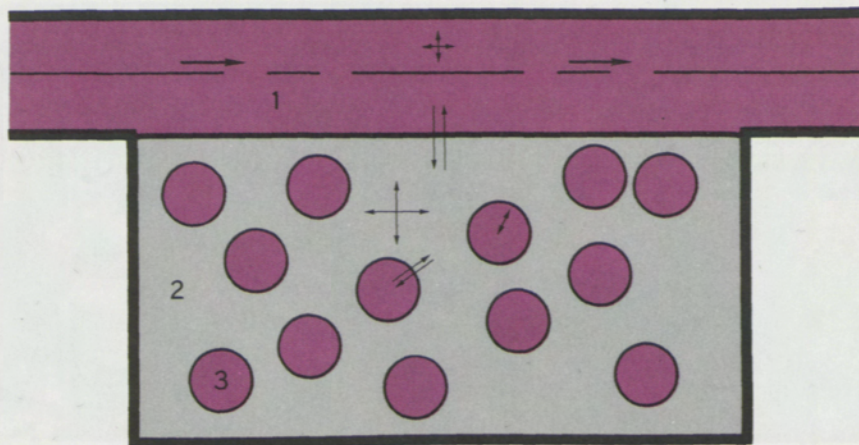


Figure 1. Schematic diagram of the flow and diffusion of drug molecules in body tissue regions. The area marked (1) represents a blood capillary, (2) is interstitial fluid, and (3) is a representative cell. The arrows indicate the direction of flow or diffusion of the drug molecules.

Figure 2

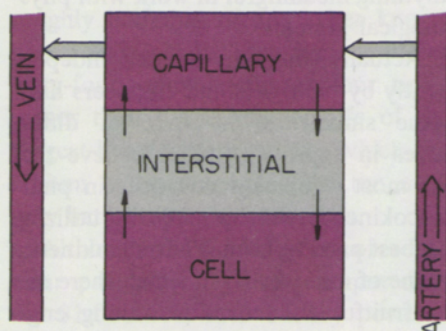
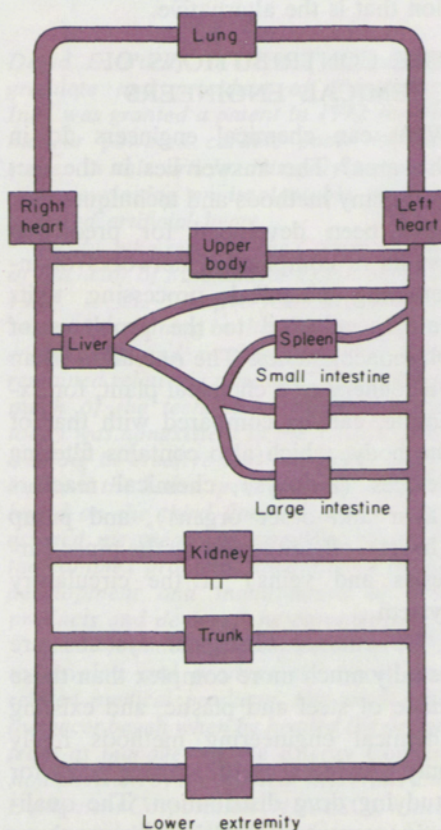


Figure 2. Simplified representation of body fluids in tissue regions. The mathematical modeling of drug distribution is handled in terms of "compartments" throughout which drug molecules become distributed.

Figure 3. Diagram of the circulatory system of a mammal. The mathematical model used for predicting drug distribution in the body is based on this general schematic. Flow and diffusion rates, along with physiological parameters appropriate to species, body, size, and other features, are used in calculations with the basic sets of equations.

Figure 3



then arranged according to the overall body anatomy of a mammal, diagrammed in Figure 3. This system is the basis of mathematical models of the distribution process after drugs have been introduced into the body.

How this mathematical modeling works is best illustrated with some examples. If a drug is injected into a large vein leading directly to the heart, concentration "waves" will pass through the circulatory system at various distances from the heart. Figure 4 shows typical concentration curves computed from the model with use of values for blood flow, organ size, etc. that are typical of adult humans. It may be seen that the "waves" dissipate rather quickly—in about one minute. A useful benchmark is that the mean circulation time in adult humans is about one minute, although from the parallel arrangement of the body flows, it is clear that some routes are faster than others.

For most drugs, the time scale of interest is much longer—of the order of hours or even days—and this "wave" characteristic can probably be ignored. This leaves open, however, the matter

“Pharmacokinetics is one of many areas in which there can be fruitful collaboration among engineers, biologists, and physicians.”

