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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. The objectives of the Institute are basic and applied biomechanical research of the locomotor system at the organism, tissue, cellular and molecular length scales. 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's efforts are directed towards the development of an integrated understanding of the structure and function of the musculo-skeletal system at the organism, tissue, cellular and molecular length scales, and the development and optimization of information, materials, and techniques for clinical application in the detection and treatment of musculo-skeletal diseases. It is thus 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.

Previous and Current 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 he has then extended the Institute's research activities to include basic and applied biological aspects of skeletal tissue structure and function at the tissue, cellular and molecular levels, such as biochemistry, molecular biology, microstructural preservation, histological-morphometric analysis, compatibility of implant materials, interfacial (adhesion) biology, mechanical properties, and metabolic cell- and tissue responses to mechanical stimuli. Research activities in the field of classical biomechanics are currently being continued by PD Dr. Lutz-P. Nolte, who broadened its scope and

extended the Institute's research activities to include computer-assisted surgery. In 1993 Dr. Nolte was appointed Head of the Institute's Division of Orthopaedic Biomechanics. Prof. Hunziker is, in addition to being Director of the Müller-Institute for Biomechanics, also the Head of the Institute's Division of Biology, of which PD Dr. Beat Trueb is Associate Head.

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 and novel biological treatment strategies.

Organization

The Institute is comprised of a staff of about 65 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, while 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. The Institute of Biomechanics can be reached through the World Wide Web (WWW) at http://www-mem.unibe.ch.

Significance of Research Program

The research activities conducted at the MIB contribute to our basic understanding of the structure and function of the musculo-skeletal system and the control mechanisms operating at both the organ, tissue, cellular and molecular levels. The knowledge thereby gained will help us to further develop and optimize materials for clinical application, conceive novel biologically based treatment strategies and assist in a rational, scientific approach to the treatment of diseases of the musculo-skeletal system.

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2 RESEARCH ACTIVITIES

2.1. Division of Biology

2.1.1 Molecular 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 level. 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.

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Characterization of Matrilin-3 from Chicken Cartilage
D. Belluoccio and B. Trueb

By subtractive cDNA cloning we have identified a novel constituent of chicken cartilage which was termed matrilin-3. This constituent is encoded by a mRNA of 2.2 kb whose expression is restricted to cartilaginous tissues. The predicted protein is composed of 452 amino acids with a molecular mass of 49 kDa. It contains a single von Willebrand factor A-like domain, four epidermal growth factor-like repeats and an α-helical region which may induce the formation of oligomers via a coiled-coil. The primary structure is similar to that of matrilin-1 (CMP) which is also expressed in a cartilage-specific manner. This similarity suggests that the genes for the two proteins may have evolved from a common ancestor by gene duplication.

Down-regulated Proteins of Mesenchymal Tumor Cells
T. Schenker and B. Trueb

To identify proteins that are lost during the establishment of the transformed phenotype of a tumor cell, we have prepared a subtracted cDNA library with mRNA from normal human fibroblasts and from their matched SV40 transformed counterparts. More than 40 clones were obtained that showed a dramatic reduction in their relative expression after oncogenic transformation. The proteins encoded by these clones could be grouped into four distinct classes: extracellular matrix proteins (fibronectin, βig-h3, collagen VI), enzymes (collagenase, urokinase), cytoskeletal proteins (vinculin, SM22) and regulatory proteins (betaglycan, integrin associated protein, myosin kinase, IGFBP-5). Six novel gene products were discovered during these experiments, including a novel serine protease, a zyxin-like protein, an ankyrin-like protein and a GTP-binding protein. Only four of all the transformation-sensitive cDNAs were consistently down-regulated when a variety of cell lines derived from spontaneous mesenchymal tumors was investigated: βig-h3, collagen VI, the novel ankyrin-like protein, and IGFBP-5. It is likely that these gene products play an important role in the maintenance of the normal phenotype.

Localization of the Gene for a Developmentally Regulated GTP-binding Protein
T. Schenker and B. Trueb

We have identified a novel GTP-binding protein, termed DRG, which is expressed by human fibroblasts but repressed in virally transformed cells. DRG has a molecular mass of 41 kDa and contains the characteristic motifs G1-G5 interacting with GTP. However, its sequence shares only 20% identity with the well characterized G proteins. DRG may therefore constitute a separate subfamily within the superfamily of GTP-binding proteins. Homologous proteins have been found in other animals, plants, yeast and archaea. The exact function of DRG is not yet known, but the striking conservation of its sequence throughout the major kingdoms indicates a fundamental role of the new protein. Since it might be involved in the development of malignant diseases, we have mapped the gene for human DRG by FISH. A cDNA probe for DRG hybridized specifically to the short arm of chromosome 17. The exact position as determined by superimposing the FISH signal with the DAPI banding pattern was found to be region 17p13-p12. The DRG gene is therefore located in close proximity to the p53 tumor suppressor gene.

Molecular Cloning of Chicken Matrix Gla Protein
M. Wiedemann, D. Belluoccio and B. Trueb

Matrix Gla protein plays an essential role in preventing the calcification of blood vessel walls, cartilage and other tissues. We have elucidated the primary structure of chicken matrix Gla protein by cloning and sequencing of the corresponding cDNA. The avian protein exhibited the characteristic motifs previously identified in the mammalian proteins, but its amino acid sequence shared only 51-56% identity with the latter proteins. Moreover, a region proposed to function as binding site for γ-carboxylase in the mammalian proteins was poorly conserved in the chicken protein. Our sequence data should be helpful in the design of mutational analyses which are intended to characterize functional interactions of matrix Gla proteins with other proteins.

2.1.2 Cellular Biomechanics

This research area concerns the mechanism by which fibroblasts in tissues exposed to large tensile stress, ie. in skin, ligaments and tendons, remodel their extracellular matrix in response to variable forces. The goal is to understand how these cells sense the mechanical signals and transform them into a specific biosynthetic response. Several matrix proteins have recently been identified, whose rates of synthesis correlate with the degree of tensile stress to which the cells are exposed. Fibroblasts are cultured on elastic substrates and subjected to controlled strain, in order to determine the effects on gene transcription of these proteins. Such knowledge should help to devise means of manipulating not only the quantity but also the composition (and hence the mechanical properties) of repair tissue formed in response to injury.

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The Collagen XII Gene Promoter: Comparison between the Chick and the Human Sequence and Identification of Active Regions

M. Chiquet, U. Mumenthaler, M. Wittwer, W. Jin and M. Koch

A single gene encodes collagen XII, an extracellular matrix protein with three large fibronectin-related subunits connected via a short collagen triple helix. Because collagen XII is a component of a specific subset of collagen fibrils in tissues bearing high tensile stress, we are interested to know how its restricted expression is regulated. To this aim, we have isolated the region around the first exon of both the chick and the human collagen α1(XII) gene. The upstream sequences of the two genes share common features but are not related. Strong homology starts about 100 bp 5' of the first exon and ends 100 bp into the first intron. In addition, two large conserved regions (56-63% identity) were found in the first intron. A single major and two clusters of minor transcription start sites were identified in both the chick and the human gene. To test for promoter activity, conserved fragments from the chick gene were cloned into reporter plasmids for transient transfection of fibroblasts. A 70 bp stretch containing a conserved nuclear factor-1 binding sequence just upstream of the first transcription start site was found to work as a basal promoter. An adjacent, but non-overlapping short segment including the more downstream start sites and a conserved TATTAA sequence exhibited independent promoter activity. GC-rich sequences just 5' and 3' of the minimal promoter fragments acted as enhancers. In contrast, inclusion of more upstream sequences (up to 2.4 kbp) had no effect. The two conserved regions in the first intron showed no promoter activity on their own but modulated activity when linked to autologous or heterologous promoters. Specifically, one of the conserved intronic regions seemed to act as a mechano-responsive enhancer when put in front of a viral promoter. This intronic sequence contains a GAGACC sequence which is found in the promoters of other genes induced by mechanical stress. We conclude that the collagen XII gene is driven by a basal promoter with two halves that can act independently; conserved control regions are located around the first exon and in the first intron.

Regulation of Collagen XII Expression by Mechanical Stress

J. Trächslin and M. Chiquet

Mechanical stimuli are of fundamental importance for the synthesis and turnover of extracellular matrix eg. during bone remodeling or wound healing. Cultured fibroblasts exert strong tractional forces on their substrate. If they are grown on a collagen I gel which is fixed to a culture dish, the cells experience tensile stress proportional to the tractional force that they generate. In contrast, fibroblasts slowly contract a freely floating (relaxed) collagen I gel, and mechanical stress remains low. Here, we studied the expression of collagen XII by fibroblasts cultured on collagen I gels under such conditions of high or low mechanical stess. The FACIT collagen XII is interesting because it is associated with collagen fibrils specifically in tissues bearing high tensile stress (eg. tendons, ligaments, periosteum). By semiquantitative immunoblotting, we

found that fibroblasts secrete 8-16 times more collagen XII when grown on stressed as compared to relaxed collagen gels. Northern blot experiments showed that mechanical stress controls collagen XII expression on the level of its mRNA. The same was found for tenascin-C mRNA, whereas the amounts of fibronectin and matrix metalloproteinase-2 mRNA were barely affected by the level of mechanical stress in the culture. Hence, the genes for various matrix components are differentially regulated by mechanical stimuli. The effect of tensile stress on collagen XII production is reversible and rapid. This was demonstrated by growing fibroblasts on collagen gels which were fixed to movable polyethylene plugs. The collagen gels with the cells were relaxed or stretched at intervals of 24 hours, and media samples were collected. By ELISA, the amount of collagen XII secreted into the medium was found to increase and decrease in accordance with the cycles of tensile stress applied. This is evidence that the mechanical stimuli per se, rather than indirect secondary effects acting on the cells, were responsible for the the observed changes in collagen XII production.

2.1.3 Tissue Biomechanics

Research in the Tissue Biomechanics area is directed at understanding the relationships between structure and function in conncective tissues, including cartilage, bone, ligament and tendon. The research emphasis lies in the role that physiologic and non-physiologic mechanical loading plays during musculoskeletal development, remodelling, disease and injury. Methodologies which are used by this research team span a wide range, including stereologic and histologic characterization of tissue microstructure, molecular and biochemical assays of connective tissue metabolism, and the measurement of tissue biophysical properties. These projects are being undertaken with a view to better understand the etiology of diseases such as osteoarthritis and to develop new therapeutic approaches for their treatment.

