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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 MIB attained legal status as a full University Institute on 1. January 1995, this decision having been reached by the Bernese Government in May 1994 and endorsed by the State the following month. The objectives of the MIB are to conduct basic and applied biomechanical research of the locomotor system at the physiological, tissue, cellular and molecular levels. It 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 MIB is currently under the Directorship of Prof. Ernst B. Hunziker, who was elected to this position by the Bernese Government in the autumn of 1989.

Objectives

The MIB's efforts are directed towards forging an integrated understanding of the structure and function of the musculoskeletal system at the physiological, tissue, cellular and molecular levels, and of developing and optimizing information, materials and techniques for the clinical detection and treatment of musculoskeletal diseases. It is thus conceived as a link between academic research, surgical practice and industrial development. Active collaborations with several research institutes at Bern and other universities, with the Department for Orthopaedic Surgery at the Inselspital and with the AO/ASIF Foundation's Research Institute in Davos, as well as with industrial partners, play an important part in building up the larger and more objective picture of the musculoskeletal system as a whole.

Previous and Current General Research Program

From the time of its foundation in 1981 until 1988, the MIB was directed by Prof. Stephan S. Perren. Its goals during this period were to study the normal and disturbed loading patterns of the locomotor apparatus, to advance our understanding of this system and to profit therefrom by improving the principles, techniques, instrumentation and implants applied in orthopaedic surgery. When Prof. Ernst B. Hunziker took over the Directorship in 1989, he broadened the MIB’s scope of research activities to include basic and applied aspects of skeletal tissue biology, from the physiological down to the molecular level. Improvements

in microstructural preservation, morphometric analyses at the histological level, the biocompatibility of implant materials, interfacial (adhesion) biology, and the micro mechanical properties of skeletal tissues, as well as their responses to mechanical stimuli at the tissue, cell and molecular levels, represent but a few of the directions followed. Research activities in the field of classical biomechanics are under the supervision of Prof. Lutz-P. Nolte, who has extended the MIB's research activities in this area to include computer-assisted surgery. In 1993, Dr. Nolte was appointed Head of the MIB's Division of Orthopaedic Biomechanics. In addition to being its Director, Prof. Hunziker is also Head of the MIB's Division of Biology, Prof Dr. Beat Trueb being its Associate Head.

With these new dimensions, the MIB is now in a better position to tackle questions raised in connection with the biomechanics of the musculoskeletal system, prostheses, endoprostheses, fracture treatment and novel biologically-based treatment strategies.

Organization

The Institute is comprised of a staff of about 65 people, including graduate students, medical scientists, biologists, engineers, computer specialists, technicians and research fellows. It consists of two divisions, with a central unit for administration and maintenance. The research activities of one division relate to orthopaedic biomechanics and surgical techniques, whilst those of the other pertain to basic and applied biological aspects of the musculoskeletal apparatus. The two divisions collaborate with one another and are supported by a basic technical staff furnishing histological, computer, mechanical and electronic services. Further information relating to the MIB is available on the Internet @ http://www.mem.unibe.ch.

Significance of Research Program

Research activities conducted at the MIB are contributing to our basic understanding of the structure and function of the musculoskeletal system and of their controlling mechanisms at the physiological, tissue, cellular and molecular levels. Knowledge thus gained will help us to further develop and optimize materials for clinical application, to conceive novel biologically based treatment strategies and to follow a more rational, scientific approach to the treatment of diseases of the musculoskeletal system.

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2 RESEARCH ACTIVITIES

2.1. Division of Biology

2.1.1 Molecular Biomechanics

Activities in 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 skeletal connective tissues being the main tissues investigated. Current topics dealt with include an analysis of the structural and functional properties of components contained within adult human articular cartilage, foetal cartilages and connective tissues. Newly-identified constituents of the extracellular matrix are being cloned, sequenced and analyzed from a functional viewpoint.

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Alternative Splicing of the First F3 Domain from Chicken Collagen XIV Affects Cell Adhesion and Heparin Binding
Imhof M. and Trueb B.

The N-terminus of chicken collagen XIV is subject to alternative splicing. The longer isoform contains a fibronectin type III (F3) domain at its N-terminus, whereas the shorter isoform is lacking this domain. Alternative splicing of the F3 domain is developmentally regulated. At early embryonic stages, both isoforms are expressed, while after hatching only the longer isoform is expressed. When immobilized on plastic dishes, the recombinant F3 domain promotes the adhesion of mesenchymal cells. Attachment to this domain is specifically inhibited by heparin, but not by other glycosaminoglycans. Molecular modeling studies illustrate that the first F3 domain harbors a positively charged groove which may accommodate the negatively charged heparin chain. Site directed mutagenesis of a single lysine residue within this groove abolishes the cell binding activity but does not affect the heparin binding activity. Cell binding and heparin binding are therefore two functionally distinct properties shared by the N-terminal F3 domain. When full-length collagen XIV polypeptides that either contain or lack the first F3 domain are tested on heparin Sepharose, a pronounced difference in their relative affinity is observed. Thus, alternative splicing of the N-terminal F3 domain influences the interaction of this FACIT collagen with cells and with glycosaminoglycans.