Figure 4

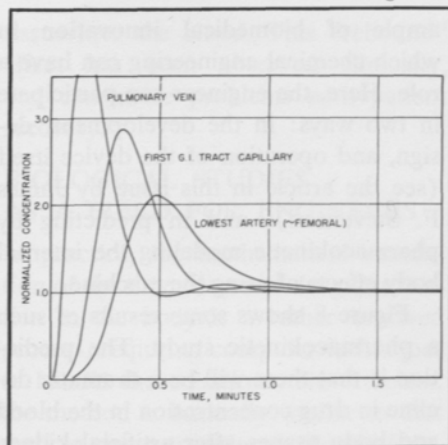


Figure 4. Calculated drug concentrations in the circulatory system after injection into a large vein. This “wave” characteristic is probably not important in many cases, but could be significant if high temporary drug levels have unfavorable physiological effects.

Figure 5. Simplified flow diagram for the calculation of drug concentration levels. This “lumping” of body regions and mass balance equations is satisfactory for relatively slow-acting drugs.

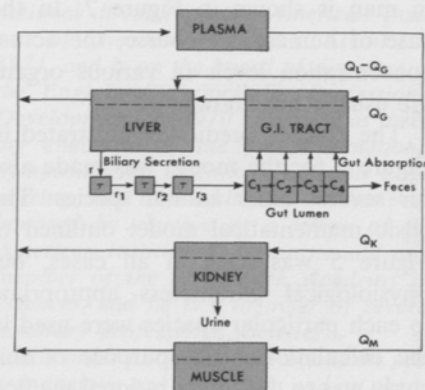
of possible toxicity from the extra-high initial concentrations, a difficult problem that needs study: it is usually empirically avoided in clinical practice by a slow drug injection. Also, there are some situations, such as in the administration of rapid-acting anesthetic agents, in which the initial “wave” distribution cannot be ignored.

For most drugs, however, the pharmacokinetics can be represented on the basis of a further “lumping” of the body compartments, as shown in Figure 5.

THE DISTRIBUTION OF AN ANTI-CANCER DRUG

This scheme was used to predict the concentrations in various important body regions of an anticancer agent called methotrexate (MTX), used in the treatment of leukemia and related diseases. MTX can help kill cancer cells, but it is also very toxic to some normal tissue cells; a successful clinical dosage regimen is one that kills the cancer cells, but is not too toxic to the rest of the body.

Figure 5



The exploration of useful dosage regimens can be guided by a model that provides approximations of drug concentration in several important organs. The usefulness of such a model is demonstrated in Figure 6, which compares predicted concentration curves of MTX for the mouse with actual measurements. These results show a good correspondence between theoretical and experimentally determined concentration levels for this particular dosage regimen.

A similar prediction for MTX levels

Figure 6

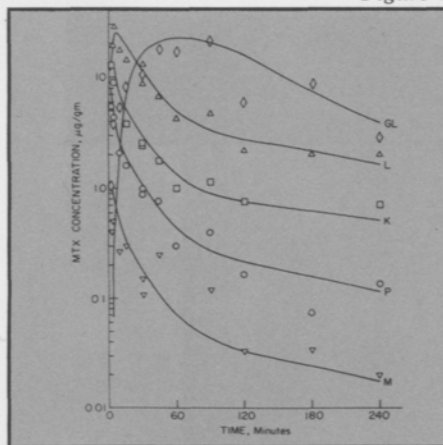
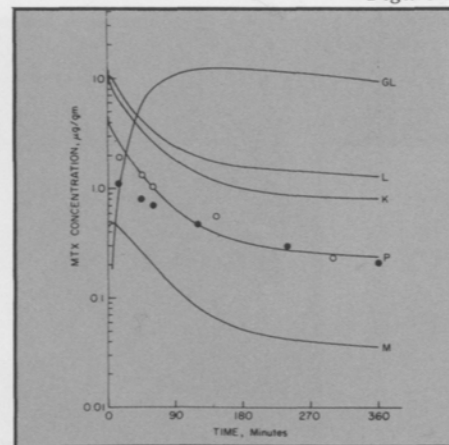


Figure 7



in man is shown in Figure 7. In the case of humans, of course, the actual concentration levels in various organs are usually not known.

The kind of prediction illustrated in Figure 6 for the mouse was made also for several other animal species. The basic mathematical model outlined in Figure 5 was used in all cases, but physiological parameters appropriate to each particular species were used in the calculations. The purpose of this study was to develop a rational method for interpreting experiments in animals, and also to aid in the final difficult extrapolation to man. This practice of preceding clinical use of a drug with experimental studies with animals is followed in virtually all drug development work, and pharmacokinetic modeling can help in the vexing problems of adapting drug regimens for use with human patients.