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Immobilization is Associated with Altered ECM Expression Patterns During Avian Synovial Joint Formation
B. Mikic, M.Wong, M. Chiquet and E.B. Hunziker

The objective of this study was to investigate how temporal and spatial patterns of characteristic extracellular matrix molecules are altered under conditions of reduced mechanical loading in developing synovial joints. In particular, we focused on ECM molecules whose synthesis is known to be influenced by mechanical stimuli: collagen XII and tenascin-C. Limb immobilization was pharmacologically induced in embryonic chicks starting at day 6 of incubation using decamethonium bromide. Using standard techniques of immunohistochemistry and in situ hybridization, the effects of immobilization on protein expression was examined. While collagens I and XII continued to be strongly expressed within the immobilized joint, the level of tenascin expression

was diminished in the chondroepiphysis, synovium and tendons. This study demonstrates that the morphological abnormalities which result from embryonic immobilization during joint formation are associated with altered patterns of molecular expression with the developing joint.

Simultaneous Determination of Poisson's Ratio and Elastic Modulus of Mature and Immature Cartilage

M. Wong, J. Jurvelin, M. Ponticiello, M. Tammi, V. Kovanen and E.B. Hunziker

The functional properties of cartilage are believed to be related to the biochemical composition of the tissue. We tested this hypothesis by directly measuring the Poisson's ratio and equilibrium modulus as well as the collagen and uronic acid content of five cartilage tissue types. Fetal, calf and full-thickness adult articular cartilage disks from the bovine glenohumeral joint were subjected to 5% unconfined compression and the time-dependent changes in geometry and load were optically recorded. The lateral expansion of the disk provided a direct, model-independent measurement of the short term and equilibrium Poisson's ratio of the tissue. In addition, equilibrium moduli (Young's modulus and aggregate modulus) were calculated based on the equilibrium stress and axial strain. In general, mature cartilage showed incompressible or nearly incompressible behavior (~ 0.5) immediately after a step compression while the behavior of the immature tissue was slightly lower than the incompressible limit (=0.34-0.38). At equilibrium, mature cartilage had a higher Poisson's ratio than fetal and calf tissue, but there were no significant differences in equilibrium moduli between the groups. The water, collagen, or uronic acid content was similar for all tissue types except for the fetal tissue, and the biochemical data could not fully explain the difference in mechanical properties amongst the tissue types. The results suggest therefore that the structural organization of the matrix components and matrix-matrix interactions also play an important role in determining the behavior during compressive loading.

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

M. Wong, P. Wüthrich, M. Buschmann, P. Eggli and E.B. Hunziker

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 axial 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 in biosynthetic activity, as reflected by ^{3}H-proline incorporation. The axial strains in the top layers were greater than the applied surface-to-surface strain whereas axial strains adjacent to the cartilage/bone border were significantly less than the applied strain. Zonal changes in cell density and axial strain which occurred during static compression correlated well with alterations in metabolic activity. These coordinated changes between cell biosynthesis and cartilage structure suggest that zone-specific variation in mechanical stimuli

could be responsible for spatially-varying patterns of cartilage metabolic activity under load.

2.1.4 Microbiomechanics and Structural Biology

The main activities in this research area are directed towards elucidating the structural characteristics 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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Local Stimulation of Aggrecan Synthesis in Cartilage Explants by Cyclic Loading Correlates with Local Interstitial Fluid Flow
M.D. Buschmann, Y.-J. Kim, M. Wong, E. Frank. E.B. Hunziker and A.J. Grodzinsky

Chondrogenesis in cartilage development and repair, and cartilage degeneration in arthritis can be regulated by mechanical-load induced physical factors such as tissue deformation, interstitial fluid flow and pressure, and electrical fields or streaming potentials. Previous animal and tissue explant studies have shown that time-varying dynamic tissue loading can increase the synthesis and deposition of matrix molecules in an amplitude-, frequency-, and spatially-(within the tissue) dependent manner, which has given rise to several hypotheses relating potential stimulating physical factors to the observed biological responses. With the goal of further specifying the cell-level physical factors which stimulate chondrocytes to increase production and export of aggrecan, the main proteoglycan component of the cartilage matrix, we compared localized changes in aggrecan synthesis within cyclically-loaded tissue explant disks to values of theoretically predicted local physical factors. Aggrecan synthesis following a 23 hour compression/radiolabel protocol was measured with a spatial resolution of ~0.1 mm across the 1.5 mm radius of explanted disks using a quantitative autoradiography method. In the absence of loading, aggrecan synthesis in this young calf cartilage explant system has been previously shown to be homogeneous within the specimen. Profiles of radial solid matrix deformation and interstitial fluid pressure and velocity predicted to be occurring across the radius of the disk during sinusoidal loading were calculated using a composite poroelastic model. Parameter values for the model were estimated by fitting the model to the measured dynamic stiffness of the explants. Comparison of the measured spatially- and frequency-varying stimulation in local aggrecan synthesis to spatially- and frequency-varying predicted values of stimulating physical factors supported the hypothesis that locally high (> ~0.25 μm/s) interstitial fluid velocities corresponded to locally stimulated (~50%) aggrecan synthesis. Previous experimental work has

demonstrated that these values of interstitial fluid velocities are sufficient to convectively increase transport of soluble macromolecules by an order of magnitude, compared to diffusive transport. Our study therefore provides support for transduction mechanisms whereby stimulation of aggrecan production during dynamic loading of cartilage is due to load-induced flow of interstitial fluid.

Proteoglycan Density Mapping in Cartilage using Ruthenium Hexaammine Trichloride Induced Chemography
M.D. Buschmann, A.-M. Maurer, E. Berger and E.B. Hunziker

Proteoglycans (PG) in cartilage are highly charged anionic macromolecules which play several important functional roles. The high negative charge of cartilage PG is due to the high degree of substitution of glycosaminoglycan (GAG) chains, constituting more than 80% of the mass of some species of PG. The charge properties of GAG chains of PG have been exploited previously for quantitative colorimetric dye-binding assays for GAG extracted or solubilized from tissue, and have been exploited in qualitative histochemical methods. We present a new quantitative histochemical method whereby the charge properties of GAGs of cartilage PGs are used to form co-precipitates in tissues with the cationic agent, ruthenium hexaammine trichloride, previously found to be a good fixative for PG stabilization and to aid in the maintenance of chondrocyte morphology. These RHT-PG precipitates generate a positive chemographic signal on autoradiography emulsions, in the absence of any radioactivity in the tissue section, via a process similar to the autometallographic process used previously for the localization of trace metals ions in tissues. By exploiting the inherent depth-dependence of GAG concentration in adult articular cartilage we demonstrated that the density of silver grains produced by RHT-derived chemography on autoradiography emulsions correlated with locally measured GAG concentration determined by the dimethylmethylene-blue (DMB) spectrophotometric assay of micro-dissected and solubilized tissue from these different depths of cartilage. We present a method of calculating the equivalent local chondroitin sulfate concentration by DMB from the spatially localized measure of RHT-derived chemographic grain density. RHT-derived chemographic grain density represents an additional quantitative tool for the histological analysis of cartilage in physiology and in arthritis. In addition, quantified changes in local PG density due to tissue compression could furnish important information on the spatial heterogeneity of functional cartilage biomechanical properties.

Confined Compression of Articular Cartilage: Linearity, Boundary Conditions and the Biphasic Model
M.D. Buschmann, J. Soulhat, A. Shirazi-Adl, J.S. Jurvelin and E.B. Hunziker

Experimental and theoretical methods were used to investigate the linearity of the stress response of articular cartilage to ramp and sinusoidal tests in confined compression, as well as the role of cartilage-porous platen and lateral

confinement boundary conditions in determining material responses. With respect to linearity, we posed the question as to whether the elicited stress responses to ramp compression, ramp release and sinusoidal tests were similar. With respect to boundary conditions we inquired as to the necessity of specifying a detailed interdigitating contact with the porous filter and of specifying the level of confinement present at the lateral edge of the disk. We found that the stress responses to the three types of tests were dissimilar, with ramp compression the only test exhibiting linear behavior. Ramp release from a static compression offset was nonlinear in a manner such that the cartilage maintained a compressive stress higher than expected by a linear theory. Sinusoidal compression also displayed a nonlinear response consistent with the presence of a release phase in each cycle. The actual boundary conditions present at the cartilage/porous-filter interface were visualized histologically. Areas (tens of microns) of cartilage in contact with the metal of the filter were interspersed with areas expanded into the pores of the filter. Finite element analysis incorporating this information suggested that precise specification of this interface and of the level of the extent of lateral confinement would be necessary for the estimation of material properties, such as the hydraulic permeability, from these tests. The trends of the linearity studies did not appear to be significantly affected by the problems posed by these difficult to quantitate boundary conditions. The nonlinear cartilage response to release and sinusoidal displacements therefore appear to be physiologically interesting. The maintained, that is higher than would be linear, compressive stress observed during release may be a beneficial adaptation to repeated loading where temporal variations in tissue stresses would be minimized.

Ultrastructure of Adult Human Articular Cartilage Matrix after Cryotechnical Processing

E.B. Hunziker, M. Michel and D. Studer

The ultrastructure of adult human articular cartilage matrix is reexamined in tissue processed according to recently improved cryotechniques [Studer et al. (1995) J. Microsc., 179:321-332]. In truely vitrified tissue, a network of fine cross-banded filaments (10 - 15 nm in diameter) with a periodicity characteristic of collagen fibrils is seen throughout the extracellular substance, even within the pericellular compartment, which has hitherto been deemed free of such components. Proteoglycans fill the interstices between these entities as a homogeneously distributed granular mass; they do not manifest a morphologically identifiable reticular structure. Longitudinally-sectioned collagen fibrils exhibit variations in thickness and kinking; they tend to align with their periodic banding in register and are frequently seen to split or fuse along their longitudinal course. The tendency of fibrils to form bundles is greater in deeper zones than in more superficial ones.

A duality in the orientation of fibrils and fibril bundles is observed within the interterritorial matrix compartment: superimposed upon the well-characterized arcade-like structure formed by one sub-population is another, more randomly

arranged one. The classical concepts of matrix organization thus need to be modified and refined to encompass these findings.

