CONTENTS

1 BACKGROUND AND PERSPECTIVES

Background

The Maurice E. Müller Institute for Biomechanics (MIB) was established as a joint venture between the Maurice E. Müller Foundation and the Medical Faculty of the University of Bern when Prof. M.E. Müller retired, in 1981, as Chairman of the Department of Orthopaedic Surgery at the Inselspital. The Maurice E. Müller Institute for Biomechanics attained the legal status of a full University Institute on January 1, 1995, this decision having been reached by the Bernese Government on May 30, 1994 and approved by the State (Grosser Rat) on June 9, 1994. Its objectives are to continue and extend the work of Maurice E. Müller in biomechanical research of the locomotor system, particularly as relating to orthopaedic surgery. The Institute is supported by a basic operation grant from the Maurice E. Müller Foundation, by funds from the University of Bern, by a grant from the AO/ASIF Foundation, and by project grants from the Swiss National Science Foundation, as well as from various other foundations and industrial sources. The Maurice E. Müller Institute for Biomechanics is currently under the Directorship of Prof. Ernst B. Hunziker, who was elected to this position by the Bernese Government in autumn of 1989.

Objectives

The Institute is conceived as a link between academic research, surgical practice and industrial development. Collaborations with various Research Institutes of the University of Bern, a number of other University Institutes, the Department for Orthopaedic Surgery at the Inselspital and other clinical partners, industrial enterprises as well as with the AO/ASIF Foundation's Research Institute in Davos, are therefore embraced in its functions.

General Research Program

Since the time of its foundation in 1981 until 1988, the MIB was directed by Prof. Stephan S. Perren. The goals of the Institute during this period were to study the normal and disturbed loading patterns of the locomotor apparatus, to improve our understanding of this system, and to promote the knowledge thereby gained in relation to the principles, techniques, instrumentation, and implants applied in orthopaedic surgery. In 1989, Prof. Ernst B. Hunziker took over the Directorship, and research activities in the field of classical biomechanics are now being continued by Dr. Lutz P. Nolte (appointed in 1993) who broadened its scope by including computer assisted surgery. Under Prof. Hunziker's directorship, the Institute's research activities were extended to include basic and applied biological aspects, such as skeletal tissue structure and function, biocompatibility of implant materials, mechanical tissue properties and interface (adhesion) biology at the histological, cellular and molecular levels. With these new dimensions, the Institute aims at an integrated approach to questions raised in connection with the

biomechanics of the musculo-skeletal system, prostheses, endoprostheses, fracture treatment, etc.

Organization

The Institute is comprised of a staff of about 45 people, including medical scientists, biologists, engineers, computer specialists, technicians and research fellows. It consists of two divisions, with a central unit for administration and maintenance. The research activities of one division relate to orthopaedic biomechanics and surgical techniques, whilst those of the other involve basic and applied research in the biology of the musculo-skeletal apparatus. The two divisions collaborate with one another and are supported by a basic technical staff furnishing histological-, computer-, mechanical- and electronic services.

Significance of Research Program

The research activities conducted at the MIB should contribute to our basic understanding of the structure and function of the musculo-skeletal system, and the control mechanisms operating at both the macroscopic, microscopic and molecular levels. The knowledge thereby gained will help us to further develop and optimize materials for clinical application and assist in a more rational rather than empirical approach to the treatment of diseases of the musculo-skeletal system.

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2 RESEARCH ACTIVITIES

2.1 Divison of Orthopaedic Biomechanics

The activities of this Division are directed towards two major areas of research: basic and clinical orthopaedic biomechanics (BCB) and computer assisted surgery (CAS). Additionally, a Clinical Support Group (CSG) was established which consists of full-time orthopaedic surgeons (provided by the Department for Orthopaedic Surgery, Inselspital, Bern and the Semmelweis University of Medicine, Department of Orthopaedic Surgery, Budapest, Hungary) and medical students working on various projects.

In basic and clinical biomechanics, the major areas of focus are state of the art implant evaluations, musculo-skeletal injury mechanisms and low back pain. Research methodologies involve primarily *in vivo* and *in vitro* experimental work as well as mathematical (FE) models. The anatomic areas of interest are the spine, hip, and knee.

Research in the area of computer assisted surgery covers orthopaedic surgical procedures. Proposed and established CAS-systems allow advanced image data acquisition and processing, pre-operative surgical planning and simulation, and intra-operative real-time control and visualization of surgical tools.

In order to account for recent developments in network technologies, the Orthopaedic Biomechanics Division can be reached through the World Wide Web (WWW) at http://cranium.unibe.ch/.

The following abstracts are derived from completed and published studies or reflect ongoing research activities.

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2.1.1 Computer Assisted Surgery (CAS)

A Pilot Study on Computer Assisted Optimal Contouring of Orthopaedic Fixation Devices
M. Liebschner, H. Visarius, E. Arm, T. Lund and L.-P. Nolte

Bending and shaping of longitudinal orthopaedic fixation devices like rods and plates is often a difficult and time-consuming process to be performed during surgery. This study introduces two strategies to obtain parameters necessary for the contouring process. The first strategy utilizes a flexible material to be used intra-operatively to model the optimal shape of the implant. Contour parameters are calculated from the depth image of the model obtained using an object scanner. The alternative strategy is based on surgical navigation techniques as recently introduced to computer assisted neurological and orthopaedic surgery. Geometrical

landmarks are collected with a custom 3D pointing device, e.g. the location of pedicle screws in case of posterior spinal fixation. Subsequently, the final shape for the implant and the associated contouring parameters are calculated. Bending of spinal rod systems is used to illustrate both strategies. Once parameters are obtained, a newly designed semi-automatic bending machine is proposed to impose the computed deformation on the implant material. Integrating the bending device into the generalized concept of local rigid bodies allows for the interactive control of the contouring process.

Image Guidance in Minimally Invasive Surgery
E. Arm, O. Schwarzenbach, B. Jost, H. Visarius and L.-P. Nolte

In a first feasibility study the potential of image guided surgical navigation for minimally invasive approaches to the spine was evaluated. The goal was to establish a safe and accurate method for pedicle screw placement through "keyhole" insertions. Based on principles of computer assisted orthopaedic surgery (CAOS) instruments (awl, probe, drill) equipped with infra-red light emitting diodes are tracked by an opto-electronic camera system. A pre-operatively inserted, calibrated reference clamp is attached to the spinous process through a small insertion. This is intra-operatively used to establish the link between the real patient and medical image (matching). The guidance for the hole preparation is displayed on the computer screen in real-time. The whole surgery can be performed without any C-arm radiation exposure.
After optimization of the clamp mechanism using cadaver spines, the system was successfully applied in three patients.

Clinical Introduction of Image Guided Computer Assistanced Hip Surgery
F. Langlotz, M. Stucki, B. Jost, U. Berlemann, H. Visarius, L.-P. Nolte and R. Ganz

The term periacetabular osteotomy (PAO) refers to a surgical intervention that attempts to correct dysplasia of the hip joint, particularly malposition of the acetabular roof which causes insufficient coverage of the femoral head. The procedure, as performed in Bern, consists of several osteotomies of the pubis, ischium, and ilium and a re-orientation of the acetabular fragment with subsequent fixation. Various solutions exist for a pre-operative determination of the optimal re-orientation of the acetabular cup. However, it has not been possible to apply the planning parameters accurately during the operation. In addition, some of the osteotomies have to be performed without direct visual access to the surgical object due to limitations in the anatomy and exposure. Consequently, there is potential to endanger the hip joint and surrounding structures. It is hypothesized that a combination of accurate 3D-motion tracking together with real-time image processing may establish a link between surgical planning and execution. To our knowledge, this study introduces for the first time an operation-system for PAO that bridges surgical planning, secure intra-operative navigation during the osteotomies, and exact guidance during the re-orientation in accordance with a pre-operative planning.