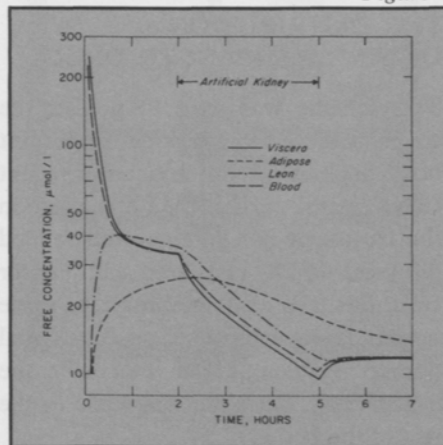
REMOVING POISONS WITH THE ARTIFICIAL KIDNEY

The use of an artificial kidney to reduce the blood and tissue levels of a poison—say, a barbiturate—is another ex-

ample of biomedical innovation in which chemical engineering can have a role. Here, the engineer can participate in two ways: in the development, design, and operation of the device itself (see the article in this issue by James F. Stevenson); and in predicting by pharmacokinetic modeling the internal body effects of using the machine.

Figure 8. Removal of pentobarbital by means of the artificial kidney.

Figure 8



ample of biomedical innovation in which chemical engineering can have a role. Here, the engineer can participate in two ways: in the development, design, and operation of the device itself (see the article in this issue by James F. Stevenson); and in predicting by pharmacokinetic modeling the internal body effects of using the machine.

Figure 8 shows some results of such a pharmacokinetic study. The prediction is that there will be a dramatic decline in drug concentration in the blood and body tissues after artificial kidney treatment is begun. Without treatment, the concentration curves would be almost flat after one or two hours; they would decline only very slowly as a result of natural body metabolism and excretion. Results such as these shown in Figure 8 can be used to determine the length and intensity of treatment that is required to achieve a desired decrease in blood level. It is also interesting to note, in Figure 8, the predicted rise in blood concentration after cessation of the artificial kidney treatment. This is caused by "back diffusion" of drug from the adipose (fatty)

tissue into the blood. This "rebound" effect has been observed clinically, and can cause problems with patient recovery.

BIOLOGICAL STUDIES AS A FIELD FOR ENGINEERS

In practice, the mathematical simulation of the time course of drug distribution in the body is a rather involved process, requiring computer techniques to handle the equations. Nevertheless, the method is basically similar to that used in more traditional chemical engineering problems, and it opens a new area of activity for chemical engineers.

Pharmacokinetic modeling is an example of the growing number of ways in which engineers can participate in biological studies. The province of the chemical engineer has expanded to include the hospital and the pharmacology laboratory as well as the chemical processing plant.



Kenneth B. Bischoff, the Walter R. Read Professor of Chemical Engineering, came to Cornell as director of the School of Chemical Engineering in 1970, and has continued his work on the mathematical description of drug distribution in the body which he had already begun in collaboration with the National Institutes of Health (NIH). In 1972 he was awarded the Ebert Prize of the Academy of Pharmaceutical Sciences of the American Pharmaceutical Association for a paper on this subject. Last November he was the keynote speaker for the symposium on pharmacokinetic modeling of anticancer drugs at the national meeting of the Academy of Pharmaceutical Sciences.

He is currently a consultant to the Biomedical Engineering Branch and the Artificial Kidney Contracts Review Group of NIH, and has served on several national committees, including the National Science Foundation (NSF) Graduate Fellowship Review Panel.

Bischoff is active also in several professional organizations. He was elected a

national director of the American Institute of Chemical Engineers (AIChE) in 1971, and is on the board of directors of the Engineers' Council for Professional Development. In 1970 he served as meeting chairman of the first International Symposium on Chemical Reaction Engineering, held in Washington. He has been honored by election as a fellow of the American Institute of Chemists and as a member of the New York Academy of Sciences, and he is a member of several honorary professional societies.

His publications include books on process analysis and simulation and on chemical reactor design, in addition to numerous papers in professional journals. He has been an editor of two volumes published by AIChE, and he serves on the editorial boards of the Journal of Pharmacokinetics and Biopharmaceutics, the Annual Reviews of Industrial and Engineering Chemistry, and the Advances in Chemistry series.

Bischoff earned the B.S. and Ph.D. degrees at the Illinois Institute of Technology, spent a year in Belgium as an NSF Postdoctoral Fellow, began his teaching career at the University of Texas, and before coming to Cornell was professor of chemical engineering at the University of Maryland. He has also had industrial experience as a consultant to Exxon, and is a registered professional engineer in Texas.