Topographical Variation of the Elastic Properties of Articular Cartilage in the Canine Knee

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

Equilibrium response of articular cartilage to indentation loading is controlled by the thickness (*h*) and elastic properties (shear modulus, *m*, and Poisson's ratio, *n*) of the tissue. In this study, we characterized topographical variation of Poisson´s ratio of the articular cartilage in the canine knee joint (N=6). Poisson´s ratio was measured using a microscopic technique. In this technique, the shape change of the cartilage disk was visualized while the cartilage was immersed in physiological solution and compressed in unconfined geometry. After a constant 5% axial strain, the lateral strain was measured during stress relaxation. At equilibrium, the lateral-to-axial strain ratio indicates the Poisson's ratio of the tissue. Indentation (equilibrium) data was combined with the thickness and Poisson´s ratio results at the test site to derive values for shear and aggregate moduli. The lowest Poisson´s ratio (0.070$\pm$0.016) located at the patellar surface of femur (FPI) and the highest (0.236$\pm$0.026) at the medial tibial plateau (TMI). The stiffest cartilage was found at the patellar groove of femur (m=0.964$\pm$0.189 MPa, H_a=2.084$\pm$0.409 MPa) and the softest at the tibial plateaus (m=0.385$\pm$0.062 MPa, H_a=1.113$\pm$0.141 MPa). The comparison of the mechanical results and the biochemical composition of the tissue at the test sites of the canine knee joint revealed a strong negative correlation between the Poisson´s ratio and collagen-to-PG content ratio. This is in harmony with our previous findings which suggested that, in unconfined compression, the degree of lateral expansion in different tissue zones is related to collagen-to-PG ratio of the zone.

Changes in Cell, Matrix Compartment and Fibrillar Collagen Volumes among Growth Plate Zones

K.J. Noonan, E.B. Hunziker, J. Nessler and J.A. Buckwalter

To define the contributions of changes in physeal cell, matrix compartment and fibrillar collagen volumes to longitudinal bone growth, we measured the differences in cell, pericellular/territorial matrix and interterritorial matrix volumes and matrix compartment fibrillar collagen concentrations between the upper proliferative zone and lower hypertrophic zone of six minipig proximal tibial physes. The mean numerical density of cells decreased from 110,000 cells/mm^3 in the upper proliferative zone to 59,900 cells/mm^3 in the lower hypertrophic zone. Mean cell volume increased nearly five fold (from 1,174 µm^3 to 5,530 µm^3) and total matrix volume per cell increased 46% (from 8,040 µm^3/cell to 11,760 µm^3/cell) between the upper prolieferative zone and the lower hypertrophic zone. Although both the pericellular/territorial matrix volume per cell and interterritorial matrix volume per cell increased between the upper proliferative zone and the lower hypertrophic zone, the pericellular/territorial matrix volume per cell increased 61% (from 4,580

μm^3/cell to 7,390 μm^3/cell), while the interterritorial matrix volume per cell increased 26% (3,460 μm^3/cell to 4,370 μm^3/cell). The total increase in mean cell volume of 4,356 μm^3 exceeded the total increase in mean matrix volume per cell of 3,720 μm^3 and the total mean pericellular/territorial matrix volume per cell increased more than the total mean interterritorial matrix volume per cell (2,810 μm^3/cell vs. 910 μm^3/cell). Fibrillar collagen concentration was greater in the interterritorial matrix than in the pericellular/territorial matrix in both zones and increased in both matrix compartments between the upper proliferative zone and the lower hypertrophic zone. The amount of fibrillar collagen per cell also increased in both matrix compartments between the upper proliferative zone and the lower hypertrophic zone (1,720 μm^3/cell to 3,100 μm^3/cell in the pericellular/territorial matrix and 1,490 μm^3/cell to 2,230 μm^3/cell in the interterritorial matrix), so that the total amount of fibrillar collagen per cell increased from 3,210 μm^3/cell to 5,530 μm^3/cell,. Growth rate was inversely related to the cell numerical density in the upper proliferative zone and pericellular/territorial matrix volume per cell in the lower hypertrophic zone. These results show that cell enlargement contributes more to longitudinal bone growth than increased matrix volume, that increased pericellular/territorial matrix volume makes a greater contribution to growth than increased interterritorial matrix volume and that the total amount of fibrillar collagen per cell increases between the upper proliferative zone to the lower hypertrophic zone. The differences between the two matrix compartments in degree of increase in volume, fibrillar collagen concentration and amount of fibrillar collagen per cell strongly suggest that they differ not only in matrix organization but in rate of matrix accumulation and assembly, and that these differences give the two compartments different roles in skeletal growth.

Growth plate chondrocyte produce longitudinal bone growth through highly ordered cell proliferation, cell enlargement and matrix synthesis [4, 5, 10, 11, 22. 27, 31, 32]. In the upper proliferative zone flattened ellipsoidal chondrocytes divide and organize themselves into columns. At the same time they synthesize an extracellular matrix that is organized into two compartments (the pericellular/territorial and the interterritorial matrix compartments) named for their relative proximity to the cells and distinguished by the predominent orientation of the fibrillar collagen [18]. In the lower portion of the proliferative zone the cells enlarge [5], primarily by increasing their height relative to the long axis of the bone, a change that is accompanied by alterations of the extracellular matrix including increases in the concentrations of proteoglycans alkaline phosphatase [2, 28]. In the middle and lower portions of the proliferative zone, the interterritorial matrix collagen fibrils become oriented parallel to the long axis of the bone and form longitudinal septa. Chondrocyte size increases dramatically in the hypertrohpic zone [5, 10, 11, 27]. In the lower portion of this zone Type X collagen appears in the matrix [1], the size of proteoglycan aggregates decreases [8, 12, 13], matrix vesicle concentration increases [9] and the interterritorial matrix begins to calcify [9]. In contrast with the interterritorial matrix, the pericellular/territorial matrix does not calcify, and its collagen fibrils remain oriented around the cells. In the lowermost region of the hypertrophic zone, after mineralization of the interterritorial matrix has started, capillaries invade the pericellular/territorial matrix compartment [20, 21] bringing with them cells that form osteoid on the calcified longitudinal septae of the interterritorial matrix.

Previous work has identified changes in cell shape and volume and demonstrated increases in matrix volume per cell from the proliferative zone to the hypertrophic zone, [5, 7, 10, 11, 27]. Examination of mouse and rat tibial physes showed ten- and four-fold increases in cell volume and height between

the proliferative and hypertrophic zones [10, 27]. Hypertrophic cells were found to have increases in absolute organelle mass, but the predominant mechanism of cell enlargement appeared to be accumulation of fluid [10]. Both studies also showed an increase in matrix volume per cell between the prolieferative and the hypertrophic zones. The study of mouse physes suggested that the pericellular/territorial matrix compartment contributed most to the increase in matrix volume per cell, but observation that the two matrix compartments differ significantly in their change in volume per cell during bone growth has not been confirmed.
The primary purpose of the current study was to define the relative contributions of the cell, pericellular/territorial matrix compartment and interterritorial matrix compartment to the increase in growth plate volume responsible for longitudinal bone growth, and to determine if the concentration and total amount of fibrillar collagen per cell change between the proliferative and hypertrophic zones. A secondary purpose was to determine if the rate of longitudinal growth correlated with changes in matrix compartment volumes.

Effects of Surgically-Introduced Defects on Cell Viability in Articular Cartilage
T.M. Quinn and E.B. Hunziker

The introduction of defects (”cuts”) into cartilage tissue is an integral part of many surgical procedures including cartilage repair methods. Cell viability in the vicinity of such defects may be adversely affected although it is of central importance to subsequent repair processes. To explore this question, surgical defects were introduced into the knee cartilage of adult rabbits, which were subsequently allowed to walk freely for two weeks to six months after surgery and prior to sacrifice. Immediately before death, ^{35}S-sulfate was injected into joint capsules for the radiolabelling of cartilage proteoglycans. Vertical sections of cartilage and bone were then taken through the defect areas and prepared for histological autoradiography by standard methods. Recently-developed (at the Müller Institute for Biomechanics) image analysis techniques were subsequently applied for the measurement of cell morphology and cell-associated matrix synthesis as a function of distance from the introduced defects. Results will be used for the development of optimal methods for cartilage manipulation during surgical procedures.

Effects of Injurious Compression on Matrix Turnover around Individual Cells in Calf Articular Cartilage Explants
T.M. Quinn, A.J. Grodzinsky, E.B. Hunziker and J.D. Sandy

The effects of mechanical injury on cartilage matrix metabolism are of interest for the understanding of the pathogenesis of osteoarthrosis and the development of strategies for cartilage repair. The purpose of the present study was to examine the effects of injury on matrix turnover in a calf articular cartilage explant system for which the effects of mechanical loading on cell activity and the cell-mediated pathways of matrix metabolism are already well characterized. New methods of quantitative autoradiography were employed in combination with established biochemical and biomechanical techniques for the analysis of cell and matrix responses to acute mechanical injury, with particular

attention to localized matrix turnover processes in the cell-associated matrices of individual chondrocytes. Matrix deposition and turnover around cells in control explants was spatially dependent, with the highest rates of proteoglycan deposition and turnover, and lowest rates of collagen deposition, occurring in the pericellular matrix. Injurious compression was associated with (1) and abrupt decrease in the tensile load-carrying capacity of the collagen matrix, apparently associated with tissue mechanical failure, (2) a significant but subtotal decrease in cell viability, marked by the emergence of an apparently inactive cell population interspersed within catabolically active but abnormally large cells, and (3) sustained elevated rates of proteoglycan turnover particularly in the cell-associated matrices of apparently viable cells, which involved the increased release of aggregating species in addition to a spectrum of degradation fragments which were also present in controls. These results may represent an *in vitro* model for the responses of chondrocytes and the cartilage extracellular matrix to mechanical injury.

Cell and Matrix Morphology in Normal Adult Human Articular Cartilage
T.M. Quinn, E. Shimaoka, H.J. Häuselmann and E.B. Hunziker

Clinical observations have shown that osteoarthritis is more common in the knee than in the ankle, suggesting that joint-specific differences in cartilage morphology may have significant implications for long-term tissue biomechancial function. In addition, the introduction of techniques for the clinical repair of cartilage defects has given rise to a need for detailed characterization of cell and matrix morphology in healthy cartilage (the desired end-point of such treatment). Therefore, morphological characterization of healthy adult human articular cartilage is important for the understanding of cartilage physiology and pathophysiology, and for the evaluation of tissue repair methods. With the approval of the Ethical Commission of the Faculty of Medicine at the University of Bern, full-thickness cartilage explants were obtained from nine distinct joint locations of ten different adult humans between the ages of 20 and 40 within 48 hours after death. Seven joint locations in the knee and two in the ankle were sampled. Explants were chemically fixed by standard methods and sectioned on a vibratome prior to the acquisition of vertical optical sections with a confocal microscope. Stereological dissectors were obtained in the form of serial optical sections and projected to a final magnification of 870∞ at which stereological measurements (eg. cell geometry, cell number density) were performed. Results highlight a relatively constant matrix volume per chondrocyte throughout all tissue examined, and knee versus ankle differences involving thinner cartilage in the ankle with a less identifiable superficial zone. These results will aid in the understanding of structure-function relationships in cartilage, and provide a useful reference point for the development of tissue repair methods.