Development of an Opto-Electronic Positioning Device for Serial Direct Digital Images from Oral Structures

C. Scheer, U. Brägger , L.-P. Nolte , N.P. Lang and W. Bürgin

Since the introduction of dental radiographs in 1986 many efforts have been made to improve the quality of this technique. One of the latest developments is the so called Direct Digital Imaging (DDI). This method promises some important progresses in dental radiology as it improves inconveniences of conventional radiographs decreasing the radiation dose, avoiding film processing procedures, and providing a flexible data storage. Subtraction radiography as another new digital imaging technique for the diagnosis of small changes in dental and bony tissues has been tested in various studies. However, this hybrid method relies on conventional film so far.

The major objective of the present series of studies is to find a way to combine the DDI with the subtraction radiography *in vivo* through the use of surgical navigation techniques. In order to produce digital subtraction images from oral structures based on two direct digital images it is necessary to develop a system which provides repeated exact 3-D-positioning of the image receptor and the X-ray source relative to the area to be evaluated. In order to provide such a controlled and reproducible technique the planned research is subdivided into two specific projects with the following goals:

Project A: To generate the hard- and software for an opto-electronic positioning device for serial direct digital oral radiography.
Project B: To assess the methodical error when obtaining serial standardized direct digital images from oral structures.

The development of the positioning device is an important step to make direct digital imaging for the first time a diagnostic tool in clinical research. Further progress may even lead to applications in the dental office chair for monitoring special sites in patients.

Man-Machine Interfaces in Computer Assisted Surgery

H. Visarius, J. Gong, C. Scheer, S. Haralamb and L.-P. Nolte

The clinical potential of Computer Assisted Surgery (CAS) is more and more acknowledged since CAS systems are emerging from the lab into the operating room (OR).
However, with the establishment of CAS in vivo a new problem complex, which was not addressed in the lab, was introduced - the man-machine interface. Currently, the complexity of available CAS systems requires the presence of at least one system engineer (often called “operator”) in the OR. In turn, there is no possibility for direct communication between the surgeon and the machine or software.

Most of the program steps involved in CAS and choices to be made intra-operatively have to be transferred to the software by means of communication of

the surgeon with the operator. Particularly, the establishment of a relation between the virtual object (i.e. a medical image) and the surgical object (i.e. the patient), often denoted as "matching" or "skeletal registration", requires intensive interaction of the surgeon with the computer.

A literature survey revealed that no CAS system in clinical use exists without a system engineer or a comparable person and our clinical experience indicated that the matching process is a weak point in most systems. Since it appears to be contradictory to cost reduction efforts in health care to have a highly paid specialist in the OR this research evaluates strategies to facilitate the man-machine interface with the final goal to establish a direct control of the system by the surgeon or the medical personal traditionally present at surgeries. Options to be comparatively investigated include: (a) a CAS Control Panel (Virtual Keyboard) as an integrated component of the existing navigation system and (b) introduction of a commercial voice recognition system. The implementation of these strategies into the existing CAS setup at the Department of Orthopaedic Surgery at the Inselspital (University of Bern) and clinical experience gained are reported.

2.1.2 Basic and Clinical Biomechanics (BCB)

A Novel Technique to Determine Interfragmentary Motions in Internally Fixed Femoral Fractures

P. Brunner, J. Bekic, A. Lustenberger and L.-P. Nolte

Despite increased recognition of the role of relative motions in the understanding of fracture healing, detailed description of the complex multidirectional movement in fracture fragments is not available. The purpose of this study was to develop an in vitro technique for direct measurement of the interfragmentary motion of fracture fragments and fixation devices in femoral fractures under quasi-physiologic loading.

Five single and twenty paired fresh human cadaveric femora were subjected to one of three injury models: i) Three-part intertrochanteric fracture (5 pairs), ii) Four-part intertrochanteric fracture (5 pairs), and iii) Subtrochanteric fracture (5 bones). One side of a femur pair was fixed with a dynamic hip screw (DHS) and the contralateral side was fixed with a prototype intramedullary implant (IM). The subtrochanteric fractures were treated with the IM design. Specimens were cyclically loaded to simulate gait with peak loads of 50%, 100%, 150% and 300% bodyweight (BW). The proximal and distal fracture fragments and fixation devices were instrumented with LED marker carriers such that clinically relevant motions (e.g. varus deformity, rotational deformity in femoral shaft and neck axis) could be determined.

In general, deformations remained approximately constant at each loading level and increased with higher loads. Fracture implant inherent mechanical characteristics could be detected: Rotational instability and/or lateral gliding nail were measured. Nevertheless, overall results of the two implant systems for the trochanteric fractures were not significantly different ($p>0.05$).

Previous investigators have used highly sensitive measurement systems to monitor motions of fracture fragments. However, the instrumentation used has typically been limited to one or two selected degrees of freedom. In any type of motion analysis systems the accurate definition of the embedded local coordinate systems is essential for reliable and comparable estimation of relative motion between fragments. The use of an optoelectronic motion tracking system in combination with space digitization of anatomical axes and local rigid body concepts provides a convenient and accurate means for the measurement of interfragmentary motion in femoral fractures in three dimensions.

A New Freezing Technique for the Fixation of Soft Connective Tissues in In Vitro Biomechanical Testing

P. Brunner, L. Schatzmann, L. Rincón, H.U. Stäubli and L.-P. Nolte

The quality of the fixation is essential for in vitro testing of musculo-skeletal soft tissues. It was the aim of this study to develop a new freezing technique for soft connective tissue testing and to validate its applicability in failure testing of two autogenous ACL substitutes.

Sixteen pairs of quadriceps tendons (QT) and patellar ligaments (PL) from human cadavers were prepared. The soft-tissue end of each specimen was placed into a pre-cooled aluminum block, filled with water which subsequently froze, thereby fixing the specimen. The other end of the specimen was attached to bone and was fixed in a traditional method. Mechanical failure testing was performed in a uniaxial tensile test at a constant deformation rate. To study the potential of this method for long term testing, the development of the temperature over time was measured with a PT100 temperature sensor placed in the aluminum block cavity where the ice was formed.

The mean ultimate loads and the failure modes of the quadriceps tendons and the patellar ligaments were determined. Most of the failures occurred at the mid-substance, 10 mm above the fixation site, with no slippage or rupture observed in the fixation zone. Three specimens had an avulsion failure at the patella and data from three specimen were missing due to data recording problems. Mean ultimate load for all tested transplants was 2220 ± 445 N. One measurement showed the ultimate load of 2551 N for the quadriceps tendon and one resulted in 3401 N for a patellar ligament specimen. The temperature measurement showed that the ice reached its lowest temperature of -115 °C after 3 minutes and gradually increased towards 0°C within the next 60 minutes.

This new technique was found to be suitable for failure testing of ligaments and tendons exceeding 3000 N. Due to the high heat capacity and the size of the aluminum block, it was possible to keep a low temperature at the fixation site. No thawing occurred during more than one hour. However, due to the very low temperatures at the fixation site and the growth of the frozen zone towards the center of the specimen, detrimental effects on the biomechanical properties may result from longer testing duration.

Three-Dimensional Motions of Femoral Prosthetic Stems: An In Vitro Evaluation of a Novel Measuring Concept
D.W. Bühler, P. Brunner, U. Berlemann and L.-P. Nolte

Primary stability of uncemented total hip replacements is regarded a major factor for the quality of bony ongrowth to the femoral stem and therefore for the long-term outcome. The objective of this study was to develop, validate, and apply a new technique which allows the precision measurement of the pure 3D interface motion at three different points along the femoral shaft.

The measuring technique is based on a sensor combining optoelectronic with precision mechanical components. The spherical measuring tip is placed on the prosthesis at predefined locations and precision ball bearing mechanics allows transition of the detected motion to a laser diode on the opposite end of the sensor. 3D motion analysis is made possible by considering output data of the PSD (x/y-axis) as well as the registered light intensity (z-axis). Static and dynamic validation indicated a maximal system error of ±4mm within a measuring range of ±750mm in each spatial orientation. Seven paired fresh cadaveric femora were used for testing of two different types of uncemented femoral stems: CLS stem and Cone Prosthesis. Following implantation of the prosthesis, the femora were subjected to sinusoidal cyclic loading in a two-axial materials testing machine at 1, 2, 3 and 4 times body-weight (BW).