New Engineering Faculty Members

■ *Five assistant professors—four in environmental engineering and one in structural engineering—are new to the faculty of the School of Civil and Environmental Engineering.*

Frank J. Cesario, a specialist in transportation engineering and planning, joined the faculty after serving at Cornell as a postdoctoral fellow in regional science, as a research associate in the Center for Urban Development Research, and as a visiting assistant professor of policy planning and regional analysis and of regional science. Before coming to Cornell, he was a senior economist at Battelle Memorial Institute. His academic degrees are the B.S. from the University of Massachusetts, the M.S. from Montana State University, and the Ph.D. in industrial and systems engineering from Ohio State University. He is a member of the Operations Research Society of America, the American Statistical Association, the American Institute of Industrial Engineers, the Transportation Research Forum, the Regional Science Association, and Sigma Xi.

Philip L.-F. Liu centers his teaching and research in the area of fluid mechanics, hydraulics, coastal engineering, and oceanography. He studied for the B.S. degree at National Taiwan University, and received his graduate education at the Massachusetts Institute of Technology. He was awarded the S.M. degree in 1971 and the Sc.D. in hydrodynamics this year. He is a member of Sigma Xi.

Peter J. Murphy came to Cornell after six years at La Universidad del Valle in Cali, Colombia, where he worked with the university development program of the Rockefeller Foundation. A specialist in hydraulics and hydrology, he designed and supervised the construction of the fluid mechanics and hydraulics laboratories at the Colombian university. He holds the B.S. degree from the Webb Institute of Naval Architecture, and the Ph.D. in fluid mechanics from Johns Hopkins University.

Robert L. Willis, a specialist in systems analysis, was educated at the University of California at Los Angeles,

which awarded him the B.S. degree in applied mathematics, the M.S. in operations research, and the Ph.D. in water resource systems analysis. He has worked as a postgraduate research engineer and postdoctoral scholar at UCLA on surface and ground water quality management systems and urban transportation systems, and he has participated in a cooperative program to plan optimal utilization of water resources in the Valle del Cauca in Colombia. He has also worked with Environmental Dynamics, Inc., on federally sponsored studies of coastal processes, water management strategies in western river basins, and optimal pricing policies for urban water supply and waste treatment systems. He is a member of the American Geophysical Union, the American Society of Civil Engineers, the American Water Resources Association, the Institute of Management Sciences, the Operations Research Society of America, Tau Beta Pi, and Phi Beta Kappa.

John F. Abel, a Cornell civil engineering graduate, has joined the faculty 28

of the Department of Structural Engineering. After receiving the B.C.E. degree from Cornell in 1963, he did graduate work in structural engineering and structural mechanics, earning the M.S. degree at Stanford University and the Ph.D. at the University of California at Berkeley. He spent two years as a research engineer at the Waterways Experiment Station of the Army Corps of Engineers, and then served for several years at Princeton University on the faculties of the School of Architecture and Urban Planning and the Department of Civil and Geological Engineering. Abel is coauthor of a text, *Introduction to the Finite Element Method* (Nostrand Reinhold, 1972). He is registered as a professional engineer in Mississippi, and is a member of the American Concrete Institute, the American Society of Civil Engineers, the American Society for Engineering Education, the International Association for Shell Structures, the International Association for Housing Science, the Society for the History of Technology, the Design Methods Group, Tau Beta Pi, Chi Epsilon, and Sigma Xi.

■ *Four assistant professors have joined the Department of Computer Science.*

Gregory R. Andrews, a specialist in operating systems, came to Cornell from the University of Washington, where he earned the Ph.D. degree in computer science. His B.S. degree in mathematics is from Stanford University. He has had professional experience as a programmer for International Business Machines in San Francisco and as an associate engineer in computer science with Boeing Aircraft in Seattle. Andrews is a member of the Association for Computing Machinery.

Alan J. Demers, another recent Ph.D. graduate, is a specialist in programming languages and systems. His academic degrees are the B.S. in physics from Boston College, and the M.A. in electrical engineering and computer science and the Ph.D. in computer science from Princeton University. Last year he was a member of the faculty of Stevens Institute of Technology. He is a member of the Association for Computing Machinery.

Shih-Ping Han is a graduate of National Taiwan University, and received his graduate education at the University of Wisconsin, earning the M.A. degree in mathematics in 1971 and the Ph.D. in computer science in 1974. His specialty is numerical analysis.