Effects of Graded Levels of Injurious Compression on Surface Cracking, Cell Viability, and Proteoglycan Release in Adult Bovine Cartilage Explants
B.J. Schalet, P. Perumbuli, T.M. Quinn, A.J. Grodzinsky and E.B. Hunziker

Excessive joint loading is thought to be associated with cartilage matrix degradation and the progression of osteoarthritis. However, the relationships between mechanical and cell-mediated biochemical events leading to tissue degradation are not completely understood. Therefore, the goals of this study were to examine the acute effects of well-defined mechanical compressions on cartilage explants, in order to characterize mechanical thresholds for injury and the morphological, biochemical, and biomechanical changes which may be expected to occur in cartilage following certain types of joint injuries. Graded levels of compression were applied to full thickness cartilage-on-bone explants of adult bovine humeral head cartilage using a range of strain rates and peak stresses, for comparison with uncompressed controls. Surface cracks were assessed visually under a dissecting microscope. Cell activity as a function of position within tissue was visualized using flourescent markers of cell viability on vertical sections. Cell-mediated matrix synthesis rates as a function of

position within tissue were quantified by histological autoradiography. Glycosaminoglycan (GAG) contents of explants and culture media were assayed by standard biochemical methods. Results indicate that cartilage matrix injury, marked by tissue cracks, superficial cell death, and release of matrix proteoglycans, occurred at compressive stresses near 7-10 MPa. Further characterization of the morphological and biomechanical sequelae of matrix injury and the conditions under which they occur, using these established methods, will be valuable for the development of clinical strategies for treating cartilage injuries and optimizing tissue repair.

2.2 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 bimechanics, the major areas of focus are state of the art implant evaluations, musculoskeletal injury mechanisms and low back pain. Research methodologies in 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.

The Orthopaedic Biomechanics Division can be reached through the World Wide Web (WWW) at http://cranium.unibe.ch or at http://www-mem.unibe.ch.

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2.2.1 Computer Assisted Surgery (CAS)

A C-arm Based System for Computer Guided Fracture Reduction
R. Hofstetter, A. Jacottet, H. Wälti, M.Slomczykowski, M. Sati and L.-P. Nolte

One of the new development breakthroughs has been the computer integration of intra-operative X-ray images from the C-arm for surgical guidance. This technology is the basis of an image-guided trauma module that is the first of its kind. Optoelectronic markers are placed on the C-arm to track its position in space. The image is then calibrated to remove distortions and account for magnification. Finally, corrections are applied to compensate for mechanical bending of the C-arm due to the effects of gravity. Efforts on the design of

marker placement and distortion correction algorithms have led to large improvements in the system's accuracy.
The result is that the surgeon can precisely see his surgical tool moving within a static X-ray view of the patient. This calibrated C-arm provides several benefits: 1) The C-arm can be numerically aligned at exact angles with the tracked patient position without X-ray exposure, 2) There is no longer a need for constant X-ray exposure to guide surgical tool movement within the image, and 3) The surgeon can view tool movement on more than one view of the bone at a time to precisely control 3D movements. 4) Semi automatic 3-D reconstruction of anatomic landmarks based on 2 or more C-arm images allows precise intra-operative geometric measurements.
One of the initial challenges undertaken by this module is to assist in the reduction of femoral shaft fractures. The entire procedure is supported by computer guidance: 1) Reaming an initial channel for an intramedular nail, 2) Nail insertion and fragment alignment, 3) Distal locking of the nail, 4) Rotational adjustments to restore the anteversion angle measured on healthy leg. Successful cadaver trials have qualified the system for first clinical trials. Research and development are underway to provide the surgeon with a "user friendly" computer interface that can be operated under sterile conditions.

Clinical Experiences with Computer Assisted Pelvic Osteotomies
F. Langlotz, R. Bächler, L.-P. Nolte and R. Ganz

Our established system for image guided computer assisted pelvic osteotomies has been improved and used clinically. In the proved modules, LED-equipped, modified osteotomes are tracked optoelectronically in order to visualize the surgical action of chiseling during the Bernese Periacetabular Osteotomy, an intervention that is performed to correct hip dysplasia. This tracking process is carried out with respect to a so-called dynamic reference base (DRB), a special LED carrier that is attached to the pelvic rim and compensates for patient motion. To expand the proportion of the operation, in which computer assistance is applied, a tracking module for fragment reorientation was added to the existing software. In general, motion of a liberated bony fragment relatively to the rest of the pelvis can be visualized in three different ways. (a) Using a numerical representation, the current configuration is expressed by means of distances and angles illustrating the spatial location and orientation of both parts in relation to each other. (b) The same information can be presented in a more abstract way by graphical objects or meters like lines, circles, or triangles. (c) A three-dimensional, reconstructed model can achieve a very intuitive display. This model then reproduces the motion, that is imposed on the bony fragment. In any of these cases, the acetabulum, that is cut free, needs to be equipped with another LED carrier before it is completely loosened from its surrounding bony structures. In our system we developed a very small fragment carrier that is fixed with one screw and we implemented a combination of numerical and three-dimensional display. This new feature has been applied during two operations so far. The current research focuses on better planning capabilities

for this kind of intervention and the integration of these planning data into the visualization of surgical action.

Computer Assisted Total Hip Replacement
U. Langlotz, J. Lawrence, Q. Hu and L.-P. Nolte

Each year, approximately 250,000 total hip replacement (THR) surgeries are performed in the US alone. Aseptic loosening and dislocation remain the most significant post-operative clinical problem and early studies showed that dislocation occurred in up to 10 percent of the primary THR cases. Although the number of complications has recently been reduced to 1 to 5 percent, this still represents a significant problem since dislocation and aseptic loosening always require a revision surgery.
The many factors that can lead to revisions include soft tissue parameters, impingement, and implant design. The perforation of the acetabulum and poor positioning of one or both implants relative to the patient's anatomy have been identified to be the most important problems. The development of a module for computer assisted total hip replacement will improve the overall accuracy of the surgery and therefore enable the surgeon to overcome these problems related to positional errors.
The CAS system is based on a standard computer tomogram that can be directly loaded into the system for pre-operative planning. By visual examination of the patient specific anatomy, the type and size of the implant are chosen and the geometric data imported from an implant database. The surgeon interactively determines the position of both implants in three perpendicular 2D cuts and one 3D view. Both size and type of these implants can be adjusted at any time if necessary. Once the final position of the implants and the resection of the femur have been defined, a simulation of the impingement-free range of motion (ROM) is performed. This simulation is specific not only to the patient's anatomy but to the surgeon's plan as well. It gives the surgeon the ability to optimise implant design and position to achieve a maximum ROM.
Intra-operatively, several main software components are necessary to guide the preparation of the acetabulum and the insertion of the implants. The most important step is the matching. This procedure allows the system to register the pre-operative data, i.e. the CT and the planning information, to the patient on the OR table. After two dynamic reference bases (DRB) are attached to the pelvis and femur the surgeon identifies 3-5 pre-operatively defined landmarks and 10-15 arbitrary surface points on each bone. With this information the computer calculates the relation between CT and patient space. This transformation between the surgical object, i.e. the patient, and the virtual object, i.e. the CT, gives the system the ability to display instruments, e.g. a reamer, in the CT space. The current position of the tool within the patient can be compared with the pre-operative plan. Possible deviations from the plan are displayed visually and numerically. The CAS system monitors the surgical actions and gives constant feedback.

Percutaneous Ultrasonic Bone Registration in Computer Assisted Orthopaedic Surgery
J.C. Moulder, M. Sati and L.-P. Nolte

Registration of computer tomographic (CT) images in our computer assisted orthopaedic systems is presently performed by physically digitising surface points on the bone with a pointing device and matching these points to the CT scan. This project proposes the use of ultrasound to obtain these points percutaneously allowing both access to more areas and development of minimally invasive procedures. Percutaneous registration could be potentially used for minimally invasive pedicle screw insertion, trans-laminar spinal fixation, cranio-facial surgery, neurosurgery, tumor resection, fracture surgery and improve registration in total hip replacement.
The probe has been custom made to send a single narrow beam from the skin surface onto the underlying bone. A modular lens system allows different focusing depths for various applications. Because of the high acoustical impedance difference between that of soft tissue and bone, a large echo is be received from the surface of the bone. The time difference between transmission of the ultrasound pulse and reception of the echo determines the distance to the surface of the bone. Since the three dimensional (3D) position and orientation of both the probe and patient reference base is tracked in space via an optical navigation system, the 3D co-ordinate of the a point on the surface of the bone can be determined. These 3D co-ordinates are equivalent to digitising directly on the bone surface with the pointer and can therefore be used for the surface registration.
A rough “pair-point registration” based on approximate anatomical landmarks is used to perform an initial registration that helps guide the acquisition of surface points. These surface points are fed into a “restrictive surface-fitting algorithm” that mathematically limits the range of possible co-ordinate system transformation solutions based on the rough anatomical landmarks.
This method of registration has successfully been used on a plastic model of a lumbar vertebra and an intact cadaver knee. In both cases acceptable registration was achieved.