The micromovements of the Cone prosthesis showed a significantly smaller amplitude in all three spatial orientations indicating larger “micro-stability” compared to the CLS prosthesis. Both prostheses showed relative stability under the 1- to 3-fold BW loadings. However, the 4-fold BW caused a considerably increased subsidence mainly for the Cone prosthesis indicating less “macro-stability”.

Our novel technique provided reliable and accurate data illustrating the pure 3D interface motion of uncemented femoral stems. Considerable differences in the “micro- and macro-stability” of two prosthesis types could be detected. Analysis of different concepts of femoral stems with the presented standardized approach may further elucidate the role of primary stability for the long-term clinical outcome.

Performance of Short Posterior Spinal Fixators Used in the Stabilisation of Severe Lumbar Anterior Column Injuries
P.A. Cripton , G.M. Jain, L.-P. Nolte and U. Berlemann

Posterior lumbar spinal fixators are commonly used for the stabilization of unstable lumbar spine segments. The objectives of this study were to estimate and measure the forces and moments occurring in these devices and to experimentally evaluate the effect of cross-bracing on their stabilizing potential.

Internal fixator components of a monosegmental posterior implant were idealised as beams and the forces and moments therein were estimated using planar beam bending equations. Material properties of the interconnecting hard and soft tissues

were modelled by linear and rotational springs. An injury parameter (IP) was defined which was a function of the spring constants. The IP was varied between 0 (complete tissue removal) and 1 (intact tissue). Fixator and tissue stresses were analysed for axial compression, flexion and extension loading. It was found that the internal forces and moments in the longitudinal rod increased exponentially as the injury parameter approached 0 (vertebrectomy or removal of disc). The maximum force and moment occurring in one longitudinal rod under simultaneous flexion/compression loading were 500 N and 25 Nm respectively.

Three fresh human lumbar cadaveric functional spinal units were instrumented with AO internal fixators. The longitudinal rods of the fixators had six strain gauges mounted on their surfaces. The forces and moments in the rods were measured for intact specimens and subsequent to removal of the intervertebral disc. The specimens were subjected to flexion/extension, torsion and lateral bending moments of 8 Nm. In the intact specimens, the disc supported significant percentages of the torsional and flexion/extension applied moments. After tissue removal the moments in the longitudinal rods were observed to increase for all loading cases. In flexion the average bending moment in one rod was observed to increase from 0.33 to 3.98 Nm (1100%). In lateral bending a 17% increase in the bending moment was measured. In torsion, an increase of 625% from 0.48 to 3.48 Nm was recorded.

The maximum bending moment some longitudinal rods can be subjected to and still allow an infinite service life has previously been reported to range between 6 and 18 Nm. Our experimental and theoretical results suggest these devices may be operating with very low factors of safety with respect to infinite service life requirements when used to stabilise severe anterior column injuries. This situation may lead to in vivo failure of device components, as has been previously reported, or to loss of correction height due to clamp failure or loosening at the screw bone interface.

Compressive Strength of Interbody Cages: The Effect of Cage Shape and Bone Density

B. Jost, P. Cripton, T. Lund, T. Oxland, K. Lippuner, Ph. Jaeger and L.-P. Nolte

Recently, many cages with different shapes were developed for lumbar interbody fusion. These implants are designed to stabilize the operated segment as well as restore and maintain the disc height. The purpose of this study was to investigate the influence of cage design, posterior instrumentation and bone mineral density on the compressive strength of lumbar spine segments.

Forty-eight human cadaveric lumbosacral functional spine units (FSU) from L2-S1 were used. DEXA scanning was performed on each specimen from a lateral and an anterior-posterior direction to obtain the bone mineral density (BMD) of the vertebral bodies. Twelve specimens were used for each of four different cage designs, six with and six without a standard pedicle instrumentation. An axial compressive displacement of 0.4mm/s was applied to the specimen until failure. The kinematics of adjacent vertebrae and each cage were measured using an optoelectronic measurement system.

There was a statistically significant relationship between all four bone densities and compressive strength. The lateral DEXA scan values (upper vert. R^2= .53; lower vert. R^2= .51) revealed a higher correlation than the A-P (upper vert. R^2= .23; lower vert. R^2= .09). Neither the implant design/ techniques nor the posterior instrumentation had a significant effect on the compressive strength (p=0.8). The average failure loads for all four cages were approximately 5000 N.

In this study, a direct relationship was observed between the failure load of the bone-implant interface and the vertebral bone density. The large range of observed failure loads overlaps the potential in vivo compressive loads, implying that failure of the bone-implant interface may occur clinically. Therefore, pre-operative measurement of BMD may be an effective tool in preventing settling around these implants.

The Effect of Interbody Cages With and Without Posterior Instrumentation on the Three-Dimensional Stability of the Spine - A Biomechanical Evaluation
T. Lund, T. Oxland, B. Jost, P. Cripton, S. Grassmann, C. Etter and L.-P. Nolte

In the past few years, several interbody cages of different designs have been developed to be used via an anterior or posterior approach. The goal of these implants is to stabilize the spine and ultimately achieve an interbody fusion. The goal of this study was to determine the effect of different interbody implant designs/surgical techniques and the effect of posterior instrumentation on the three dimensional stability of the lumbar spine.

Twenty-four human cadaveric lumbar functional spinal units (FSUs) were tested in four different conditions: i) intact, ii) posterior cage insertion, iii) cages with posterior instrumentation and iv) with additional cross bracing. Four different cage types were compared. Pure moments of flexion-extension, lateral bending and axial rotation were applied individually to the upper vertebra in four steps to a maximum of 10 Nm. Custom made markers with light emitting diodes were attached to each block and the movements of these markers were measured with an optoelectronic camera system. The rigid body motion in terms of the top vertebra with respect to the bottom was calculated using custom software.

In flexion-extension, the rectangular and cylindrical cages stabilized the spine to 50-60% of its intact motion but the difference between the four cages was not statistically significant (p=.60). In axial rotation, the cylindrical cage reduced the motion to less than intact but due to variation, the difference between the cages was only marginally significant (p=.07). In lateral bending, the rectangular cage was most stable but the difference between the cages was not statistically significant (p=.30). Universally, the posterior instrumentation significantly reduced the motion in all directions and for all cage types. In flexion-extension and lateral bending, the posterior instrumentation reduced motions to between 10 and 20% of intact motion and to approximately 40% of intact motion in axial rotation. These changes with posterior instrumentation were statistically significant (p<.005) with no differences between the cages. Cross bracing further improved the stability in axial rotation, but the magnitudes were very small.

All cage types included in this study provided the greatest stabilization when used together with posterior instrumentation. The main question lies with what degree of primary stabilization is required to obtain a successful interbody fusion.

2.2. Division of Biology

2.2.1 Tissue Biomechanics and Structural Biology

The main activities in this research area are directed towards elucidating the structural charactersistics of skeletal tissues, particularly of cartilage and bone, and their functional correlates, using both *in vitro* and *in vivo* systems. Current topics include analysis of the mechanical properties and structural composition/organisation of growth- and articular cartilages, as well as investigations relating to the basic physiological mechanisms underlying the differentiation and activity regulation in these tissues.

With respect to bone tissue, studies pertain to mechanisms of osseoinduction and tissue integration processes (particularly as regards to implant materials). These projects are being undertaken with a view to developing new strategies for the treatment of traumatized or diseased cartilage and bone tissue.