BSPRY, a Novel Protein of the Ro-Ret Family
Schenker T. and Trueb B.

Zyxin is a component of the focal adhesion plaques of mesenchymal cells. It appears to be involved in the transduction of mechanical stress from the environment to the interior of the cells. In order to elucidate the molecular mechanism of signal transduction, we have searched for interaction partners of human zyxin. Utilizing the yeast two-hybrid system we have identified a novel protein of the Ro-Ret family that was termed BSPRY. This protein is composed of a B-box, an α-helical coiled coil and a SPRY domain. BSPRY from human beings shares 80% sequence identity with the homologous protein from mice. The gene for BSPRY resides on human chromosome 9 and is specifically expressed in testis. It comprises 6 exons and 5 introns and possesses a GC rich promoter forming a typical CpG island. The function of BSPRY is not known, but several related proteins of the RBCC family have been implicated in cell transformation.

Characterization of a Novel Protein (FGFRL1) from Human Cartilage that is Related to FGF Receptors
Wiedemann M. and Trueb B.

Utilizing a subtractive cDNA cloning approach we have identified a novel protein from human cartilage. This protein represents an integral membrane protein with 504 amino acids and a molecular mass of 55 kDa. It is composed of a signal peptide, three extracellular Ig-like modules, a transmembrane segment and a short intracellular domain. The extracellular domain is closely related to the extracellular domain of FGF receptors. The intracellular domain, however, does not show any similarity to the protein tyrosine kinase domain of FGF receptors. The novel gene (FGFRL1) is located on human chromosome 4 band p16 in close proximity to the gene for FGFR3. Its mRNA is preferentially expressed in cartilaginous tissues. Owing to the structural similarity, it is conceivable that the novel protein plays a role in the modulation of FGF receptor activity.

2.1.2 Cellular Biomechanics

Research activities in this area are concerned with elucidating the mechanisms whereby fibroblasts within highly tensile-stressed tissues i.e., the 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. In order to assess the effects of these proteins on gene transcription, fibroblasts are cultured on elastic substrates and subjected to controlled strain. Such knowledge should help us to devise the 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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A Novel Device to Study the Effects of Equi-Biaxial Strain on Extracellular Matrix Expression by Fibroblasts

Chiquet M., Tunç-Civelek V. and Trächslin J.

We have designed and tested a new device for applying cyclic, equi-biaxial strain to fibroblasts cultured on fibronectin-coated silicon elastomer membranes. Six-well cell culture dishes are assembled from a polyethylene frame and a stainless steel base plate with circular holes corresponding to the size of the wells. The silicon membrane is mounted between the frame and the base plate, forming the bottom of the culture wells. The central area of each well is coated with fibronectin, and cells are plated. Two six-well culture dishes are mounted on the upper, fixed platform of the stretch machine. The lower, movable platform of the machine is equipped with teflon rings that fit into the culture wells from below, touching the silicon membranes. A motor drives the lower platform in a sinusoidal movement. Thus, the teflon rings are pressed against the membranes, stretching the cells equally in all directions. Our machine combines the advantages of equi-biaxial strain with a multiwell design; it is much simpler and cheaper than commercially available devices.

Using our machine, we were able to show that tenascin-C mRNA is upregulated more than 3-fold after applying cyclic (0.3 Hz) strain (15%) to chick embryo fibroblasts for 6 hours. This stretch response was not inhibited by the radical scavenger, N-acetyl cysteine, arguing against an involvement of reactive oxygen species in the mechanotransduction mechanism in our case. This is in contrast to a report on tenascin-C mRNA induction by cyclic stretch (1 Hz, 9%) in cardiomyocytes (Yamamoto et al., *J. Biol. Chem*. **274**: 21840-46, 1999). In additional preliminary experiments, we found that stretch-induced tenascin-C mRNA upregulation in fibroblasts is abolished by staurosporin, an inhibitor of protein kinase C, and by monoclonal antibody JG-22 against the chick β1-integrin subunit, which blocks extracellular matrix receptors. Our device will aid us to elucidate the signal transduction mechanisms involved in mechanical stimulation of connective tissue cells, as well as to further investigate the control of extracellular matrix gene expression by mechanical stress at the promoter level.

Expression of Tenascin-C and Collagen XII in Dystrophic Human Skeletal Muscle

Flück M., Billeter R., Burgunder J.-P., Koch M. and Chiquet M.