Intra-Operative Planning and Guidance of ACL Graft Placement
M. Sati, Y. Bourquin, H.U. Stäubli and L.-P. Nolte

Rupture of the anterior cruciate ligament (ACL) is a pathology that can destabilize the knee and lead to premature degenerative arthritis. Reconstruction of this structure via an autogenous graft is difficult since destructive loading occurs when it is improperly placed. In this project, a computer assisted system has been developed to perform intra-operative planRupture of the anterior cruciate ligament (ACL) is a pathology that can ning of ACL replacement. Dynamic reference bases are fixed on the femur and tibia to track the knee’s movement. Unlike many other computer assisted systems, this system allows

surgeons to interactively define the structures they judge are important for the proper placement. These structures can be identified in a minimally invasive fashion when used in conjunction with arthroscopy using standard endoscopic tools. Specialized computer graphics allow representation of relevant structures in surgeon-defined viewpoints. The computer helps in situ planning of ligament placement by graphically simulating ligament insertion, predicting graft impingement and elongation in real-time for various simulated surgical insertions and graft sizes. Flexibility of the system allows it to be used to optimize the placement according to a variety of surgical techniques. The system is then used to precisely guide the surgical drill to the planned insertion site. Current work is being performed to improve the surgical interface and develop algorithms to optimize graft placement with respect to elongation and impingement. The approach provides valuable quantitative information on ligament deformations that are normally not measurable in standard procedures. This technology is minimally invasive and does not require the need for X-ray exposure.

2.2.2 Basic and Clinical Biomechanics (BCB)

Compressive Force Transmission in the Human Cervical Spine: Effect of Superimposed Flexion Moments
P.A. Cripton, G.A. Dumas and L.-P. Nolte

Axial compression has been implicated as a common injury mechanism in many impact-related traumatic injuries to the cervical spine. The hypothesis that injurious axial compression occurs secondary to muscle activation during rear-end motor vehicle accidents and the associated “whiplash” related distortions of the cervical spine has also recently been proposed. The objectives of this study were therefore to characterise the load transmission paths through cervical functional spinal units (FSUs) as a function of pure moment application with and without superimposed axial compression.
Six lower cervical FSUs (one C2-3, one C3-4, two C4-5, one C5-7 and one C6-7 levels) where subjected to flexion moments of 1.0 Nm. Moments were applied, in four equal steps, using a pneumatic testing machine capable of producing pure moments while preserving the specimen’s six degrees of freedom. Each moment direction was tested first without axial compression and then with a superimposed 200 N axial compression. Rotations and translations of the cranial vertebra with respect to the caudal vertebra were measured using an optoelectronic motion analysis camera (Optotrak, Northern Digital, Waterloo, Canada) and infrared light emitting diodes mounted to each of the vertebrae. Load transmission paths were identified by instrumenting each FSU. Strain gauge rosettes were glued to the anterior surface of the caudal vertebral body and beneath the left and right facet joints on the lateral masses. A disc-shaped miniature pressure transducer (model 060 S, Precision measurement company, Ann Arbor, USA) of diameter 1.5 mm and thickness 0.3 mm was inserted into the centre of the intervertebral disc through a 2.2 mm diameter needle which was subsequently removed leaving only the lead wire passing

through the disc annulus. Principal strain magnitudes and orientation were calculated for each strain rosette.
In general, all strains increased with increasing moment application. The anterior vertebral body strains were primarily compressive and the lateral mass strains were primarily tensile. Lower magnitude principal strains consistent with a Poisson contraction or expansion of the bone (i.e. approximately 30 % of the primary principal strain) were often evident. Strains were approximately aligned with the cranial-caudal axis of the spine. Intervertebral pressure increased in a manner similar to the anterior body strains in the no-compression case but remained approximately constant, for tests with axial compression. The three strain rosettes allowed sensitive analysis of the relative loads being transmitted through the anterior and posterior columns of the cervical spine. In flexion, disc pressure and anterior body strain data suggest compression forces are primarily induced in the anterior column and are probably being transmitted through the intervertebral disc. The tensile strains measured in the lateral mass rosettes are likely induced as a result of tension in the facet joint capsules. Because the cervical intervertebral disc pressure is invariant with flexion moment application under superimposed axial compression; it may be a better indicator of the global compression force passing through the FSU than it is of anterior column load sharing.

Sequence of Injury in the Thoracolumbar Spine under Lateral Shear
H.P. Frei, T.R. Oxland, M.A. Slomczykowski and L.-P. Nolte

The human spine is subjected to a highly complex combination of compression, shear and bending loads during normal activity and particularly under injury-producing conditions. The behavior of the spine has been studied extensively in compression and bending but there remains a lack of fundamental data under shear loading. The goal of this work was to investigate the sequence of injury in the thoracolumbar spine due to lateral shear. Six human cadaveric T12-L1 functional spine units (FSUs) were tested At six sites on each L1-vertebra, tri-axial strain gauges were applied. In addition the intervertebral motions and the disk pressure was measured. A left to right shear loading was applied through the specimen centre of shear at 0.5 mm/s. All specimens were loaded to failure. The average shear force to failure was 2240N at a displacement of 7.3mm. During loading the strains increased linearly at all locations up to 500N. We hypothesised that any substantial change in the linear behaviour was related to tissue damage near the measured location. The tissue damages found after the tests were then related to the events found in the measured strains at the specific location. Disk pressure and 3D motions of the vertebral bodies confirmed these findings. The following graphs show the sequence of injury in four different specimens. All specimens showed some evidence of damage in the early test phase (i.e. prior to the peak loads). In general, a rather consistent injury sequence was observed in that some posterior element damage occurred first followed by a major disc or vertebral body injury. The initial posterior element damage typically involved capsule rupture.

The Effect of Proximal Design Differences on the Three-Dimensional Micromotion of Hip Prostheses

D.J. Goertzen, M.A. Slomczykowski, T.R. Oxland, D.W. Bühler and L.-P. Nolte

Limiting the initial micromotion between the implant and the contacting bone is important for obtaining bony ingrowth and consequently, for secure long term fixation of the implant. A variety of cementless hip prosthesis designs are available and the effect of a design modification on prosthesis-bone micromotion is advantageous for evaluating implant designs. *In vitro* simulation of implant loading with micromotion measurement provides an effective method to compare and assess design differences. The objective of this study was to compare the *in vitro* three dimensional micromotion characteristics of similar cementless hip prostheses with only a proximal design difference: one had a full width proximal lateral shoulder and the other had a narrowed lateral trochanteric fin.

Two straight cementless hip prosthesis stems were tested: the BEO and CLW (Sulzer Orthopedics Ltd., Switzerland). Both prostheses were collarless titanium with a straight stem, wedge shaped in the frontal plane and a continuous medial arch proximally. The distinguishing design difference was the addition of a narrowed, trochanteric fin on the CLW which protruded further laterally than the full width shoulder of the BEO. Five paired human cadaveric femurs were used in this study. Three-dimensional micromotion was measured simultaneously at three locations using a custom made device with an optoelectronic position sensor. The three sensors were fixed to the femur at proximal, middle, and distal locations directly over the prosthesis measurement points. A cyclic biaxial loading regime simulating normal gait was applied2. Load levels of 1, 2, and 3 times body weight (BW) were used.

Micromotion was characterised by dynamic motion (DM), the reversible motion during a single loading cycle, and range of total motion (TM), irreversible migration during each load level. Results were expressed in the implant coordinate system; ML (Medial-Lateral), AP (Anterior-Posterior), and PD (Proximal-Distal). At 1xBW loading, all median TM and DM components for both implants were less than 16 and 18 μm, respectively. Motion results during the 2xBW load level are shown for TM and DM. All significant differences were for BEO motion less than the CLW. At each load level, differences in the dynamic AP and ML components at the proximal location were significant. No significant differences were observed for any distal measurement.

The results demonstrated that a relatively minor design change can have a significant effect on implant micromotion characteristics. Significantly greater motions in the proximal and middle regions suggested that the addition of a narrow proximal lateral fin is not as effective in the initial stabilization of the implant. It was surprising that the subsidence was influenced so greatly by the slight proximal design differences. The varied geometry of the proximal CLW may have prevented the proper surgical shaping required for a tight proximal fit and this manifested itself as greater implant motion.

Influence of Surface Characteristics on the Interface Shear Strength between Titanium Implants and Bone

T. Nydegger, D. Buser, T.R. Oxland, H.P .Hirt, D. Cochran and L.-P. Nolte

In the past 30 years, endosseous dental implants have become a scientifically accepted and well documented treatment modality for fully and partially edentulous patients. Fundamental animal and clinical studies have documented successful implant anchorage with direct bone contact. Thomas and Cook (1985) examined the variables that potentially influence bone apposition to an implant surface. Of 12 parameters studied, only surface characteristics demonstrated to have a significant effect on bone integration of an implant. The purpose of the present study was to evaluate the interface shear strength of titanium implants with three different surfaces in the maxilla of miniature pigs by measuring removal torques after 4, 8 and 12 weeks of healing.

Solid-screw titanium implants (Institute Straumann AG, Waldenburg, CH) of identical macroscopic shape, but three different surfaces (Type SM = Smoothly machined, Type TPS = Titanium plasma-sprayed, Type SLA = Sandblasted and acid attacked) were inserted in edentulous areas of the anterior maxilla of nine miniature pigs. A total of 54 implants were inserted, six in each animal. After 4, 8 and 12 weeks of healing, the pigs were sacrificed and mechanical removal torque testing was performed to evaluate the shear strength of the bone-implant interface for each implant type at each healing period and each implant position. For mechanical testing, the exposed implants were secured to a servohydraulic testing machine (MTS Minibionix 358.02 Minneapolis MN, USA) and they were removed by rotating at 1°/sec and torque was recorded. A three factor analysis of variance (ANOVA) was conducted for implant type, position, and healing time. Post-hoc Scheffé's F-tests were used for paired comparisons.

The test results demonstrated statistically significant differences between the smoothly machined surface (SM) and the two rough titanium surfaces ($p<0.00001$). The TPS and SLA surfaces, however, were not statistically different. There was no significant difference between the healing periods for any of the tested implant types ($p<0.14$). The implant position, on the other hand, had a significant influence on removal torques for each implant type ($p<0.0001$), as removal torques were lower for more posterior locations. It can be concluded that surface characteristics have an important influence on bone integration of titanium implants. The smoothly machined titanium surface demonstrated significantly reduced removal torques when compared with the two tested rough surfaces. There were no significant differences between the TPS and SLA surfaces. Therefore, a direct comparison of SLA and TPS implants is necessary in a split mouth designed study to exclude the variable of the implant position, as demonstated in the present study.