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A Molecular Model of Proteoglycan-Associated Electrostatic Forces in Cartilage Mechanics
M.D. Buschmann and A.J. Grodzinsky

Measured values of the swelling pressure of charged proteoglycans (PG) in solution (Williams RPW, and Comper WD; Biophysical Chemistry 36:223, 1990) and the ionic strength dependence of the equilibrium modulus of PG-rich articular cartilage (Eisenberg SR, and Grodzinsky AJ; J Orthop Res 3: 148, 1985) are compared to the predictions of two models. Each model is a representation of electrostatic forces arising from charge present on spatially fixed macromolecules and spatially mobile micro-ions. The first is a macroscopic continuum model based an Donnan equilibrium that includes no molecular-level structure and assumes that the electrical potential is spatially invariant within the polyelectrolyte medium (i.e. zero electric field). The second model is based on a microstructural, molecular-level solution of the Poisson-Boltzmann (PB) equation within a unit cell containing a charged glycosaminoglycan (GAG) molecule and its surrounding atmosphere of mobile ions. This latter approach accounts for the space-varying electrical potential and electrical field between the GAG constituents of the PG. In computations involving no adjustable parameters, the PB-cell model agrees with the measured pressure of PG solutions to within experimental error (10%), whereas the ideal Donnan model overestimates the pressure by up to 3-fold. In computations involving one adjustable parameter for each model, the PB-cell model predicts the ionic strength dependence of the equilibrium modulus of articular cartilage. Near

physiological ionic strength the Donnan model overpredicts the modulus data by 2-fold, but the two models coincide for low ionic strengths (C-0 < 0.025M) where the spatially invariant Donnan potential is a closer approximation to the PB potential distribution. The PB-cell model result indicates that electrostatic forces between adjacent GAGs predominate in determining the swelling pressure of PG in the concentration range found in articular cartilage (20-80 mg/ml). The PB-cell model is also consistent with data (Eisenberg and Grodzinsky, 1985, Lai WM, Hou JS, and Mow VC; J Biomech Eng 113: 245, 1991) showing that these electrostatic forces account for similar to 1/2 (290kPa) the equilibrium modulus of cartilage at physiological ionic strength while absolute swelling pressures may be as low as similar to 25 - 100kPa. This important property of electrostatic repulsion between GAGs that are highly charged but spaced a few Debye lengths apart allows cartilage to resist compression (high modulus) without generating excessive intratissue swelling pressures.

Tenascin-C Expression by Fibroblasts is Elevated in Stressed Collagen Gels
R. Chiquet-Ehrismann, M. Tannheimer, M. Koch, A. Brunner, J. Spring, D. Martin, S. Baumgartner and M. Chiquet

The extracellular matrix protein, tenascin-C, is expressed in tissues subjected to high mechanical strain such as tendons, ligaments, perichondrium and periosteum. Fibroblasts cultured on a collagen matrix exert tractional forces leading to the contraction of floating, unrestrained, collagen gels and to the development of tension in attached, restrained gels. On a restrained collagen gel the fibroblasts synthesize large quantities of tenascin-C, whereas on an unrestrained gel tenascin-C synthesis is decreased. This regulation of tenascin-C synthesis can be observed by the secretion of metabolically labeled protein into the conditioned medium, as well as by the deposition of tenascin-C into the collagen matrix. Regulation appears to occur on the transcriptional level, because when cells on restrained or unrestrained collagen gels are transfected with promoter constructs of the tenascin-C gene, luciferase expression driven by the tenascin-C promoter parallels the effects measured for endogenous tenascin-C synthesis. The promoter region responsible for tenascin-C induction on restrained collagen gels is distinct from the region important for the induction of tenascin by serum, and may define a novel kind of response element. By joining this tenascin-C sequence to the SV40 promoter of a reporter plasmid, its activity can be transferred to the heterologous promoter. We propose that the tenascin-C promoter is directly or indirectly activated in fibroblasts generating and experiencing mechanical stress within a restrained collagen matrix. This may be an important aspect of the regulation of expression of tenascin-C and other matrix proteins during morphogenetic processes such as eg. bone remodeling.

A New Approach for High Resolution Cytochemistry and In Situ Hybridisation of Cartilage Optimally Preserved by Cryoimmobilisation

D. Studer and E.B. Hunziker

The general aim is to understand more about cartilage biology. This is important since cartilage injuries are frequent and in most cases they lead to arthrosis. Induction of regeneration (healing) of cartilage is difficult and often fails since cartilage is neither innervated nor vascularised. The accurate localisation of molecular components in optimally preserved cartilage and the monitoring of their synthesis during regeneration (or development) are two important possibilities to check for example the effects of therapies. The preservation of cartilage ultrastructure, however, especially of the extracellular matrix, is difficult and up to date only satisfying when the tissue is in a first fixation step frozen under high pressure. Establishing cytochemistry and in situ hybridisation protocols on sections optimally preserved by high pressure freezing should allow a precise spatial localisation of molecules and of transcription sites. As a test system we started with rat growth plate where we applied tissue transglutaminase antibodies and riboprobes.

Chondrocyte Biosynthesis Correlates With Local Tissue Strain in Statically Compressed Adult Articular Cartilage

M. Wong, P. Wuethrich, M.D. Buschmann, P. Eggli and E.B. Hunziker

In this study, we investigated the depth-dependent metabolic and structural response of adult articular cartilage to large strain, static, unconfined compression. Changes in cell biosynthetic activity and several morphometry-based structural parameters (cell density, cell volume fraction, cell surface area density, mean cell surface area, and mean cell volume) were measured at eight sites representing different depth-zones between the articular surface and the cartilage/bone border. In addition, local tissue strain in the superficial, transitional, upper radial and lower radial zones was estimated based on the change in cell density values. Static compression of articular cartilage resulted in a highly heterogeneous deformation profile through the depth of the disk as well as zone-specific changes biosynthetic activity, as reflected by ^{3}H-proline incorporation. The strains in the transitional and superficial zones were greater than the applied surface-to-surface strain whereas strains adjacent to the cartilage/bone border were significantly less than the applied strain. Inhibition in biosynthesis was greatest in the upper zone and minimal in the lower zones. Additionally, there was a good correlation between magnitude of compressive strain and change in biosynthetic activity over all zones of articular cartilage. These coordinated changes between cell biosynthesis and cartilage structure provide strong evidence that site-specific variation in mechanical stimuli such as stress and strain is responsible for spatially-varying patterns of cartilage metabolic activity under load. These results are consistent with the hypothesis that interactions between the cell and components in the extracellular matrix form the basis of the transduction mechanism by which mechanical signals direct remodelling of the cartilage extracellular matrix.

Topographical Variation of the Elastic Properties of Canine Knee Articular Cartilage

J.S. Jurvelin, J.A. Arokoski, E.B. Hunziker and H.J. Helminen

Equilibrium response of articular cartilage to indentation loading is controlled by the thickness and elastic properties (shear modulus and Poisson's ratio) of the tissue. In this study, we characterized topographical variation of h, ms and ns in the canine knee joint (N=16). Poisson's ratio of the articular cartilage was measured using a newly developed microscopic technique. In this technique, the shape change of the cartilage disk was visualized, while immersed in physiological solution and compressed in unconfined geometry. After producing a constant 5% axial strain, the lateral strain was quantitated during the stress relaxation. At equilibrium, the lateral-to-axial strain ratio indicates the Poisson's ratio. Indentation creep data was combined with the thickness and Poisson's ratio results at the test site to derive values for shear and aggregate moduli. The elastic properties of the canine knee joint cartilage showed topographical variations. The lowest Poisson's ratio (0.070+/-0.016) was located at the patellar surface femur (FPI) and the highest (0.236+/-0.026) at the medial tibial plateau (TMI). The stiffest cartilage, as judged by the (equilibrium) values of aggregate or shear modulus was found at patellar groove of femur (shear modulus=0.964+/-0.189 MPa, Aggregate modulus=2.084+0.409 MPa) and the softest at the tibial plateaus (shear modulus=0.385+/-0.062, Aggregate modulus=1.113+/-0.141). Similar topographical variation of stiffness over the canine knee joint could be verified using shear modulus calculated either from instantaneous or equilibrium responses. The comparison of the mechanical results and the biochemical composition of the tissue at the test sites of the canine knee joint suggested a strong negative correlation between the Poisson's ratio and collagen-to-PG content ratio. The experimental results of the present study support the idea that, in addition to axial (perpendicular to articular surface), the transverse (parallel to articular surface) tensile stiffness of articular cartilage significantly affects compression of articular cartilage in indentation geometry.