David G. Kirkpatrick came to Cornell from the University of Toronto, where he earned the M.S. and Ph.D. degrees in computer science with a specialization in the theory of algorithms. His B.S. degree in mathematics is from the University of British Columbia. He is a member of the Association for Computing Machinery.

■ *Three specialty fields are represented by assistant professors named this year to the faculty of the Sibley School of Mechanical and Aerospace Engineering.*

William W. Carson, a specialist in processing design, received his undergraduate and graduate education at the Massachusetts Institute of Technology.

He was awarded the Sc.D. degree this winter, after beginning his activities at Cornell. Carson is a member of the American Society of Mechanical Engineers, the Society of Automotive Engineers, and Sigma Xi.

Stuart L. Phoenix earned his doctorate in theoretical and applied mechanics at Cornell in 1972, and spent two years as a senior research associate at Fabric Research Laboratories in Dedham, Massachusetts. His previous degrees are the B.Sc.Eng. and the M.Sc.Eng. in agricultural engineering from the University of Guelph in Canada. His specialty fields are probabilistic aspects of materials fracture and mechanical reliability analysis. He is a member of the American Society for Testing and Materials and the Marine Technology Society.

William E. Tobler, who has served as a teaching assistant and a research associate in the Sibley School and holds Cornell M.S. and Ph.D. degrees in mechanical engineering, became a member of the faculty this fall. His B.S. degree is from Rutgers University. Tobler is a specialist in simulation and vehicle dynamics. He is a member of the American Society of Mechanical Engineers, Pi Tau Sigma, and Phi Kappa Phi.

■ *The Department of Operations Research added two new members to its regular faculty this year.*

John A. Muckstadt, who had spent eight years as a faculty member of the Air Force Institute of Technology and as an operations research analyst in materiel management for the Air Force

Logistics Command, was named associate professor in the Cornell department. He holds the A.B. degree in mathematics from the University of Rochester, and the M.S. in industrial administration, the M.A. in mathematics, and the Ph.D. in industrial engineering from the University of Michigan. In addition to his service with the Air Force, Muckstadt has worked in the logistics program at the RAND Corporation, and taught part-time at the University of Dayton. He is a member of the Operations Research Society of America, the Institute of Management Sciences, the Mathematics Association of America, and Sigma Xi and Alpha Pi Mu.

Murad Taqqu, an assistant professor, came to Cornell from Israel, where he spent a year as a lecturer in probability and statistics at the Hebrew University in Jerusalem, and then a year as a postdoctoral research fellow at the Weizmann Institute of Science. A native of Iraq, he received his undergraduate education at the Université de Lausanne, Switzerland, earning B.A. degrees in mathematics and in physics. He went to Columbia University for his graduate education in mathematical statistics, and received the M.A. and Ph.D. degrees. He has had research experience at the National Bureau of Economic Research in New York on computer simulation of statistical models in economics and hydrology, and at the International Business Machines Research Center in Yorktown Heights, New York, on computer simulation of models of dams. He is a member of the Institute of Mathematical Statistics, the Operations Research Society of America, and Sigma Xi.

■ *Two new members were appointed to the faculty of the Department of Theoretical and Applied Mechanics this year.*

Francis C. Moon, who did his graduate work in mechanics at Cornell, joined the faculty in the spring term as an associate professor. He came to Cornell from Princeton University, where he was an assistant professor of aerospace and mechanical science and, until recently, a lecturer and research engineer. Since leaving Cornell eight years ago, he has also taught at the University of Delaware and served as a consultant to the Rand Corporation. He was a faculty fellow at the NASA-Lewis Research Laboratory for two summers, and has recently consulted for the Boeing-Vertol Corporation on magnetic levitation of trains.

At Princeton, Moon conducted a research program on various problems of the dynamics of solids and structures, including the interaction of magnetic fields and elastic solids, magnetic levitation of vehicles, dynamics of composite materials, and the mechanics of superconducting magnets for fusion reactors. This research was supported by grants from the National Science Foundation, the National Aeronautics and Space Administration, and the Atomic Energy Commission.

Moon holds the B.S.M.E. from the Pratt Institute, and the M.S. and Ph.D. from Cornell. He is a member of the American Society of Mechanical Engineers, the Society of Engineering Science, the American Academy of Mechanics, and the American Association for the Advancement of Science.