Several published reports indicate that tenascin-C is upregulated in muscle connective tissue during muscular dystrophy both in mice and humans. We speculated that part of this increased tenascin-C expression might be due to

chronic mechanical overload of diseased muscle, and that a second mechanoresponsive extracellular matrix protein, collagen XII, might be induced as well under these conditions. Polyclonal antisera were raised in rabbits against a recombinant fragment of the large splice variant of human collagen XII. Immunblotting experiments verified that antisera from two animals specifically recognized the large human collagen XII subunit in conditioned media of IMR-90 human fibroblasts. Immunocytochemical characterization of cryosections from normal human muscle with these antisera demonstrated restricted expression of the large collagen XII variant in the myotendinous junctions and in blood vessel walls, tissues which are also rich in tenascin-C. Analysis of muscle biopsies from 10 dystrophic patients showed the expected abnormal, patchy expression of tenascin-C in the endomysium. In contrast, no indication for upregulated expression of the large subunit of collagen XII was found in these cases of muscular dystrophy. These preliminary results argue against the use of collagen XII as a marker of focal lesions in dystrophic muscle. They also suggest that a mechanism other than mechanical overload (eg., chronic inflammation) may be responsible for the induced expression of tenascin-C during muscular dystrophy.

Rapid and Reciprocal Regulation of Tenascin-C and Tenascin-Y Expression by Loading of Skeletal Muscle

Flück M., Tunç-Civelek V. and Chiquet M.

Tenascin-C and tenascin-Y are two structurally related extracellular matrix glycoproteins that in many tissues show a complementary expression pattern (Hagios et al., *J. Cell Biol.* **134**: 1499-1512, 1996). Tenascin-C and the fibril-associated minor collagen XII are expressed in tissues bearing high tensile stress and are located, in normal skeletal muscle, predominantly at the myotendinous junction that links muscle fibers to tendon. In contrast, tenascin-Y is strongly expressed in the endomysium surrounding single myofibers, and in the perimysial sheath around fiber bundles. Our previous studies showed that tenascin-C and collagen XII expression in primary fibroblasts is regulated by changes in tensile stress (Trächslin et al., *Experimental Cell Research* **247**: 320-328, 1999). We tested the hypothesis that the expression of tenascin-C, tenascin-Y and collagen XII in skeletal muscle connective tissue is differentially modulated by mechanical stress in vivo.

Chicken anterior latissimus dorsi muscle (ALD) was mechanically stressed in vivo by applying load to the left wing. Within 36 hours of loading, expression of tenascin-C protein was ectopically induced in the endomysium along the surface of single muscle fibers throughout the ALD, whereas tenascin-Y protein expression was barely affected. Expression of tenascin-C protein stayed elevated after 7 days of loading whereas tenascin-Y protein was reduced. Northern blot analysis revealed that tenascin-C mRNA was induced in ALD within 4 hours of loading while tenascin-Y mRNA was reduced within the same period. In situ hybridization indicated that tenascin-C mRNA induction after 4 hours of loading was uniform throughout the ALD muscle in endomysial fibroblasts. In contrast, the level of tenascin-Y mRNA expression in endomysium appeared reduced

within 4 hours of loading. Tenascin-C mRNA and protein induction after 4-10 hours of loading did not correlate with signs of macrophage infiltration. Tenascin-C protein decreased again with removal of the load and nearly disappeared after 5 days. Furthermore, loading was also found to induce expression of collagen XII mRNA and protein, but to a markedly lower level, with slower kinetics and only partial reversibility. The results suggest that mechanical loading directly and reciprocally controls expression of extracellular matrix proteins of the tenascin family in skeletal muscle.

2.1.3 Tissue Biomechanics

Research in this area is directed towards understanding the structural-functional relationships pertaining in skeletal connective tissues, i.e., in cartilage, bone, ligaments and tendons. Emphasis is being placed on the role not only of physiological, but also of non-physiological, mechanical loading during musculoskeletal development, remodelling, disease and injury. Methodologies employed include the stereological and histological characterization of tissue microstructure, molecular and biochemical assaying of connective tissue metabolism, and the measurement of tissue biophysical properties. These projects are being undertaken with a view to improving our understanding of the aetiology of diseases such as osteoarthritis and to developing new therapeutic strategies for their treatment.

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Expression of Cartilage Oligomeric Matrix Protein (COMP) in Articular Chondrocytes is Regulated by Mechanical Loading
Giannoni P., Siegrist M., Gaschen V., Hunziker E.B. and Wong M.

The synthesis and degradation of cartilage matrix proteins is regulated in part by the mechanical loads applied to the tissue during physical activity. One of the cartilage matrix proteins whose expression is particularly sensitive to mechanical loading is COMP (cartilage oligomeric matrix protein). In *in vitro* studies, we have shown that dynamic compression of articular cartilage disks at a wide range of amplitudes (5-25%) and frequencies (0.1-0.8 Hz) results in a significant upregulation of COMP protein as seen on 2D SDS-PAGE. RT-PCR and Northern blotting were used to investigate the effect of dynamic loading on COMP mRNA expression. Native cartilage tissue and chondrocytes seeded in alginate gels were subjected to cyclic loading. In both systems, a significant upregulation of the COMP transcript was measured in comparison to unloaded controls. The upregulation of COMP in the alginate system was dependent on the presence of a pericellular matrix, suggesting that cell/matrix interactions are crucial for the mechanical signal transduction mechanism to take place. Further, integrins are implicated in this process of mechanotransduction, as the COMP upregulation was blocked by incubation of the chondrocyte/alginate constructs with -1 integrin antibodies prior to loading. To summarize, COMP is emerging as one of the key mechanical-sensitive proteins of the cartilage extracellular matrix. The

elucidation of the signal transduction pathway may prove a useful paradigm for the understanding of how remodelling of connective tissue is controlled by mechanical loading.