Surface and Sub-Surface Morphology of Bovine Humeral Articular Cartilage as Assessed by Atomic Force- and Transmission Electron Microscopy
J. S. Jurvelin, D. J. Müller, M. Wong, D. Studer, A. Engel and E.B. Hunziker

Maintenance of superficial structural integrity is essential for the load-bearing function of articular cartilage. In this study, we used atomic force microscopy (AFM) to image the 3-D surface and subsurface morphology of fresh bovine humeral head articular cartilage maintained in physiological solution. Complementary ultrastructural data were obtained by transmission electron microscopy (TEM) of cryoprocessed samples. The surface irregularities observed in previous scanning electron microscopic studies were not apparent with AFM. The most superficial layer, typically 200-500 nm thick, consisted of acellular and non-fibrous tissue. Occasionally, it exhibited local discontinuities through which the underlying network of collagen fibrils, oriented parallel to the surface and displaying the characteristic periodic banding, could been seen. Local variations in force-curve measurements indicate the existence of differences in micromechanical properties along the articular surface. AFM thus furnishes a new method for characterizing the surface structure and properties of freshly excised articular cartilage in physiologically relevant conditions. It confirms the existence of an

amorphous, non-fibrous articular surface which may be vital for its normal lubrication and wearing properties in vivo.

Significance of the Superficial Tissue Layer on the Indentation Response of Articular Cartilage

J.S. Jurvelin, M. Wong, J. Arokoski, H.J. Helminen and E.B. Hunziker

Articular cartilage is unhomogeneous and anisotropic tissue. In this study, we investigate experimentally and theoretically the effect of the superficial, collageneous tissue layer on the indentation response of canine articular cartilage. Indentation creep technique was used to characterize compressive stiffness of canine femoral, tibial and humeral articular cartilage (n=57). Cartilage thickness and Poisson's ratio, necessary for the calculation of the compressive moduli, were determined optically for the tissue. Using a polarization microscopic technique the thickness of the tissue zones (superficial, intermediate, deep) were determined. Experimental indentation geometry was modelled with an FEM-technique. In the model tissue consisted of 10 elastic, transversely isotropic layers. For each layer, anisotropic material parameters could be adjusted. The layered, transversely isotropic model was compared with the single layer isotropic model and, thereby, used to quantitate influence of the thickness and transverse modulus of the superficial layer on the instantaneous (dynamic) and equilibrium (static) indentation behaviour. Significant, site-dependent variation of structural and functional tissue parameters was found in the canine articular cartilage. The mean values for thickness, (equilibrium) shear modulus and Poisson's ratio were 0.74+/-0.24mm, 0.67+/-0.26 MPa and 0.14+/-0.06, repectively. Relative thickness of the superficial tissue layer varied from 4.53+/-1.32 % (lateral condyle of tibia) to 20.32+/-5.77 % (femoral groove). A highly significant correlation was found between relative thickness of the superficial cartilage layer and the dynamic (r=0.78, n=57) or static (r=0.60, n=57) indentation stiffness. The FEM analyses revealed that the properties and thickness of the superficial tissue layered significantly influenced the indentation response. By implementing typical values of axial (1 MPa) and tranverse modulus (10 MPa) for the superficial tissue layer a significant reduction (>20%) of the indentation deformation, as compared to isotropic indentation model, was found, especially if high axial Poisson's ratio was assumed. Our experimental results indicate a strong positive correlation between the indentation shear modulus of uncalcified cartilage and relative thickness of the superifical tissue layer. The FEM-analyses confirm that the high transverse tensile stiffness of the superficial tissue increases the mechanical resistance of articular cartilage to indentation. The contribution of the superficial tissue to indentation resistance is most significant during high strain rate loading when interstitial water flow is negligible, tissue volume is preserved and extensive lateral expansion of the tissue under load is produced.

2.2.2 Molecular and Cellular Biomechanics

The main activities encompassed within the scope of this research area are directed towards elucidating the composition and functional properties of skeletal tissue elements at the molecular and cellular levels. Experimental methodology involves principally in vitro systems, cartilage and connective tissues being the main tissues investigated. Current topics dealt with include the analysis of structural and functional properties of components contained in adult human articular cartilage, foetal cartilages and loose connective tissues. Newly-identified extracellular constituents are being cloned, sequenced and analyzed from a functional viewpoint.

* * *

Large and Small Splice Variants of Collagen XII: Differential Expression and Ligand Binding

M. Koch, B. Bohrmann, M. Matthison, C. Hagios, B. Trueb and M. Chiquet

Collagen XII colocalizes with collagen fibrils mainly in skin, bone, tendons and ligaments. The molecule has a short collagenous tail and a very large, three-armed NC3 domain consisting primarily of fibronectin type III repeats. Differential splicing within this domain gives rise to a large (320 kD) and a small (220 kD) subunit; the large but not the small can carry glycosaminoglycan. To investigate whether collagen XII variants have distinct expression patterns and functions, we generated antibody and cDNA probes specific for the alternatively spliced domain. We report that the large variant has a more restricted expression in embryonic tissue than the small. For example, whereas the small variant is widespread in the dermis, the large is limited to the base of feather buds in the chick. Distinct proportions of mRNA for the two variants were detected depending on the tissue. Monoclonal antibodies allowed us to separate collagen XII variants, and to show that homo- and heterotrimers exist. Collagen XII variants differ in ligand binding. Small subunits interact weakly with heparin via their C-terminal domain. Large subunits have additional, stronger heparin binding site(s) in their N-terminal extra domain. In vivo, both large and small collagen XII are associated with interstitial collagen. We showed biochemically and ultrastructurally that collagen XII can be incorporated into collagen I fibrils when it is present during, but not after, fibril formation. Removal of the collagenous domain of collagen XII reduces its coprecipitation with collagen I. Our results indicate that collagen XII is specifically associated with fibrillar collagen, and that the large variant has binding sites for extracellular ligands not present in the small variant.

Age Dependent Accumulation of HABR Fragments Takes Place Between Truly Immature and Young Cartilage

H.J. Häuselmann, E.J.-M.A Thonar, B.A Michel and M. Paulsson

Articular cartilage undergoes a number of characteristic but not well understood changes with aging. The tissue becomes enriched in aggrecan-derived fragments that contain few if any CS or KS chains and consist predominantly of the HABR of the aggrecan molecule; it has been suggested, although not shown directly, that these fragments are retained in the tissue through their interaction with HA (Roughley et al., 1986; Bayliss, 1990). Aging appears to have the most profound effect on the composition and stability of proteoglycans (PGs) and is considered the main risk factor in the pathogenesis of osteoarthrosis. Our studies were performed to identify the HABR-containing fragments (HABR fragments) in human and bovine cartilages of different ages and to determine if the changes are related to an age-dependent increase in the production of the fragments by the chondrocytes.
Our findings that the quantity and size of HABR fragments is very different in immature bovine cartilage than in the 14-18 month old steer or the 6 year old cow suggest that the previously reported age-related increase in the concentration of HABR fragments may reflect mostly differences in the metabolism of mature and immature cartilages rather than a progressive accumulation of these fragments during adult life.