Lateral Insertion of Anterior Lumbar Interbody Cages: A Comparative Biomechanical Investigation

T. Nydegger, T.R. Oxland, Z. Hoffer and L.-P. Nolte

Recent studies have found that cages for anterior interbody fusion (ALIF) do not stabilize the spine in extension. The goal of the current study was to evaluate the immediate stabilisation of these devices, when inserted from a lateral direction, thereby preserving the anterior longitudinal ligament and annulus, and contrast the results with those from an anterior insertion. Six, human cadaveric lumbar functional spinal units (FSUs) were tested using a 3-D flexibility protocol. The cage was a central, porous contoured implant with endplate fit [SynCage®, Mathys Medical Ltd.], inserted from a lateral direction. The flexibility test involved the application of unconstrained pure moments in flexion-extension, axial rotation, and lateral bending. The ranges of motion (ROM) were compared to data recorded using the same protocol in a previous study, with the same implant inserted from an anterior direction.
The ratio of cage to intact ROM with lateral insertion, was not different to anterior insertion in loading directions of flexion ($p=0.36$) and extension ($p=0.35$). This ratio with lateral insertion was significantly different in axial rotation ($p=0.007$) and lateral bending ($p=0.003$), than with anterior insertion. Additional translaminar screw fixation stabilized the FSUs in all conditions with respect to intact motion (flexion: $p=0.0003$; extention: $p=0.0003$; axial rotation: $p=0.0007$; lateral bending: $p=0.0003$). Earlier investigations demonstrated that anterior interbody cages do provide good primary stability in all loading directions, except in extension. The present study showed that this problem could not be eliminated through lateral insertion, and an additonal instability was introduced under axial rotation and lateral bending.

Intramedullary Deformation of Unreamed Femoral Nails
M.A. Slomczykowski, D.J. Goertzen , T.R. Oxland and L.-P. Nolte

Recently, solid unreamed femoral nails (UFN) have been introduced for the treatment of femoral fractures. This type of nail requires the distal end to be locked with two screws inserted in the latero-medial direction. Intramedullary deformation of the nail is a known phenomenon that can make locating the distal locking screw holes a difficult procedure. Although fluoroscopically controlled distal locking is possible, radiation exposure to the surgeon and patient remains a controversial issue. Information regarding nail deformation is important for future development of distal locking systems. Currently there are no data available describing the deformation of the distal nail tip resulting from installation in the intramedullary canal. The goal of this study was to measure the three-dimensional deformation of the distal end of the nail after insertion into the femur.
Prior to installation, sixteen 0.5mm diameter indents were machined in each nail. Four levels along the length of the nail were used; proximal, between the distal locking holes and two evenly spaced distances between the proximal and distal locations. At each level, 4 indents were made around the circumference of the nail at 90° increments, defining anterior-posterior and medial-lateral

directions. Prior to nail insertion, indents on each level were digitized 3 times using an infrared optoelectronic position sensor (OPTOTRAK 3020, Northern Digital, Waterloo, Canada). Ten cadaveric human femora were used for the study. Standard templating and surgical procedure were used for each UFN (Synthes, Stratec Medical, Oberdorf, Switzerland). Six different nail sizes were required. After nail insertion, the locations of indents were identified and exposed by an 8 mm drill hole. The DRB was reattached to the nail in the identical position and digitization of the inserted nail was performed 3 times. The same transformation from the DRB to the nail coordinate system was applied to obtain data for the deformed nail in the same coordinate system as the respective undeformed measurement. The 3 repeated measurements were averaged to account for random error and the distal end translation was taken as the center of the nail (average of the 4 distal measurement locations).
In the sagittal plane, six nails deformed posteriorly with the largest deformation (15.4mm) also posteriorly. In the frontal plane, seven nails deformed laterally with the largest value (22.5mm) also laterally. The translation vector, which describes total movement of the distal part of the nail, had an average value of 12.3mm, with a maximal value of 26.5mm. This study demonstrated that considerable nail deformation can occur after insertion into the femur. The data may help explain the problems of distal locking and the associated problems when using mechanical aiming devices. An accurate aiming device for distal locking should be capable of compensating for nail deformation.

Effect of Sterilization Treatments on the Mechanical Properties of Ossicle Allografts

A. Speirs, T.Orr and T.Oxland

One of the major concerns when using allograft tissues is the transmission of diseases from the donor to the recipient. Despite screening to exclude infected tissues, some diseases can be undetectable during the incubation period. It is therefore necessary to treat allograft tissues with a safe and effective sterilization procedure. The purpose of this study was to examine the effect of various sterilization techniques on the mechanical properties of ossicle allografts.
Frozen human cadaveric hammer and incus bones were thawed and sterilized using recommended procedures for cialit (n=22), NaOH (n=12), LpH (n=12) or autoclaving at 134°C (n=18). A group of control specimens (n=26) did not receive sterilization treatment. The mechanical testing consisted of destructive axial compression loading between flat platens of a mechanical testing machine (MiniBionix, MTS) at a rate of 0.05 mm/s, while measuring the force and displacement. The material properties of interest were: yield strength, ultimate strength and elastic modulus; structural properties of interest were: ultimate force and stiffness (N/mm). Statistical analysis involved within-treatment unpaired student-t tests of hammer-incus differences, and a one-way ANOVA across treatment groups for each parameter. Student Newman-Keuls (SNK) post-hoc tests were performed to determine treatment differences.

No significant differences were found between hammers and incuses in any of the treatment groups for any of the mechanical properties ($p>0.05$). Significant differences were found across sterilization techniques for all material properties ($p<0.01$), and especially for the structural properties ultimate force and stiffness ($p<0.01$).
This study has shown that sterilization techniques can have an effect on allograft ossicle properties. LpH does not significantly affect the strength and stiffness of the ossicles, unlike cialit, NaOH, and autoclaving. LpH has also been shown to be effective against some of the more resilient disease agents [3], so it is the preferable sterilizing agent for allograft materials, from a structural properties viewpoint.

3 PUBLICATIONS

3.1 Division of Biology

Original Articles

Belluoccio D. and Trueb B.: Matrilin-3 from chicken cartilage. FEBS Lett. 415:212-216, 1997

Chiquet M., Matthison M., Koch M., Tannheimer M. and Chiquet-Ehrismann R.: Regulation of extracellular matrix synthesis by mechanical stress. Biochem. Cell Biol. 74:737-744, 1996

Denzer A. J., Brandenberger R., Geesemann M., Chiquet M. and Ruegg, M.: Agrin binds to the nerve-muscle basement membrane via laminin. J. Cell Biol. 137:671-683, 1997

Epperlein H., Schwarz H., Piendl T., Löfberg J., Studer D., Spring H. and Müller M.: Improved preservation of the subepidermal extracellular matrix in Axolotl embryos using electron microscopical techniques based on cryoimmobilisation. J. of Struct. Biol. 118:43-61, 1997

Häuselmann H.J., Hunziker E.B.: Läsionen des Gelenkknorpels und ihre Behandlung, Schweiz. Med.Wochenschr. 127:1911-1924, 1997

Hunziker E.B., Michel M. and Studer D.: Ultrastructure of adult human articular cartilage matrix after cryotechnical processing. Micr. Res. and Tech. 37:271-284, 1997

Jürgensen K., Aeschlimann D., Cavin V., Genge M., Hunziker E.B.: A new biological glue for cartilage-cartilage interfaces: tissue transglutaminase. J. Bone Joint Surg. (Am). 79A(2):185-193, 1997

Jurvelin J.S., Buschmann M.D., Hunziker E.B.: Optical and Mechanical Determination of Poisson's Ratio of Adult Bovine Humeral Articular Cartilage. J. Biomechanics. 30(3):235-241, 1997

Kopp M.U., Winterhalter K.H. and Trueb B.: DNA methylation accounts for the inhibition of collagen VI expression in transformed fibroblasts. Eur. J. Biochem. 249:489-496, 1997

Kostoulas G., Lang A., Trueb B. and Baici A.: Differential expression of mRNAs for endopeptidases in phenotypically-modulated (dedifferentiated) human articular chondrocytes. FEBS Lett. 412:453-455, 1997

Lepault J., Bigot D., Studer D. and Erk I.: Freezing of aqueous specimens: an X-ray diffraction study. J. Microsc. 187:158-166, 1997

Meier Th., Landmann L., Hauser D., Chiquet M. and Brenner H.R.: Ectopic agrin induces a full ectopic postsynaptic apparatus in innervated muscle fibers. J. Neurosci. 17:6534-6544, 1997

Ryser U., Schorderet M., Zhao G., Studer D., Ruel K., Hauf G. and Keller B.: Structural cell-wall proteins in protoxylem development: evidence for a repair process mediated by glycine-rich protein. The plant Journal. 12(1):97-111, 1997

Wong M., Wüthrich P., Buschmann M., Eggli P. and Hunziker E.B.: Chondrocyte biosynthesis correlates with local tissue strain in statically compressed adult articular cartilage. J. Orthop. Res. 15:189-196, 1997

Zumbrunn J. and Trueb B.: Localization of the gene for a serine protease with IGF binding domain (PRSS11) to human chromosome 10q25.3-26.2. Genomics 45:461-462, 1997

Book Articles

Grodzinsky A.J., Kim Y.J., Buschmann M.D., Garcia M.L., Quinn T.M., Hunziker E.B.: Response of the chondrocyte to mechanical stimuli. In: Osteoarthritis, Eds. Brandt K.D., Lohmander S., Doherty M. Oxford University Press, 1997.

Hunziker E.B., Kuettner K.E.: Cartilage. In: Crystal RG, West JB, eds. The Lung: Scientific Foundations. Second Edition. Philadelphia: Lippincott - Raven Publishers. 793-801, 1997

Hunziker E.B., Rosenberg L.C.: Articular Cartilage Repair. In: Arthritis and Allied Conditions - A Textbook of Rheumatology. McCarty DJ, Koopman WJ, eds. Philadelphia: Lea & Febiger. 2027-2038, 1997

3.2 Division of Orthopaedic Biomechanics

Original Articles

Berlemann U., Langlotz F., Langlotz U., Nolte L.-P.: Computer assisted orthopaedic surgery (CAOS) - Beyond the pedicle (in German), Der Orthopäde 22, 463-469, 1997

Berlemann U., Monin D., Arm E., Nolte L.-P., Ozdoba C.: Planning and insertion of pedicle screws with computer assistance, J. Spinal Disorders 10(2), 117-124, 1997

Bühler D.W., Berlemann U., Lippuner K., Jaeger P., Nolte L.-P.: Three-dimensional primary stability of cementless femoral stems, Clin. Biomech. 12(2), 75-86, 1997

Bühler D.W., Oxland T.R., Nolte L.-P.: Design and evaluation of a device for measuring three-dimensional micromotions of press-fit femoral stem prostheses, Med. Eng. & Phys. (19)2, 187-199, 1997

Caversaccio M., Lädrach K., Stucki M., Bächler R., Nolte L.-P., Schroth G., Häusler R.: Concept of a frameless image interactive navigation system at the skull base (in German), Otorhinolaryngol Nova 7, 121-126, 1997

Fernandez P.M., Zamorano L., Nolte L.-P., Jiang Z., Kadi M., Diaz F.: Interactive image guidance in skull base surgery using an opto-electronic device, J. Skull Base Surgery (7)1, 15-21, 1997

Laine T., Schlenzka D., Mäkitalo K., Tallroth K., Nolte L.-P., Visarius H.: Improved accuracy of pedicle screw insertion with computer assisted surgery - A prospective clinical trial of 30 patients, Spine 22(11), 1254-1258, 1997

Langlotz F., Stucki M., Bächler R., Scheer C., Ganz R., Berlemann U., Nolte L.-P.: The First twelve cases of computer assisted periacetabular osteotomy, Comp. Aid. Surg. 2(6), 317-326, 1997

Nolte L.-P., Langlotz F., Klaue K., Stucki M., Ganz R.: Advancements in pelvic osteotomies by means of computer assistance, Seminars in Arthroplasty 8(1), 108-113, 1997.