The Use of Hydrogels as a Synthetic Cartilage Matrix
Goodwin K., Lyton F., Tighe B. and Wong M.

The goal of this work is to develop biomaterials with mechanical properties that approach those of normal articular cartilage. One group of materials that offers a mechanically stronger alternative to alginate are semi-interpenetrating polymer network hydrogels. In the initial stages of this work we are testing three hydrogel samples to determine the polymer composition and equilibrium water content that optimizes the material‘s mechanical properties. The three hydrogels examined are as follows: a 10:55:35 ratio of polyurethane (PU), acryloyl morpholine, and tetrahydrofurfuryl methacrylate (THFMA); a 20:50:30 ratio of PU, N,N-dimethyl acrylamide, and THFMA; and a 20:50:30 ratio of PU, N-vinyl pyrrolidone, and THFMA. The equilibrium water contents of the three samples are 44.2, 58.6, and 51.3% respectively. Mechanical tests have shown the equilibrium modulus of the three hydrogel samples in compression (1.4±0.3, 1.1±0.2, and 2.5±0.3 MPa) to be comparable to that of cartilage (0.8±0.1 MPa) and superior to other common scaffolds such as alginate (0.03 MPa). The response of the hydrogels to sinusoidal dynamic compression was more variable, with dynamic modulus values ranging from 4.5±1.2 to 26.2±1.9 MPa at a frequency of 0.0025 Hz and from 6.1±1.7 to 46.6±5.6 MPa at a frequency of 0.833 Hz. In comparison, the dynamic modulus of articular cartilage was 7.5±1.3 and 15.4±2.1 MPa at frequencies of 0.0025 and 0.833 Hz respectively. This initial data will be used to modify hydrogel composition and tailor the material properties to meet our needs. We can then proceed with tests to address the biocompatibility of the hydrogel. The hydrogel-chondrocyte system will provide an additional model system in which to study cell-matrix interactions and the response of chondrocytes to mechanical loads.

Differential Effect of Embryonic Immobilization on the Development of Fibrocartilaginous Skeletal Elements
Mikic B., Johnson T.L., Chhabra A.B., Schalet B.J., Wong M. and Hunziker E.B.

The importance of mechanical influenes during skeletal development has been well established in both experimental studies and computer models. Under conditions of embryonic immobilization, it has been observed that the early stages of joint formation proceed normally, but the later stages of joint cavitation and maintenance are impaired, resulting in fusion of the cartilaginous elements across the presumptive joint line. Two structures in particular are noticeably absent from late-stage synovial joint in immobilized chick embryos: the menisci of the tibiofemoral joint and the plantar tarsal sesamoid of the tibiotarsal joint.

Both of the fibrocartilaginous structures are known to serve mechanical functions in postnatal animals, helping to distribute loads within a joint and, in the case of sesamoid structures, to provide a mechanical advantage to muscles acting across that joint. We demonstrate in this study that embryonic immobilization differentially affects the developmental fate of these two distinct fibrocartilages. The absence of the plantar sesamoid in late-stage immobilized embryos is due to a failure in the initial stages of this structure. In contrast, the early stages of meniscus formation proceed normally. Without the normal mechanical stimuli of skeletal muscle contractions, however, the meniscus fails to mature and ultimately degenerates.

Collagen Fibrillogenesis in Chondrocyte/Alginate Cultures
Wong M., Gaschen V., Siegrist M. and Hunziker E.B.

Constructs for cartilage repair which are seeded with chondrocytes often have proteoglycan levels which approach native cartilage, but have much lower collagen contents. The goal of this study was to search for chemical agents which affect collagen fibril diameter in alginate culture. One substance which has a known affect on collagen fibrillogenesis is beta-aminopropronitrile (BAPN), a potent inhibitor of lysyl oxidase and collagen crosslinking. Chondrocytes were seeded in alginate gel and cultured in the presence and absence of 0.25 mM BAPN for up to 7 weeks. Although there was no increase in total glycosaminoglycan and collagen contents over a 49 day culture period, we observed a significant increase in mean fibril diameter from 40 nm in the control cultures to 120 nm in BAPN cultures. The collagen volume density also increased from 5% to 15% in the presence of the crosslink inhibitor. Although the increased collagen in the BAPN cultures did not contribute to the mechanical strength of the constructs, this study may have important implications for the role of crosslinking in controlling collagen fibrillogenesis. Studies are also underway examining the effect of decorin and other small proteoglycans on collagen fibril diameter by chondrocytes.

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 and tendons, 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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GDFf-5 Deficiency in Mice Leads to Disruption of Tail Tendon Form and Function

Clark R.C., Johnson T.L., Schalet B.J., Davis L., Gaschen V., Hunziker E.B., Oldberg Å. and Mikic B.