Nitric Oxide and the Synthesis of Prostaglandin E_2 and Cytokines by Human Articular Chondrocytes

H.J. Häuselmann, L. Oppliger, M. A. Michel, M.Cao, L.A. Larkin, M. Stefanovic-Racic and C.H. Evans

Although it is now well established that articular chondrocytes synthesize large amounts of nitric oxide (NO) in response to cytokines such as interleukin-1 (IL-1), the physiological significance of this remains unclear. Endogenously synthesized NO appears to inhibit the biosynthesis of aggrecan and promote lactate production, but little other information is available. To further our understanding of how NO affects chondrocyte metabolism, we have evaluated the effect of L-mono-methylarginine (L-NMA), an inhibitor of NO synthase, on the production of prostaglandin E_2 (PGE_2), interleukins-1 and 6 and the interleukin-1 receptor antagonist (IL-1ra) by human articular chondrocytes tretated with human recombinant IL-1.
The addition of hrIL-1α or β failed to induce detectable amounts of chondrocytes' IL-1α or β, regardless of the presence or absence of L-NMA. Production of IL-1ra increased approximately ten-fold in response to added IL-1, but this was only sligthly affected by L-NMA. PGE_2 and IL-6 production increased considerably in response to IL-1 and were further stimulated when NO synthesis was inhibited by L-NMA.
These data suggest that endogenously produced NO limits the ability of chondrocytes to synthesize PGE_2 and IL-6 in response to IL-1. Further studies are necessary to determine whether this is related to the ability of NO to suppress matrix synthesis in this system.

Small Fragments of Cartilage Oligomeric Matrix Protein in Synovial Fluids of Rheumatoid Arthritis Patients

M. Neidhart, N. Hauser, M. Paulsson, P. DiCesare, B.A. Michel and H.J. Häuselmann

Cartilage oligomeric matrix protein (COMP), a pentameric chondrocyte binding glycoprotein is abundant in articular cartilage and tendon. In joint fluid, increased level of COMP is found after knee injury, in early stage osteoarthritis (OA) and in reactive arthritis. In contrast, in patients with rheumatoid arthritis (RA) and advanced destruction of the joints and in patients with long standing reactive arthritis, COMP is decreased. In serum , increased level of COMP occurs in early stage OA and RA, as well as in reactive arthritis. RA patients with rapidly progressive joint destruction have increased levels of COMP initially, which subsequently decreases.
Our studies demonstrate that in synovial fluid, COMP greatly varied quantitatively and qualitatively from one person to another. Interestingly, small fragments (50-70 kDa) were found almost exclusively in patients with RA or other forms of inflammatory arthritis, but much less in OA. These small fragments could reflect the action of various proteases involved in the degradation of articular cartilage. In serum the levels of COMP were increased in all patient groups.
Thus the serum levels of COMP and the pattens of its degradation products in synovial fluid seem to be promising as markers of articular cartilage damage.

The Promoters of the Type VI Collagen Genes
T.E. Willimann, M.U. Kopp and B. Trueb

Collagen VI is a hybrid molecule with a central triple helix flanked by large globular domains. It is composed of three polypeptide chains that are encoded by three distinct genes. The heterotrimeric protein serves as an important cell adhesion substrate and it has attracted considerable attention because it is completely lost after oncogenic transformation. To study its regulation, we have isolated the complete genes for the α1(VI) and the α2(VI) subunit. Both genes exhibited a complex multi-exon structure that reflected the multi-domain structure of the polypeptides. The promoters resembled the 5' flanking regions of house-keeping genes and of some oncogenes. So far we have identified three DNA elements in the two promoters that interacted with nuclear proteins. Two elements bound the transcription factors Sp1 and Sp3 while the third elements bound a novel factor of 43 kDa. When linked to a reporter gene, the three elements were sufficient to induce a high level of transcription in chicken fibroblasts. As soon as a single element was deleted from this construct, the promoter activity decreased dramatically. Thus, the three elements are essential for the transcriptional activation of the α1(VI) and the α2(VI) collagen gene.

Alternative Splicing of Type VI Collagen
C. Wälchli and B. Trueb

Alternative splicing of the primary gene transcript plays an important role in the generation of diversity within a protein family. In the case of collagen VI, two

types of mRNA molecules with different 3' ends are transcribed from the α2(VI) collagen gene. The major splice variant encodes a polypeptide with a von Willebrand factor A domain at its carboxyl terminus. In the minor splice variant, this A domain is replaced by a novel motif which reveals some similarity to a fibronectin type III repeat. In situ hybridization experiments demonstrated that the major transcript is ubiquitously expressed. Substantial amounts were found in skeletal and cardiac muscle, gizzard, skin, tendon, liver, the wall of blood vessels and the connective tissue of peripheral nerves. In contrast, the minor transcript was expressed at a very low level and could hardly be detected in any tissue by in situ hybridization. Only the aortic wall contained a considerable amount of this splice variant. However, no difference was observed by Northern blotting and the polymerase chain reaction in the ratio of the two transcripts when aorta and the other tissues were compared. Thus, the minor splice variant is not expressed in a tissue specific manner and consequently, it does not play a tissue specific role. It might rather serve a general function in the structure and assembly of type VI collagen microfibrils.

Loss of Tissue Transglutaminase by Tumor Cells
T. Schenker, J. Zumbrunn and B. Trueb

Eukaryotic cells that are transformed by oncogenic viruses undergo dramatic changes in their phenotype. It is generally assumed that these changes are caused by the loss of distinct proteins which are involved in cell adhesion and attachment. To investigate these alterations at the molecular level, we prepared a subtracted cDNA library with RNA from normal and transformed fibroblasts. This library contained many clones for proteins of the extracellular matrix (fibronectin) and the cytoskeleton (vinculin). One of the clones that was largely down-regulated in the transformed state was found to code for human tissue transglutaminase. The complete loss of tissue transglutaminase in transformed fibroblasts is intriguing. This protein belongs to a growing family of enzymes that catalyze the formation of ε-(γ-glutamyl) lysine cross-links between two polypeptide chains. Tissue transglutaminase seems to play an additional role in the growth and progression of human tumors. An inverse correlation has been observed between the activity of the enzyme and the development of the malignant phenotype. We analyzed ten human tumor cell lines for the expression of tissue transglutaminase by Northern blotting experiments. Some of these cell lines did not reveal any traces of the mRNA for this enzyme, while others possessed large amounts. Thus, the mRNA level for tissue transglutaminase does not strictly correlate with the establishment of the transformed phenotype.

Regulation of Collagen XII Synthesis in Transformed Cells
M. Kopp and B. Trueb

Recently a new group of proteins has been identified that is associated with interstitial collagen fibrils. We have cloned and characterized two members of this

group, termed collagen XII and XIV. These proteins contain a short triple helix at their C-terminus and a very large globular domain at their N-terminus. The N-terminal domain is composed of many type III repeats (as found in fibronectin) and of several A-modules (as found in von Willebrand factor). It is likely that these proteins mediate essential interactions between collagen fibrils and other components of the extracellular matrix. We could now demonstrate that collagen XII is produced in large amounts by fibroblasts cultivated in vitro. However, this protein was completely absent from cells transformed by the oncogene *v-myc* or *v-src* as well as from cells derived from a methylcholanthrene induced fibrosarcoma. Since all these cells lacked any mRNA for collagen XII, it seemed likely that the synthesis was blocked at the transcriptional level. Experiments with a temperature-sensitive mutant of Rous sarcoma virus demonstrated that a single oncogene product was sufficient to inhibit the synthesis. A reduction in the expression of collagen XII may have profound effects on the stability of the extracellular matrix of transformed cells.

Transglutaminase-Catalyzed Matrix Cross-Linking in Differentiating Cartilage: Identification of Osteonectin as a Major Glutraminyl Substrate
D. Aeschlimann, O. Kaupp and M. Paulsson

The expression of tissue transglutaminase in skeletal tissues is strictly regulated and correlates with chondrocyte differentiation and cartilage calcification in endochondral bone formation and in maturation of tracheal cartilage (D. Aeschlimann, A. Wetterwald, H. Fleisch, and M. Paulsson. 1993, J. Cell Biol. 120:1461-1470). We now demonstrate the transglutaminase reaction product, the gamma-glutamyl-epsilon-lysine cross-link, in the matrix of hypertrophic cartilage using a novel cross-link specific antibody. Incorporation of the synthetic transglutaminase substrate monodansylcadaverine (amine donor) in cultured tracheal explants reveals enzyme activity in the pericellular matrix of hypertrophic chondrocytes in the central, calcifying areas of the horseshoe-shaped cartilages. One predominant glutaminyl substrate (amine acceptor) in the chondrocyte matrix is osteonectin as revealed by incorporation of the dansyl label in culture. Indeed, nonreducible osteonectin-containing complexes of similar to 65, 90, and 175 kD can be extracted from mature tracheal cartilage. In vitro cross-linking of osteonectin by tissue transglutaminase gives similar products of similar to 90 and 175 kD, indicating that the complexes in cartilage represent osteonectin oligomers. The demonstration of extracellular transglutaminase activity in differentiating cartilage, i.e., cross-linking of osteonectin in situ, shows that tissue transglutaminase-catalyzed cross-linking is a physiological mechanism for cartilage matrix stabilization.