Subrata Mukherjee, a specialist in plasticity and viscoelasticity, is an as-

sistant professor of theoretical and applied mechanics. He received the B.Tech. degree in mechanical engineering at the Indian Institute of Technology, Kharagpur, and then came to the United States for his graduate education, earning the M.S. in mechanical and aerospace engineering at the University of Rochester and the Ph.D. in applied mechanics at Stanford University. He has had consulting experience with Cartridge Television, Inc., in San Jose, California, and spent a year as a research associate in plasticity and viscoelasticity at Stanford before coming to Cornell. He is an associate member of the American Society of Mechanical Engineers and a member of Sigma Xi.

■ *The School of Electrical Engineering and the Department of Geological Sciences have each added an assistant professor to their faculties.*

Vincent Chan, in electrical engineering, came to Cornell from the Massachusetts Institute of Technology, where he recently completed his graduate work. He holds the degrees of B.S., M.S., Electrical Engineer, and Ph.D., all from the Massachusetts Institute of Technology. Chan is a specialist in communications, particularly at optical frequencies. He is a member of the honorary societies Eta Kappa Nu, Tau Beta Pi, and Sigma Xi.

Percy R. Luney, acting assistant professor of geological sciences, specializes in both law and geology, and has also spent a year as a Thomas J. Watson Fellow studying the use and management of natural resources in sub-Saharan African countries. He offered a new

course this fall in Mineral Resources—An Interdisciplinary Approach. Luney holds the A.B. degree in geology from Hamilton College and the J.D. in law from Harvard University.

■ *The engineering faculty is augmented also by a number of visiting professors here for the 1974-75 academic year.*

Barrington deV. Batchelor, visiting professor of structural engineering, has been a member of the faculty of Queen's University, Ontario, Canada, since 1966. He is a specialist in concrete structures and structural dynamics. A native of Jamaica, West Indies, he studied for the B.Sc. degree in civil engineering at the University of Edinburgh. He did his graduate work at the Imperial College of Science and Technology, with specialization in concrete structures. Batchelor's professional experience includes two years with a British consulting firm, three years as an executive engineer for the Government of Jamaica, and two years in pri-

vate consulting in Jamaica. He is a citizen of Canada and is registered as a professional engineer in Ontario. He is a founder-member of the Institution of Engineers in Jamaica, and a member also of the Canadian Society of Civil Engineers, the American Society of Civil Engineers, the American Concrete Institute, and the Institution of Civil Engineers.

Albert W. Tucker came to Cornell as the Mary Shepard B. Upson Visiting Professor in the Department of Operations Research for the fall term, after concluding a distinguished career in mathematics at Princeton University. Tucker's research contributions have spread over large areas of finite mathematics and its modern applications, including combinatorial topology, graph theory, game theory, and mathematical programming, and he is recognized as a leading authority in mathematical education. In addition to teaching at Princeton and serving as head of the mathematics department there for many years, he has held numerous visiting profes-

sorships and special lectureships, and has served in many capacities in professional organizations. Among honors he has received are the Distinguished Service Medal of the Mathematical Association of America, an organization he served as president. Tucker has published extensively, and edited and helped establish several professional publications. His academic degrees are the B.A. and M.A. from the University of Toronto and the Ph.D. in topology from Princeton.

John R. Zimmerman, professor of mechanical engineering at Clarkson College of Technology and a specialist in mechanical design, is a visiting professor in the Sibley School of Mechanical and Aerospace Engineering. He holds the degrees of B.E. in mechanical engineering from Yale University, the S.T.B. in the philosophy of religion from Boston University, and the M.S. and Ph.D. in mechanical engineering from Lehigh University. For nineteen years, before joining the Clarkson faculty, he taught in the mechanical engineering department at Pennsylvania State University. He is a member of the American Society for Engineering Education, the American Society of Mechanical Engineers, the American Association of University Professors, and Sigma Xi.

Frank V. Nolfi, Jr., a metallurgist at the Argonne National Laboratories, is at Cornell this year as a visiting associate professor of materials science and engineering. He is a specialist in the thermodynamics of materials and the kinetics of solid state processes. Nolfi

received his B.S. degree in metallurgical engineering at the Drexel Institute of Technology, and the M.S. and Ph.D. degrees in metallurgy and materials science at the Carnegie Institute of Technology. He is a member of the American Institute of Mining, Metallurgical, and Petroleum Engineers, and several honorary societies.

David A. Caughey of the McDonnell Douglas Corporation is spending the year at Cornell as a visiting assistant professor in the area of aerodynamics. He holds the degrees of B.S.E. in aeronautical and astronautical engineering from the University of Michigan and the Ph.D. in aerospace and mechanical sciences from Princeton University. He is a member of the American Institute of Aeronautics and Astronautics and Tau Beta Pi.