Although the biological factors which regulate tendon homeostasis are poorly understood, recent evidence suggests that Growth and Differentiation Factor-5 (GDF-5) may play a role in this important process. The purpose of this study was to investigate the effect of GDF-5 deficiency on mouse tail tendon using the brachypodism mouse model. We hypothesized that GDF-5 deficient tail tendon would exhibit altered composition, ultrastructure, and biomechanical behavior when compared to heterozygous control littermates. Mutant tail tendons did not display any compositional differences in sulfated glycosaminoglycans (GAG/DNA), collagen (hydroxyproline/DNA), or levels of fibromodulin, decorin, or lumican. However, GDF-5 deficiency did result in a 17% increase in the proportion of medium diameter (100-225 nm) collagen fibrils in tail tendon (at the expense of larger fibrils) when compared to controls ($p < 0.05$). Also, mutants exhibited a trend toward an increase in irregularly-shaped polymorphic fibrils (33% more, $p > 0.05$). While GDF-5 deficient tendon fascicles did not demonstrate any significant differences in quasistatic biomechanical properties, mutant fascicles relaxed 11% more slowly than control tendons during time-dependent stress-relaxation tests ($p < 0.05$). We hypothesize that this subtle alteration in time-dependent mechanical behavior is most-likely due to the increased prevalence of irregularly shaped type I collagen fibrils in the mutant tail tendons. These findings provide additional evidence to support the conclusion that GDF-5 may play a role in tendon homeostasis in mice.

Growth-Factor-Induced Healing of Partial-Thickness Defects in Adult Articular Cartilage

Hunziker E.B.

Objective: We have previously shown (Hunziker and Rosenberg, J Bone Joint Surg, 1996; 78A:721-33) that synovial cells can be induced to migrate into partial-thickness articular cartilage defects, therein to proliferate, and subsequently to deposit a scar-like tissue. We now wished to ascertain whether these synovial cells could be stimulated to transform into chondrocytes, and thus to lay down cartilage tissue, by the timely introduction of a differentiation factor.
Design: Partial-thickness defects were created in the knee-joint cartilage of adult miniature pigs. These were then filled with a fibrin matrix containing a free chemotactic/mitogenic factor and a liposome-encapsulated chondrogenic differentiation one. Tissue was analyzed (immuno)histochemically at 2, 6 and 12 months.
Results: Defects became filled with cartilage-like tissue which registered positive for all major cartilage-matrix components; it remained compositionally stable throughout the entire follow-up period.
Conclusion: Although still requiring considerable refinement, our one-step, growth-factor-based treatment strategy has the basic potential to promote intrinsic healing of partial-thickness articular cartilage defects, thus obviating the need for transplantating cells or tissue.

Chondrogenesis in Cartilage Repair is Induced by Members of the TGF-ß Superfamily

Hunziker E.B., Driesang I.M.K. and Morris E.A.

We recently reported on the principle of an intrinsic repair strategy for partial-thickness articular-cartilage defects which is based on the introduction of a biocompatible and biodegradable matrix loaded with a free chemotactic/mitogenic factor (TGF-ß1, at a low concentration) and a liposome-encapsulated chondrogenic one (TGF-ß1, at a high concentration). In the present study, we evaluated the potential of other members of the TGF-ß superfamily (TGF-ß2, TGF-ß3, BMP-2 and BMP-13), as well as IGF-1, EGF, FGF-2 and Tenascin-C to induce chondrogenesis within our adult miniature pig articular-cartilage defect model. The degree of chondrogenic tissue differentiation was assessed 6 weeks after surgery, on a semi-quantitative basis, with histological assessment of cell morphology and intercellular-matrix staining used as the relevant criteria. All selected members of the TGF- ß superfamily were efficacious in inducing chondrogenic tissue transformation, whereas the other signalling substances tested were not. When encapsulated at high activity levels, BMPs were less prone than TGF-ß1, 2 and 3 to evoke undesired side-effects as a result of incidental leakage into the joint cavities and subsynovial connective-tissue spaces, and they are thus potentially more suitable candidates for use in human patients.

Structural Barrier Principle for Growth-Factor-Based Articular Cartilage Repair
Hunziker E.B., Driesang I.M.K. and Saager C.

A growth-factor based strategy has been recently demonstrated to induce the intrinsic repair of partial-thickness articular cartilage lesions, thereby obviating the need for transplanting cells or tissue. It was the purpose of the present study to ascertain whether this principle could be applied to full-thickness articular cartilage defects created in adult rabbits and mature miniature pigs. The TGF-ß1 contained within our chondrogenic matrix-complex proved to be potent in its osteogenic capacity when liberated into the bone compartment of such lesions, inducing the rapid upgrowth of osseous tissue and vascular buds into the cartilage one. This is an unwanted response that must be prevented. With this aim in view, we inserted a cell- and blood-vessel-excluding membrane (Millipore® in rabbits and Goretex® in miniature pigs) at the interface between cartilage and bone compartments, both of which were filled at the appropriate juncture with our chondrogenic matrix-complex. These structural barriers were effective in preventing the upgrowth of blood vessels into the cartilage compartment, and thus in preventing osteogenic tissue differentiation due to the absence of the blood vasculature.