Schwarzenbach O., Berlemann U., Jost B., Visarius H., Langlotz F., Nolte L.-P., Ozdoba C.: Accuracy of computer assisted pedicle screw placement - An in vivo computed tomography analysis, Spine 22(4), 452-458, 1997

Visarius H., Gong J., Scheer C., Haralamb S., Nolte L.-P.: Man-maschine interface in computer assisted surgery, Comp. Aid. Surg. 2(2), 102-107, 1997

Visarius H., Nolte L.-P., Pietraszkiewicz W.: Closed-Form Force-Elongation Relations for the uniaxial viscoelastic behaviour of biological soft tissues, Mechanics Research Communications 24(5), 575-581, 1997

Book Articles

Caversaccio M., Remonda L., Lädrach K., Godoy N., Stucki M., Bächler R., Nolte L.-P., Seiler R., Häusler R.: Image guided cranial operations (indication, methodology, first results) (in German), 9th Anual Meeting of the Swiss Society for Neuroradiology, Zürich, Neuroradiologia Helvetica, Special Edition 8, 93, 1997

Hofstetter R., Slomczykowski M., Bourquin Y., Nolte L.-P.: Fluoroscopic based surgical navigation - Concept and clinical Applications, Computer Assisted Radiology and Surgery, 956-960, 1997

Special Report. Excerpts from the Final Report for the Second International Workshop on Robotics and Computer Assisted Medical Interventions, Bristol England, Workshop Report Contributors: Bowersox J.C., Bucholz R.D., Delp S.L., Gronemeyer D., Jolesz F.A., Nolte L.-P., Stuhlberg M.D., Taylor R., Comp. Aid. Surg. 2, 69-101, 1997

4 RESEARCH PROJECT GRANTS

The M.E. Müller Institute for Biomechanics is indebted to the M.E. Müller- and AO-/ASIF-Foundations for their generous annual contributions to its budget.

The support of a large number of specific research projects by various foundations and firms, in particular the Swiss National Science Foundation, is gratefully acknowledged.

* * *

Chiquet M.: Regulation of extracellular matrix protein expression by mechanical stress. Swiss National Science Foundation, Bern. 1.4.1996-31.3.1999

Hunziker E.B.: EU-Forschungsprogramm BIOMED 2. Autologous implantation of de novo cartilage as a therapy for joint cartilage defects, BBW Nr. 96.0288-2. EU resp. Bundesbeitrag. 1.8.97-31.7.2000

Hunziker E.B.: Articular Cartilage Repair. Orthogene, Inc., Sausalito, CA, USA. 1.1.97-31.1.1998

Hunziker E.B.: Animal model for osteoarthritis. Osiris Therapeutics, Baltimore, MD, USA 1.10.97-30.9.1998

Hunziker E.B.: Sulzer - BP for cartilage repair. Sulzer Innotec, Winterthur. 1.10.97-31.1.1998

Hunziker E. B. and Chiquet M.: Regulation of extracellular connective tissue matrix formation. ITI Foundation for the promotion of oral implantology, ITI Stiftung, Waldenburg. 1.4.1996-30.6.1998

Hunziker E.B. and Grodzinsky A.: Structural and Metabolic Response of Chondrdocyte to Mechanical Loading. Swiss Federal Office of Public Health, Bern. 1.1.96-31.12.1997

Hunziker E.B and Häuselmann H.J.: Alginat, ein verfeinertes dreidimensionales Kultursystem zur Erforschung von Gelenkknorpelerkrankungen. Stiftung Forschung 3R, Münsingen. 1.10.1995-30.9.1998

Hunziker E.B. and Jurvelin J.: Structural Organization and Functional Properties of Adult Human and Bovine Articular Cartilage. Swiss National Science Foundation, Bern. 1.4.1995-30.6.1998

Hunziker E.B., Schenk R.K. and Buser D.: Ceros TCP as a carrier and matrix for osteoinduction (E-94-09). Dr. H.C. Robert Mathys Stiftung, Bettlach. 1.10.1994-1.3.97

Nolte L.-P., Sati M.: Sulzer Orthopedics. Computerized Reconstruction of the Whole Human Spine 1.1.1997-31.12.1998

Nolte L.-P., Oxland T.R.: Sulzer Orthopedics. Development and Validation of an In Vivo Sensor for Bone Implant Micromotions. 1.8.1996-31.12.1997

Nolte L.-P.: Data acquisition unit for the ESI. Departement Klinische Forschung der Universität Bern, CH. 1.9.1996-15.3.1997

Nolte L.-P.: Control and graphical user interface for the MOFLEX fitness and rehabilitation system. Recotec AG, Steckborn, CH. 1.10.1996-31.12.1997

Nolte L.-P.: GUI development for computer aided ENT surgery. Departement Klinische Forschung der Universität Bern, CH. 1.6.1996-30.6.1997

Nolte L.-P.: Medical image based morphology of the human spine. Sulzer Orthopedics, Wintherthur, CH. 1.1.1997-30.9.1997

Nolte L.-P.: A methodology for in vivo analysis of micromotion in total hip replacement. Sulzer Orthopedics, Wintherthur, CH. 1.1.1997-31.12.1997

Nolte L.-P.: ALIF - Evaluation of a novel surgical instrument. Mathys Medical, Bettlach, CH. 1.5.1997-30.5.1997

Nolte L.-P.: Injury pattern of the thoracolumbar spine in lateral and anterior/posterior shear. Ford Motor Company, Dearborn, MI, USA. 1.4.1997-31.12.1998

Nolte L.-P..: Micromotion in noncemented total hip replacement Stratec Medical, Oberdorf, CH. 1.10.1997-31.10.1997

Nolte L.-P.: Biomechanical evaluation of a nucleus protheses. Sulzer Orthopedics, Wintherthur, CH. 1.3.1997-30.6.1998

Nolte L.-P.: The navigated hospital. Forschungsmittel des Inselspitals der Universität Bern, CH. 1.10.1996-31.12.1998

Nolte L.-P.: Computer Assisted Orthopaedic Surgery. AO/ASIF Foundation, Davos, CH. 1.1.1997-31.12.2001

Oxland T.R., Hoffer Z.: Mathys Ltd. Biomechanical Investigation of SynCage with Lateral Insertion. 1.5.1997-31.12.1997

Oxland T.R., Nolte L.-P., Speirs A.: Sulzer Orthopedics. Micromotions of the Cement-Prosthesis Interface: An investigation of the new setzholz prosthesis. 1.9.1997-31.3.1998

Oxland T.R., Nolte L.-P. Frei H.P.: Sulzer Orthopedics Regional Strains in the Lumbar Spine. 1.3.1997-31.12.1997

Oxland T.R., Nydegger T., Buser D.: Straumann AG. Biomechanical evaluation of dental implants - Phase II. 1.1.1997-31.12.1997

Oxland T.R., Speirs A.: HNO-Klinik. Mechanical Properties of Sterilized Ear Bones. 1.1.1997-31.10.1997

Oxland T.R.: ALIF - Compression and Flexibility - Phase II. Mathys Medical, Bettlach, CH. 1.8.1996-31.12.1997

Nolte L.-P.: Endoscopic computer assisted spine surgery. Spine-Tech, Minneapolis, MN, USA. 1.11.1996-31.12.1997

Oxland T.R.: ALIF - Comparative flexibility testing. Mathys Medical, Bettlach, CH. 1.10.1996-31.3.1997

Oxland T.R.: ALIF prototyp implant evaluation - Part I. Spine-Tech, Minneapolis, MN, USA. 1.3.1997-31.7.1997

Oxland T.R.: ALIF prototyp implant evaluation - Part II. Spine-Tech, Minneapolis, MN, USA. 31.7.1997-30.9.1997

Schawalder P., Oetliker M.: Swiss National Science Foundation. Cementless fixation of joint prostheses with a new concept - clinical and biomechanical concepts. 1.10.96-30.9.98

Trueb B.: Down-regulated Proteins of Tumor Cells. Research Grant from the Swiss Federal Institute of Technology, Zürich. 15.6.94-31.12.97

Trueb B.: Transformation-sensitve Proteins of Tumor Cells. Swiss National Science Foundation, Bern. 1.10.1994-30.9.1997

Trueb B: Transformation-sensitve Proteins of Tumor Cells. Swiss National Science Foundation, Bern. 1.10.1997-30.9.2000

Wong M.: Effects of Impact Loading on the Initiation of Osteoarthritic Changes in Articular Cartilage: An In Vitro Model. Roche Research Foundation. 1.1.1997-31.12.1997

Wong M. and Hunziker E.B.: Effect of Repetitive Impact Loading on the Initiation of Osteoarthritic Changes in Articular Cartilage. Swiss National Science Foundation, Bern. 1.10.1996-30.9.1999

5 TEACHING ACTIVITIES

University of Basel:

- 4498: Cell communication and extracellular matrix

- 4519 and 6542: New literature in extracellular matrix biology

University of Bern:

- 4011: Coordinated lecture series in physics, chemistry, embryology, ecology, genetics, molecular biology, anatomy and psychology at the University of Bern
- 3rd study year: Introduction into Biomechanics of the Locomotor Apparatus
- Angewandte Molekularbiologie, interfakultäre Vorlesung für Vorgerückte an der Universität Bern

Inselspital Bern:

- Biomechanics for Physiotherapists

Federal Institute of Technology, Zürich:

- 01-319: Kolloquium in Biochemie

Teaching of MD- and PhD students in the lab

6 FELLOWSHIPS, DISSERTATIONS AND MASTER THESES

6.1 Dissertations Completed

Bühler D.W., Dr. sc. tech. ETH Zürich, Zürich, CH, 1997
Biomechanical aspects of bone-implant interfaces in Orthopaedics,

Schimpf S., Dr. med. Ruhr-Universität Bochum, 1997
Comparative biomechanical study on intradiscal therapies using lasers and the Nucletom

6.2 Masters Theses Completed

Akbari T.: Development of a PC based 8-Channel Telemetry for the biomechanical evaluation of implants, dipl.-Ing. FH, Department of Electrical Engineering, FH Giessen-Friedberg, 1997

Portmann D.: Design of navigated instruments for the preoperative planning and intraoperative computerassisted positioning of prosthetic hip joint components, dipl.-Ing., Department of Mechanical Engineering, ETH Zürich, CH, 1997

Hirsiger M.: Fixation system for human vertebrae, dipl.-Ing. HTL, Department of Mechanical Engineering, Ingenieurschule Bern, CH, 1997

6.3 Fellowships

Quinn, T. M.: Post-Doctoral Research Fellowship from The Arthritis Society of Canada.