Marshall L. Fisher, an assistant professor of management science at the Graduate School of Business of the University of Chicago, is serving as a visiting assistant professor in the Cornell Department of Operations Research this year. He received his university education at the Massachusetts Institute of Technology, earning degrees in several disciplines: the S.B. in electrical engineering, the S.M. from the Sloan School of Management, and the Ph.D. in operations research. In addition to his teaching and research activities, he serves as an industrial consultant and as a referee for several professional journals. He is a member of the Operations Research Society of America, the Institute of Management Sciences, and Sigma Xi.

FACULTY PUBLICATIONS

The following publications and conference papers by faculty members and graduate students of the Cornell College of Engineering were published or presented during the period May through July 1974. Earlier publications inadvertently omitted from previous listings are included here with the date in parentheses. The names of Cornell personnel are in italics.

■ AGRICULTURAL ENGINEERING

Davis, D. C., and Rehkugler, G. E. 1974. Agricultural wheel-tractor overturns. Part I: Mathematical models. Part II: Mathematical model verification by scale-model study. *Transactions of ASAE* 17(3):477-492.

Irwin, L. H. 1974. Development of a Curriculum in Community and Resource Development. Paper read at 82nd Annual Conference of the American Society for Engineering Education, 17-20 June 1974, at Rochester Polytechnic Institute, Troy, New York.

———. 1974. Stabilization of Base Course Materials. Paper read at 29th Annual School for Highway Superintendents, 19-31 June 1974, at Cornell University, Ithaca, New York.

Ku, A. C.-C.; Furry, R. B.; Jordan, W. K.; and Dropkin, D. Heat and Mass Transfer During Freeze-Drying of Food Products: Simulation and Application Results. Paper read at Summer Meeting of the American Society of Agricultural Engineers, 23-26 June 1974, at Oklahoma State University, Stillwater, Oklahoma.

Loehr, R. C., and Johanson, K. J. 1974. Phosphate removal from duck farm wastes. *Journal of the Water Pollution Control Federation* 46(7):1692-1714.

Loehr, R. C.; Klausner, S. D.; and Scott, T. W. 1974. Disposal of agricultural wastes on land. In *Proceedings of the fourth environmental engineers conference*, ed. R. L. Sanks and T. Asana, pp. 151-176. Bozeman: Montana State University.

Martin, J. H., Jr.; Loehr, R. C.; Anthonisen, A. C.; and Nieswand, S. P. 1974. Aerobic Treatment of Poultry Wastes. Paper read at 67th Annual Meeting of the American Society of Agricultural Engineers, June 1974, in Stillwater, Oklahoma.

Prakasam, T. B. S.; Joo, Y. D.; Srinath, E. G.; and Loehr, R. C. 1974. Nitrogen Removal from a Concentrated Waste by Nitrification and Denitrification. Paper read at 29th Annual Purdue Industrial Waste Conference, May 1974, at Purdue University, West Lafayette, Indiana.

———. 1974. On the Behavior of Nitrifying Populations in a Highly Nitrogenous Waste. Paper presented at the 75th Annual Meeting of the American Society for Microbiology, May 1974, in Chicago, Illinois.

Prakasam, T. B. S.; Loehr, R. C.; Yang, P. Y.; Scott, T. W.; and Bateman, T. W. 1974. *Design parameters for animal waste treatment systems*. Report no. EPA660/2-74-063 at the Office of Research and Development, Environmental Protection Agency.

Rehkugler, G. E. (1974). Thermally induced stresses in eggshells. *Journal of Agricultural Engineering Research* 18:275-279.

Shepardson, E. S.; Pollock, J. G.; and Rehkugler, G. E. 1974. Research and development of a lettuce harvester. *Transactions of ASAE* 17(2): 212-216.

Srinath, E. G.; Prakasam, T. B. S.; and Loehr, R. C. 1974. Estimation of the Mass of Actively Nitrifying Bacteria in a Heterotrophic Eco-system. Paper read at 75th Annual Meeting of the American Society for Microbiology, May 1974, in Chicago, Illinois.

———. 1974. A Technique for Estimating Active Nitrifying Mass and its Application in Designing Nitrifying Systems. Paper read at 29th Annual Purdue Industrial Waste Conference, May 1974, at Purdue University, West Lafayette, Indiana.

Wong-Chong, G. M., and Loehr, R. C. 1974. The Kinetics of Microbial Nitrification. Paper read at the ASCE Environmental Engineering Specialty Conference, 9-11 July 1974, at Pennsylvania State University, University Park, Pennsylvania.