Surgical Removal of Articular Cartilage Leads to Loss of Chondrocytes from Cartilage Bordering the Wound Edge
Hunziker E.B. and Quinn T.M.

A number of arthroscopic procedures implemented in the general handling of osteoarthritic joints or in the treatment of focal pathological or sport lesions therein, involve the removal of diseased, but also healthy articular cartilage tissue (e.g., shaving, debridement and laser abrasion). The excision of such tissue, whether for therapeutic or technical reasons, has the effect of generating "artificial" lesions within articular cartilage tissue. The reaction and fate of chondrocytes bordering the edges of such lesions have not been evaluated to date. It was the purpose of this investigation to ascertain whether the surgical creation of lesions in articular cartilage induces loss of chondrocytes from tissue bordering the wound edge and to determine whether the synthetic activity of cells in this region is compromised.
Partial-thickness defects of defined dimensions were created in the femoral condyle and/or groove of rabbits and miniature pigs. Cell volumes, cell volume densities and numerical cell densities within tissue close to (within 100 µm) and further away (control site) from the wound edge were estimated by quantitative histomorphometry at various time intervals up to 6 months after surgery. Proteoglycan synthesis by cells in both regions was determined by quantitative autoradiography following ^{35}S-sulphate labelling *in vivo*.
Results indicate that the surgical creation of partial-thickness lesions in articular cartilage induces a significant loss of cells in tissue near the wound edge. However, the surviving cell population maintains a normal rate of matrix proteoglycan deposition. The implication of these findings is that maintenance of matrix close to the wound edge is compromised, since fewer cells are sustaining larger matrix domains.

The long-term benefits from arthoscopic treatments such as shaving, debridement or laser abrasion may therefore be seriously questioned, in light of these disadvantageous effects on cell and matrix microstructure.

Altered Achilles Tendon Composition, Biomechanics and Ultrastructure in GDF-5 Deficient Mice
Mikic B., Schalet B.J., Clark R.T., Gaschen V. and Hunziker E.B.

Acromesomelic dysplasia of the Hunter-Thompson and Grebe types are rare human disorders based on GDF-5/CDMP-1 genetic mutations. Numerous skeletal abnormalities are present in these individuals, including shortened limb bones and severe dislocations of the knee. In the GDF-5 deficient brachypodism mouse, similar, although less severe, phenotypes are observed. It is unknown whether the joint dislocations observed in these disorders are due to a defect in the original formation of joints such as the knee, or to abnormalities in the tendons and ligaments themselves. We hypothesized that tendons from GDF-5 deficient mice would exhibit altered composition, mechanical properties, and ultrastructure when compared with heterozygous control littermates. GDF-5 deficient Achilles tendons were structurally weaker than controls, and structural strength differences appeared to be caused by compromised material properties: after normalizing by collagen per unit length, mutant tendons were still 50% weaker ($p < 0.0001$) and 50% more compliant ($p < 0.001$) than controls. Despite comparable levels of skeletal maturity in the two cohorts, the majority of mutant tendon failures occurred in the mid-substance of the tendon (64% of all failures), whereas the majority of control failures occurred via avulsion (92% of all failures). Mutant Achilles tendons contained 40% less collagen per microgram of DNA when compared to controls ($p = 0.004$). No significant difference in GAG/DNA was detected. Ultrastructural analyses indicated a slight trend toward increased frequency of small diameter (30 - 100 nm) collagen fibrils in the mutant Achilles. Our findings suggest that increased tendon and ligament laxity may be the cause of the joint dislocations seen in patients with Hunter-Thompson and Grebe type dysplasia, rather than developmental abnormalities in the joints themselves.

Matrix and Cell Injury Due to Subimpact Loading of Adult Bovine Articular Cartilage Explants: Effects of Strain Rate and Peak Stress
Quinn T.M., Alan R.G., Schalet B.J., Perumbuli P. and Hunziker E.B.

Mechanical overloading of cartilage has been implicated in the initiation and progression of osteoarthrosis. Our objectives were to identify threshold levels of strain rate and peak stress at which sub-impact loads could induce cartilage matrix damage and chondrocyte injury in bovine osteochondral explants and to explore relationships between matrix damage, spatial patterns of cell injury, and applied loads. Single sub-impact loads characterized by a constant strain rate between 3¥10-5 and 0.7 s-1 to a peak stress between 3.5 and 14 MPa were

applied, after which explants were maintained in culture for four days. At the higher strain rates, matrix mechanical failure (tissue cracks) and cell deactivation were most severe near the cartilage superficial zone and were associated with sustained increased release of proteoglycan from explants. In contrast, low strain rate loading was associated with cell deactivation in the absence of visible matrix damage. Furthermore, cell activity and proteoglycan synthesis were suppressed throughout the cartilage depth, but in a radially-dependent manner with the most severe effects at the center of cylindrical explants. Results highlight spatial patterns of matrix damage and cell injury which depend upon the nature of injurious loading applied. These patterns of injury may also differ in terms of their longer-term implications for progression of degradative disease, and possibilities for cartilage repair.