7 HONORS AND AWARDS

04/1997 Nolte L.-P., (Co-Author) Preis des Jahres 1996 der Finnischen Gesellschaft für Wirbelsäulenforschung

06/1997 Frei H.P., Oxland T.R., Slomczykowski M.A., Nolte L.-P., Best Basic Science Paper Award, International Society for the Study of the Lumbar Spine, Singapore

06/1997 Lund T., Rathony G., Oxland T., Nolte L.-P., Third Poster Award, International Society for the Study of the Lumbar Spine, Singapore

1997 Trueb B., has been elected as editor of the Journal Biochimica et Biophysica Acta (Elsevier)

8 GUEST PRESENTATIONS

14.1. - Prof. Dr. R. Ganz: Osteoarthritis of the hip - The acetabular rim as possible place of origine. Inselspital Bern, Klinik für Orthopädische Chirurgie, CH

6.3. - Dr. P. Peter: Acetabular Revision Operations using the Cranial Cup. Klinik für Orthopädie, Medizinische Universität Lübeck, Germany

30.10. - Michael Liebschner: Cortical Bone Exhibits Hydraulic Strengthening - Innovative Techniques for Examination of Rabbit Knee Ligament Mechanical Properties. University of Vermont, Department of Mechanical Engineering, Vermont, USA

2.12. - Prof. Dr. Robert K. Schenk: Basic Bone Histology. Inselspital Bern, Klinik für Oralchirurgie, CH

9 PERSONNEL

9.1 Faculty

Hunziker Ernst B., M.D., Prof.	Director	11.89 -
	* * *	
Nolte Lutz-Peter, Ph.D.	Division Head	05.93 -
Trueb Beat, Ph.D., PD	Deputy Division Head	04.95 -
Chiquet Matthias, Ph.D. PD	Research Group Head (80%)	05.95 -
Orr Tracy, Ph.D.	BCB Group Head	10.97 -
Oxland Thomas, Ph.D	BCB Group Head	08.95 - 09.97
Quinn Tom.M., Ph.D.	Research Group Head	07.96 - 12.97
Sati Marwan, Ph.D.	Research Group Head	07.96 -
Studer Daniel, Ph.D.	Research Group Head (40%)	03.92 -
Wong Marcy, Ph.D.	Research Group Head (70%)	02.92 -

9.2 Research Associates

Bächler Richard, dipl. Ing.	Ph.D.-Student	06.96 -
Belluoccio Daniele, dipl. Biol.	Ph.D.-Student	05.95 -
Bourquin Yvan, dipl. Ing. HTL	Assistant	11.95 -
Bruehlmann Sabina, B.Sc.	Exchange Student	07.97 -
Bühler Daniel, dipl.Ing. ETH	Ph.D.-Student	08.93 - 12.97
Corday Jacques, dipl. Phys.	Assistant	05.97 - 12.97
Cripton Peter, B.Sc., M.Sc.	Ph.D.-Student	11.93 -
Döppenschmitt Ingo, cand. Ing.	Guest Student	10.96 -
Driesang Iris, V.M.D.	Assistant	06.96 -
Frei Hanspeter, dipl. Ing.	Assistant	05.94 -
Friedrich Thomas, cand. Ing.	Guest Student	11.97 -
Geiss Jana, cand. med.	M.D.-Student	09.94 -
Goertzen Darrell, dipl. Ing.	Ph.D.-Student	10.96 - 09.97
Griessen Roland, dipl. Ing. HTL	Assistant	11.96 -
Hoffer Zoltan, M.D.	Assistant	10.96 - 07.97
Hofstetter Robert, dipl. Ing.	Ph.D.-Student	06.96 -
Hu Qingmao, Dr. Ing.	Postdoc	10.97 -
Imhof Martin, dipl. phil. II	Ph.D.-Student	01.96 -
Jaccottet Alain, dipl. Ing.	Ph.D.-Student	03.97 -
Jaquemar Daniel, dipl. Natw. ETH	Ph.D.-Student	08.95 -
Kowal Jens, cand. Ing.	Guest-Student	10.97 -
Kamibayashi Lynne, Ph.D.	Postdoctoral Fellow	01.96 -
Langlotz Frank, dipl. Ing.	Ph.D.-Student	05.93 -
Langlotz Ulrich, cand. Ing.	Ph.D.-Student	07.96 -
Larouche Susanne, M.Sc.	Assistant	01.97 - 06.97
Lawrence Jeffrey, M.Sc.	Assistant	04.97 -
Long Gong, Ph.D.	Postdoc	11.97 -
Mikic Borjana, Dr. Ing.	Postdoc	01.97 -
Moulder Chris, M.Sc.	Exchange Student	09.97 -
Nydegger Thomas, dipl. Ing. HTL	Assistant	05.96 -
Oetliker Martina, Dr. med. vet.	Ph.D.-Student	11.95 -

Ponticiello Michael, M.S.	Assistant	09.95 - 08.97
Portmann Daniel, cand. med.	M.D.-Student	10.96 - 04.97
Rathonyi Gabor, M.D.	Assistant	01.97 - 12.97
Rubino Raffaele, cand. med.	M.D.-Student	11.96 -
Schauer Dirk, cand. Ing.	Guest Student	11.97 -
Scheer Carsten, dipl. Ing.	Ph.D.-Student	07.94 - 06.97
Schalet Ben, M.S.	Assistant	01.97 -
Schmid Pirmin, cand. med.	M.D.-Student	09.96 -
Siegrist Mark, dipl. phil. nat.	Assistant	07.97 -
Slomczykowski Mike, M.D.	Assistant	04.96 -
Speirs Andrew, B.Sc.E.	Ph.D.-Student	11.96 -
Strauss J. Matthias, M.D.	Assistant	07.96 - 03.97
Stucki Manfred, cand. med.	M.D.-Student	03.95 -
Trächslin Jonas, dipl. phil II	Ph.D.-Student	06.96 -
Wälti Heinz, dipl. Inf.	Assistant	12.96 -
Wentkowski Michael, dipl. Ing.	Ph.D.-Student	07.96 -
Wiedemann Markus, dipl. phil. II	Ph.D. Student	03.97 -
Wittwer Matthias, dipl. phil. II	Guest Student	10.97 -
Zumbrunn Jürg, dipl. Biol.	Ph.D.-Student	04.95 -

9.3 Technical and Administrative Staff

Berger Elke	Res. Technologist (50%)	01.90 -
Fahnemann-Nolte Karin	Secretary (60%)	03.96 -
Fiechter Esther	Secretary (90%)	07.95 -
Gaschen Véronique	Chief Technician	09.95 -
Gnahoré Esther	Secretary (50%)	12.90 -
Hutzli Walter	Aid Lab. Technician	11.89 -
Kapfinger Eva	Res. Technologist (75%)	11.89 -
Mühlheim Erland	Mechanicien (50%)	01.92 -
Mumenthaler Urs	Res. Technologist (80%)	06.95 -
Neseli Güler	Res. Technologist	08.96 -
Neuenschwander Annelies	Secretary (35%)	04.95 -
Perumbuli Prasanna	Res. Technologist	08.96 -
Rohrer Urs	Head Mech. Workshop	07.91 -
Schenker Thomas	Chief Technician	04.95 -
Walther Remo	Apprentice in Fine Mechanics	08.96 -

9.4 Scientific Consultant

Prof. Dr. Robert K. Schenk, Clinic for Oral Surgery, University of Bern, Switzerland

9.5 Guest Scientists

Alan J. Grodzinsky, Professor, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA (6.1.-19.1.97)

Manuel Koch, Ph.D, Cutaneous Research Institute, Harvard Medical School, Charlestown, Massachusetts, USA (08.97-11.98)

10 MISCELLANEOUS

10.1 Conferences Organized

Symposium on "Cell-Based Cartilage Repair: Research Considerations" at the 43rd Annual Meeting of the Orthopaedic Research Society, San Francisco, CA, USA, February 9-13, 1997

Speciality Symposia 'Computer Assisted Surgery of the Spine', 3rd EFORT Congress, Barcelona, Spain, April 24-27, 1997

CAOS/USA '97 - First Annual North American Program on Computer Assisted Orthopaedic Surgery, Co-chairman, Pittsburgh, PN, USA, June 12-14, 1997

Special Workshop - Computer Assisted Orthopaedic Surgery (CAOS) at the CAR '97 - Computer Assisted Radiology-11th International Symposium and Exhibition, Berlin, June 28, 1997

2nd Fribourg International Symposium - Cartilage Repair - Fribourg, Switzerland, October 29-31, 1997

3rd CAOS Symposium - Computer Assisted Orthopaedic Surgery, University of Bern, Bern, Switzerland, November 6-8, 1997

11 MEMBERS OF THE SCIENTIFIC ADVISORY BOARD (KURATORIUM)

- Prof. Dr. H. Reuter (President), Dept. of Pharmacology, University of Bern, Bern
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- Mr. U.G. Jann, AO/ASIF-Foundation, Davos
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- Prof. Dr. E.R. Weibel (Secretary and Vice President), M.E. Müller Foundation, Bern
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