Cartilage Oligomeric Matrix Protein: Isolation and Characterization from Human Articular Cartilage
P.E. DiCesare, M. Mörgelin, C.S. Carlson, S. Pasumarti and M. Paulsson

Cartilage oligomeric matrix protein was purified in a native form from normal adult human articular cartilage. The key steps in the purification scheme were

selective extraction with buffer containing EDTA, wheat germ agglutinin affinity chromatography, and removal of the related protein thrombospondin by heparin affinity chromatography. Particles of cartilage oligomeric matrix protein viewed by electron microscopy after rotary shadowing revealed structures similar to the prototype molecule purified from Swarm rat chondrosarcoma. The protein demonstrated a bouquet-like five-armed structure, with peripheral globular domains connected by thin flexible strands to a central assembly domain. Immunohistochemistry revealed age-dependent differences in the protein's distribution in cartilage. In normal human adult articular cartilage, there was a relatively uniform distribution throughout the interterritorial extracellular matrix, whereas in fetal articular cartilage, immunostaining was localized to the extracellular matrix directly adjacent to the chondrocytes. The isolation and characterization of human cartilage oligomeric matrix protein will facilitate its study in pathological conditions of human cartilage.

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4 RESEARCH PROJECT GRANTS

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Visarius H.: CT Data Decoding, Sulzer Medica, Winterthur, 1.7.1995 - 1.4.1996

Visarius H.: Introduction of a touch-screen monitor as a man-machine interface in CAS, University of Bern - Josephine Clark Fonds, Bern. 1.2.1995 - 1.5.1995

Wong M.: The Effect of Dynamic Mechanical Loading on Gene Expression and Biosynthesis in Adult Articular Cartilage, Swiss National Science Foundation, Bern, 1.10.1994 - 1.10.1996

Wong M., Hunziker E.B. and Grodzinsky A.: Structural Response of Chondrocytes to Mechanical Loading, AO/ASIF Research Commission, Bern. 1.1.1995 - 31.12.1995

5 TEACHING ACTIVITIES

University of Bern:

- 4011: Coordinated lecture series in physics, chemistry, embryology, ecology, genetics, molecular biology, anatomy and psychology at the University of Bern
- 4021: Coordinated lecture series in biochemistry, morphology, physiology and psychology
- 4013: Histology course
- 4031: Clinical-theoretical course on the locomotor apparatus
- 7202: Lecture at the Philosophisch-naturwissenschaftliche Fakultät der Universität Bern. Biochemische Methoden II.
- Lectures on ‘Biomechanics of the locomotor apparatus’ for students of the School of Physiotherapy, Inselspital, Bern

University of Basel:

- Lecture series at the Biocenter, University of Basel:
- 4453: Extracellular matrix molecules and their receptors

Federal Institute of Technology, Zurich:

- 01-319: Kolloquium in Biochemistry at the ETH Zürich

University of Zürich

- Nr. 718: Fallbesprechungen

Teaching participation in hip courses for orthopaedic surgeons; seminars and colloquia within the postgraduate training program.

Doctoral students: E. Arm, D. Bühler. P. Cripton, J. Geiss, N. Hauser, F. Langlotz, M. Oetliker, P. Wüthrich

6 FELLOWSHIPS, DISSERTATIONS AND MASTER THESES

6.1 Fellowships

Jurvelin Jukka: Postdoctoral fellowship of the M.E. Müller Foundation, Bern, Switzerland

Shimaoka Eva: Combined postdoctoral fellowship between the Swiss National Science Foundation, Bern, Switzerland and the National Institutes of Health, Washington, USA

6.2 Dissertations completed

Renfer Katharina, M.D. University of Zürich, Medical Faculty
A new instrument to measure skin elevation (Sklerimeter)

Marti Kornelia, M.D. University of Zürich, Medical Faculty
Correlation of quantitative and qualitative measurements of cartilage oligomeric matrix protein in patients with rheumatoid arthritis, osteoarthritis and other forms of arthritis to disease activity or joint damage

Koch Manuel, Ph.D. University of Basel
Collagen XII splice variants: extracellular matrix proteins with distinct structure, expression and function

6.3 Masters theses completed

Stange Holger: Contribution to the development and clinical evaluation of instruments for computer assisted surgical procedures (In German).

Liebschner Michael: A pilot study on computer assisted contouring of spinal implants (In German).

7 HONORS AND AWARDS

The research group "Computer Assisted Surgery" of the Orthopaedic Biomechanics Division was selected to be a representative for innovative technologies in Switzerland for 1995. This award was granted by the Swiss Chamber of Commerce.

In December 1995, Dr. Lutz-Peter Nolte was nominated as Adjunct Associate Professor of Mechanical Engineering by the Faculty of Applied Science of Queen's University, Kingston, Ontario, Canada.

8 GUEST PRESENTATIONS

12.1. - Dr. rer. nat. Christoph Bourauel: Aspects of Orthodontic Biomechanics. Poliklinik für Kieferorthopädie, Bonn, Germany.

7.2. - Stéphane Lavallée, PhD: Computer-integrated Surgery at TIMC. Technique de l'Imagerie, la Modelisation et la Cognition, Grenoble, France.

24.2. - Dr. H. Hohenberg: Mikrotechniken und Hochdruckgefrieren: Neue Wege zur lebensnahen Abbildung nativen zellulären Materials im Elektronenmikroskop. Universität Hamburg, Germany

8.3. - Prof. Peter Bösiger: Magnetic Resonance Imaging for the Assessment of Cardiovascular Functions. Institut für Biomedizinische Technik und Medizinische Informatik, ETH, Zürich, CH.

18.4. - Stephen Ferguson: Research Overview: Fracture Fixation, Resorbable Orthopaedic Implants. AO Forschungsinstitut, Davos, CH.

26.4. - Prof. Dr. W. Pietraskiewicz: Basic problems of the Nonlinear Theory of Thin Shells. Polish Academy of Sciences, Gdansk, Poland.

20.6. - Prof. Dr. R. Friis: Searching for Programmed Cell Death Genes. Dept. of Clinical and Experimental Research, University of Bern, CH.

27.6. - Dr.-Ing. Egbert Schopphoff: Contribution to the Biomechanics of the Human Lumbar Spine. Ruhr-Universität Bochum, Germany.

10.7. Genevieve Dumas, PhD: Risk Factors for Low Back Pain in Industry: Queen's-Dupont Longitudinal Study. Queens University, Kingston, Canada.

11.7. - Prof. Dr.-Ing. Ulrich Hahn: Digital Filters - An Introduction. FH Giessen-Friedberg, Germany

11.7. Marwan Sati, M.Sc.: Computer-assisted Knee Surgery. Ecole Polytechnique, Montreal, Canada.

14.9. - Prof. Dan Daniels, PhD: Spine Stabilization Systems: Rationale & Results for Displacement-Based Evaluation Using Cadaver Spines. University of Tennessee College of Medicine, Memphis, USA

21.9. - Dr.med. Dipl.-Ing. H.M. Overhoff: Computer-assisted Planning of Pelvic Surgeries. Universität Hildesheim, Germany.