Minimal Compression of Ultrathin Sections with Use of an Oscillating Diamond Knife
Studer D. and Gnaegi H.

With the aim to minimize compression artefacts in ultrathin sections, coincident with the stroke direction, we have invented an oscillating diamond knife. Results and theoretical considerations explaining its function are discussed. During conventional ultrathin sectioning the resultant compression is in the order of 20-35% of section height. This holds true for sections of samples embedded into Lowicryl HM20 and the polymer polystyrene, cut with a 45° diamond knife and floated on water. The oscillating knife reduces this compression almost completely. It consists of a diamond knife on which a low voltage piezoelectric translator (piezo) is mounted, which oscillates when the piezo is driven by an alternating voltage source. No additional cutting artefacts were observed in the micrographs when they were compared with sections produced without oscillating the knife.

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).

In basic and clinical biomechanics, the major areas of research are state-of-the-art implant evaluations, muskuloskeletal injury mechanisms and appropriate treatment strategies. Research methodologies involve primarily *in vitro* and *ex vivo* experiments, as well as mathematical (finite element) models. The focus of the work is the biomechanics of the normal and pathologic human spine. Other anatomic areas of interest are the hip and shoulder.

Research in the area of computer assisted surgery covers orthopaedic-, ENT-, maxillo-facial-, and dental 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 www.mem.unibe.ch.

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2.2.1 Computer Assisted Surgery (CAS)

A Novel Concept to Track Deformable Tools in Image Guided Surgery
Amstutz C.A., Kowal J. and Nolte L.-P.

Objective: In a variety of image-guided interventions, the application accuracy of tracked slender tools such as drill bits may be limited by their mechanical deformation, thus violating the underlying rigid body assumptions. For possible correction, only navigated cannulated guides are available, which may, however, complicate or even prevent surgical workflow in deep soft and hard tissue. Therefore, the objective of the present paper is to develop, implement, and evaluate a novel concept to track and visualize possible deformation of image-guided instruments.
Material and Methods: Our approach is based on a combination of online coordinate measurements with online computations of deformations based on analytical solutions for the mechanical instrument model. It was implemented for the special case of a drill bit, its deformation being computed and displayed in the 3D scene graph of an existing CAOS environment. Laboratory experiments were performed to (a) study the relevance of drill bit deformations in CAOS systems and (b) to evaluate the potential of the novel concept to overcome limitations from the rigid body assumption. Holes were drilled in plastic bone models and cadaveric human femora. Deformations and associated forces were measured by an optical tracker and a load cell. Various drill sizes were studied.
Results: Drill bit deformation could explicitly be determined as a function of its diameter and length. The experiments suggest that application accuracy may indeed become a critical issue for drill bits with slender geometry. Associated critical lower limits were computed. Online modelling of the instrument deformation proved to minimize the application error for most drill bit geometries to a measure that is not relevant in CAOS.
Conclusions: Deformable structures can be tracked in image-guided surgery. Our concept was successfully implemented for the special case of a drill bit, but can be transferred to other tools or structures as well. Deformation modelling is mandatory if slender drill bits should not be excluded from many of the existing CAOS applications.

Noninvasive Registration in Head Surgery by A-Mode Ultrasound

Guinand N., Amstutz C.A., Kowal J., Nolte L.-P., Häusler R. and Caversaccio M.

Objective: In existing computer assisted surgery systems, the registration of bone structures is often accomplished by the use of a physical pointing device. Such an invasive registration is not well suited for acquiring bone surface points distant from the operation situs or for minimal invasive surgical procedures. We investigate an optically tracked A-mode ultrasound probe for the registration of the human skull in computer assisted head and neck surgery.

Material and Methods: A 10MHz A-mode ultrasound probe equipped with an acoustic lens focusing the beam at 5 to 15 mm depth was tested for accuracy in tempered water. A human skull bone specimen was equipped with seven fiducial marker screws. A golden standard registration was established by digitizing the fiducial markers with a special pointing device. Registration by A-mode ultrasound and registration using a standard sharp pointer were compared to each other and to the golden standard. For a limited number of patients, in addition to the usual computer assisted head and neck surgery procedure, an A-mode ultrasound registration was performed and compared to standard pointer registration.

Results: In tempered water, measured errors of the ultrasound setup were below 0.2 mm. For the tests on the human skull bone specimen and the operated patients, ultrasound registration and pointer registration were equivalent with respect to the measured accuracy.

Conclusions: A-mode ultrasound is a means for registration of the human skull in computer assisted head and neck surgery. The proposed set-up provides automatic detection of the bone surface points. To perform a registration by A-mode ultrasound, more time is needed than using a standard pointer. The time difference decreases with increasing operator experience.