■ APPLIED AND ENGINEERING PHYSICS

Buhrman, R. A., and Jackel, L. D. 1974. Noise Limits of RF-Biased SQUIDS. Paper read at International Magnetism Conference, 14-17 May 1974, in Toronto, Canada.

Chou, M. S., and Cool, T. A. 1974. Chemiluminescence from Short Duration Discharges. Paper read at First Summer Colloquium on Electronic Transition Lasers, 17-19 June 1974, at the University of California, Santa Barbara.

Dionne, N. J., and Rhodin, T. N. 1974. D-band contributions to the energy distribution

of field-emitted electrons from platinum-group metals. *Physical Review Letters* 32: 1311-1314.

Dragsten, P. R.; Webb, W. W.; Paton, J. A.; and Capranica, R. R. 1974. Auditory membrane vibrations—measurements at sub-Angstrom levels by optical heterodyne spectroscopy. *Science* 185:55-57.

Halperin, W. P.; Archie, C. N.; Rasmussen, F. B.; Buhrman, R. A.; and Richardson, R. C. (1974). Observation of nuclear magnetic order in solid ^3He . *Physical Review Letters* 32:927-930.

Lovelace, R. V. E. 1974. Propagation of Electromagnetic Waves through Turbulent Plasmas. Paper read at Second European Conference on Cosmic Plasma Physics, 1-5 July 1974, at Culham Laboratory, England.

McHenry, F.; Hoffman, P.; and Salpeter, M. 1974. Uptake of ^{35}S -sulfate by morphologically differentiated replication chondrocytes in vivo: a double isotope EM autoradiographic study. *Developmental Biology* 39: 96-104.

McIntire, W. R., and Batterman, B. W. 1974. Electron momentum distribution in vanadium and vanadium hydride. *Physical Status Solidi (b)* 63(2):621-624.

Pettit, R. B., and Silcox, J. 1974. Oxide structure of evaporated aluminum films. *Journal of Applied Physics* 45:2858-2866.

Roberto, J. B.; Batterman, B. W.; and Keating, D. T. (1974). Diffraction studies of the (222) reflection of Ge and Si. Anharmonicity and the bonding electrons. *Physical Review B* 10:2148-2158.

Rosch, N., and Rhodin, T. N. 1974. Bonding of ethylene to diatomic nickel according to a self-consistent-field $X\alpha$ scattered wave model. *Physical Review Letters* 32:1189.

Salpeter, M.; McHenry, F.; and Feng, H. 1974. Myoneural junctions in the extraocular muscles of the mouse. *The Anatomical Record* 179:201-224.

■ CHEMICAL ENGINEERING

Bischoff, K. B. 1974. Asymptotic solutions for gas absorption with reaction. *Chemical Engineering Science* 29:1348-1349.

Hamed, G., and Rodriguez, F. 1974. Gelation of Dilute Collagen Solutions by Ultraviolet Light. Paper read at 77th National Meeting of the American Institute of Chemical Engineers, 2-5 June 1974, in Pittsburgh, Pennsylvania.

Stevenson, J. F. 1974. Unsteady mass transfer in a long composite cylinder with inter-

facial resistances. *AIChE Journal* 20:461-466.

Tsuchiya, H. M.; Trivedi, N. C.; and Shuler, M. L. 1974. Microbial mutualism in ore leaching. *Biotechnology and Bioengineering* 16:991-995.

■ CIVIL AND ENVIRONMENTAL ENGINEERING

Armstrong, N. E.; Gloyne, E. F.; Wyss, O.; and Behn, V. C. 1974. Biological Countermeasures to Mitigate the Effects of Hazardous Material Spills. Paper read at Meeting of the American Institute of Chemical Engineers, 25-28 July 1974, in San Francisco, California.

Belcher, D. J. 1974. Land Use and Natural Resources Inventories. Paper read at ASCE Land Use Planning Workshop, 16-17 May 1974, in Washington, D.C.

———. 1974. New techniques of prospecting the littoral. In *Il curso de analisis planeamiento y gestion del medio litoral*, ed. L. L. Pelaez, pp. 264-306. Madrid: Centro de Perfeccionamiento y empresarial.

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Bereano, P. L. 1974. *Air pollution and land use*. Air Resources report no. 2, Hudson Basin Project.

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Cesario, F. J. 1974. Environmental Implications of Transportation Fuel Shortages. Paper read at Symposium on the Effects of Energy Shortages on the Transportation Balance, 8-10 May 1974, at Pennsylvania State University, State College, Pennsylvania.

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Dalla, A. K., and Winter, G. (1974). Steel ductility measurements. *Proceedings of the ASCE, Journal of the Structural Division* 100(ST2):427-444.

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