23.10. - Catherine M. Ford, PhD Candidate: Predicting Hip Fracture Using Finite Element Models: Factors Affecting Femoral Strength. Orthopaedic Biomechanics Laboratory, Beth Israel Hospital, Harvard University, Boston, MA, USA

25.10. - Prof. Dr. P. Rüegsegger: From Bone Density to Bone Strength - A New Approach to Analyze Bone Quality. Institut für Biomedizinische Technik und Medizinische Informatik, ETH, Zürich, CH.

9 PERSONNEL

9.1 Faculty

Hunziker Ernst B., M.D., Prof.	Director	11.89 -
	* * *	
Nolte Lutz-Peter, Ph.D.	Division Head	05.93 -
Paulsson Mats E., M.D., Prof.	Deputy Division Head	10.90 - 01.95
Trueb Beat, Ph.D., PD	Deputy Division Head	04.95 -
Chiquet Matthias, Ph.D. PD	Research Group Head (80%)	05.95 -
Häuselmann Hans Jörg, M.D.	Research Group Head (External Funding)	10.93 -
Oxland Thomas, Ph.D	BCB Group Head	08.95 -
Studer Daniel, Ph.D.	Research Group Head (80%)	03.92 -
Visarius Heiko, Ph.D.	CAS Group Head	02.94 -
Wong Marcy, Ph.D.	Research Group Head (70%)	02.92 -

9.2 Research Associates

Akbary Temor, cand. Ing.	Guest Student	10.95 -
Arm Erich, dipl.Ing. ETH	Ph.D.-Student	09.93 - 12.95
Belluoccio Daniele, dipl. Biol.	Ph.D.-Student	05.95 -
Bourquin Yvan, Dipl. Inf. HTL	Assistant	11.95 -
Brandenberger Ralph, dipl. Biol.	Ph.D.-Student	05.95 -
Brunner Peter, dipl.Ing. ETH	Assistant	06.91 -
Bühler Daniel, dipl.Ing. ETH	Ph.D.-Student	08.93 -
Cripton Peter, B.Sc., M.Sc.	Ph.D.-Student	11.93 -
Frei Hanspeter, dipl. Ing.	Assistant	05.94 -
Geiss Jana, cand. med.	M.D.-Student	09.94 -
Gleising Volker, cand. Ing.	Guest Student	04.95 - 10.95
Gong Jianxing, Ph.D.	Assistant	07.94 -
Grassmann Stephanie, M.Sc.	Exchange Student	09.95 -
Haralamb Sorin, Dipl. Ing HTL	Assistant	10.94 - 09.95
Hauser Niklaus, dipl. Biol.	Ph.D.-Student	03.92 - 01.95
Hofstetter Robert, cand. Ing.	Guest Student	11.95 -
Jaquemar Daniel, dipl. Naturw.	Ph.D.-Student	08.95 -
Jost Bernhard, M.D.	Assistant	01.95 - 12.95
Jurvelin Jukka, Ph.D.	Fellow	09.93 - 08.95
Koch Manuel, Ph.D.	Assistant	05.95 - 09.95
Kopp Martin, dipl. Naturw.	Ph.D.-Student	10.92 -
Langlotz Frank, dipl. Ing.	Ph.D.-Student	05.93 -
Liebschner Michael, cand. Ing	Guest Student	01.95 - 09.95
Lund Teija, M.D.	Assistant	01.95 -
Maurer Anne Marie, B.Sc., M.Sc.	Ph.D.-Student	05.93 - 06.95
Michel Martin, Ph.D.	Assistant	04.93 - 03.95
Monin Daniel , cand. med.	M.D.-Student	01.94 -
Neidhart Michael, Ph.D.	Assistant	04.94 - 08.95
Oetliker Martina, Dr. med. vet.	Ph.D.-Student	11.95 -
Ponticiello Michael	M.S.	09.95 -
Pfister Martin	Assistant	07.95 - 07.95
Rincón Liliana, M.Sc.	Exchange Student	10.94 - 09.95
Scheer Carsten, dipl. Ing.	Assistant	07.94 -
Shimaoka Eva, M.D.	Fellow	01.95 - 08.95
Siragusa Patrick, cand. med.	M.D.-Student	02.95 -
Stange Holger, cand. Ing.	Guest Student	08.94 - 01.95
Stucki Manfred, cand. med.	M.D.-Student	03.95 -
Tobler Markus, Ph.D.	Assistant (65%)	08.94 - 02.95
Wälchli Chantal, Ph.D.	Postdoctoral Fellow	10.95 - 10.95
Wüthrich Patrick, cand. med.	M.D.-Student	08.94 -
Zumbrunn Jürg, dipl. Biol.	Ph.D.-Student	04.95 -

9.3 Technical and Administrative Staff

Berger Elke	Res. Technologist (50%)	01.90 -
Buchschacher Bruno	Technician	05.95 - 09.95
Fiechter Esther	Secretary (80%)	07.95 -
Finsterwald Karin	Res. Technologist	09.93 - 05.95
Gnahoré Esther	Secretary (50%)	12.90 -
Hubler Roswitha	Secretary (90%)	03.95 - 05.95
Hutzli Walter	Aid Lab. Technician	11.89 -
Kapfinger Eva	Res. Technologist (75%)	11.89 -
Kaufmann Nicole	Res. Technologist	08.95 -
Kaupp Tanja	Res. Technologist	11.89 - 04.95
Künzli Silvia	Res. Technologist	08.95 -
Mühlheim Erland	Mechanicien (50%)	01.92 -
Mumenthaler Urs	Res. Technologist (60%)	06.95 -
Neuenschwander Annelies	Secretary (35%)	04.95 -
Oppliger Elisabeth	Res. Technologist	11.93 - 04.95
Rickli Verena	Secretary (90%)	03.90 - 03.95
Rohrer Urs	Head Mech. Workshop	07.91 -
Schaub Ursula	Res. Technologist	01.95 - 12.95
Schenker Thomas	Chief Technician	04.95 -
Wagner Jeannine	Res. Technologist	11.89 - 03.95

9.4 Scientific Consultant

Prof. Dr. Robert K. Schenk, Institute of Pathophysiology, University of Bern, Switzerland

9.5 Guest Scientists

Prof. Dr. Carl De Silva, Wayne State University, Detroit, MI, USA

Dr. Ing. hab. Marek Szwabowicz, Institute of Fluid Flow Machinery, Polish Academy of Sciences, Gdansk, Poland

Thomas Quinn, Ph.D.-Student, Massachusetts Institute of Technology, Cambridge, MA, USA

10 MISCELLANEOUS

10.1 Conferences Organized

International Symposium on the Structure and Function of Extracellular Matrix, in Honour of Profs. Jürgen Engel and Kaspar Winterhalter, Schloss Ringberg, Germany, March 20-21, 1995

Workshop on 'Computer Signal Processing in Clinical Medicine and Biomedical Engineering (in collaboration with the Department of Cardiology), University of Bern, Bern, Switzerland, June 9-10, 1995

1st CAOS-Symposium, Computer Assisted Orthopaedic Surgery, University of Bern, Bern, Switzerland, Nov 30 - Dec 1, 1995

10.2 Exhibits

Hannover Industrial Exhibition, Hannover (GER), Apr 3-8, 1995: Swiss Chamber of Commerce Technology Award: A Technique for Computer-assisted Spine Surgery

11 MEMBERS OF THE SCIENTIFIC ADVISORY BOARD (KURATORIUM)

- Prof. Dr. A. Geering (President), Dept. for Dental Prosthetics, Dental Clinics, University of Bern, Inselspital, Bern
- Prof. Dr. R. Ganz, Department of Orthopaedic Surgery, University of Bern, Inselspital, Bern
- Mr. U.G. Jann, AO/ASIF-Foundation, Davos
- Prof. Dr. J. Reichen, Depts. for Clinical Research and Clinical Pharmacology, University of Bern, Bern
- Prof. Dr. H. Reuter, Dept. of Pharmacology, University of Bern, Bern
- Prof. Dr. E.R. Weibel (Secretary and Vice President), M.E. Müller Foundation, Bern
- Prof. Dr. M.E. Müller, Honorary Board Member, President of the M.E. Müller Foundation, Bern