On B-Mode Ultrasound Based Registration for Computer Assisted Orthopaedic Surgery Orthopaedic Surgery
Kowal J., Amstutz C.A. and Nolte L.-P.

Objective: One prerequisite for the successful use of computer-assisted surgery in minimally invasive approaches is an accurate and reliable percutaneous registration device. Beside other techniques, the non-invasive, widespread brightness-mode ultrasound (B-mode) is accepted to be promising, however, associated devices should preferably be fully automatic to minimize user interactions and to avoid manual segmentation. So far, minimally invasive B-mode ultrasound registration has shown to be successful mostly in artificial environments, such as plastic bones in water baths, with no report available on the gross clinical success of this technology. Therefore, the objective of the present paper is to investigate if conventional B-mode ultrasound is qualified for automatic detection of bone-surfaces and in this case to develop a registration device that detects bone surfaces covered by soft tissue.
Material and Methods: Ultrasound images are recorded with their spatial orientation in the anatomical coordinate system using an optically tracked B-Mode probe. The 7.5MHz linear array-probe is previously calibrated in a water bath. One of the crucial aspects in the bone surface detection process based on B-mode ultrasound images is to determine the area where the algorithm should search for the bony structure. Our approach, in a first step, combines bright pixels within the images into clusters. Then through several iteration steps a special 'buy-and-sell-strategy' determines the cluster with the highest probability of containing the bone-surface. Accuracy tests involving cadaveric long bone material were performed. The registration accuracy was evaluated by calculating the distances between the bone surface models and the reconstructed "bone-contours".
Results: The results of our in vitro tests indicate that the new algorithm may be capable of detecting bone surfaces up to 60mm below the skin. The overall accuracy of the method when applied to uniform bone structures, such as a femur was shown to be sufficient.
Conclusions: For depths up to several centimetres, the tracked b-mode ultrasound registration with the proposed image-processing algorithm allows sufficient registration of bone surfaces. For more complex and deeper anatomical structures, such as spinal vertebrae, further refinements of the technology are required.

"Confidence Volumes" as a Visual Feedback of Registration Accuracy
Nemec B., Bächler R. and Nolte L.-P.

To establish the correlation between the patient's anatomy to be operated on ("therapeutical object") and the preoperative image data ("virtual object"), a registration process has to be executed. This is normally achieved by matching points collected on bony surfaces to features defined in the virtual object's space. The result of this step is a number representing the deviation of the data from the

therapeutical object's space from the predefined features after registration has been carried out. The deviation might be calculated, e.g., as a root mean square error of deviations of corresponding points (i.e., when a paired-points matching has been applied). This numerical value is often used to provide feedback on the quality and hence accuracy of the registration. Unfortunately, this is no suitable base for the surgeon to determine whether the registration will actually provide the accuracy he requires to carry out his task, as registration accuracy depends on the location within the therapeutical object's space. This cannot be represented as a single number. To overcome this problem, a new model of accuracy estimation for registration has been developed. By estimating error probabilities for the image source and the pointing device, the accuracy of any point may be calculated as the probability for its actual error to exceed a certain amount. By specifying a threshold for the probability and the maximum allowable error, a visual representation of the volume that meets the accuracy requirements can be presented to the surgeon. As an example, the regions that meet the accuracy requirements can be colored differently than the rest of the volume. The implementation of the algorithm to calculate the confidence volumes is very fast and allows a real-time feedback when new data is entered. Thus, the surgeon can already get feedback during the capturing of points, which enables him, e.g., to determine the necessary points for a surface based registration as he captures points.

A Novel Mobile C-Arm System for Use in Image Guided Surgery – A Feasibility Study

Nolte L.-P., Wälti H., Fujita H., Zheng G., Seißler W., Hey J. and Kusch J.

Objective: Preop CT and MRI scanners and intraop 2D image intensifiers are standard means for image acquisition in orthopaedic surgery. However, there does not exist an easy to handle and cost-effective means to provide intraoperative 3D updates to the surgeon. This is of key importance for the surgical treatment of various congenital, traumatic, and degenerative diseases of the locomotor apparatus. In this study a novel mobile iso-centric 3D C-arm system (Siemens, Erlangen, D) was evaluated for its potential in image-guided surgery.

Material and Methods: The motorized iso-centric C-arm allows the creation of high resolution 3D data. After initial testing on isolated cadaveric specimens, the study involved image acquisition, processing, and evaluation of long bones and spines from five human full body cadavers. Cadavers were placed on a special unit, which allowed intraoperative positions to be simulated. 3D image data sets were acquired and automatically loaded into our SurgiGATE navigation software (Medivision, Oberdorf, CH) for processing and evaluation. For further evaluation, the C-arm was inherently registered to the SurgiGATE tracking system.

Results: Handling of the novel device was found to be quite easy, i.e., comparable to existing image intensifiers. 3D data sets were acquired effectively

in less than two minutes. The system allowed identification of all important surgical landmarks and zones with high image quality for the long bones. Image quality was lower for the torso, but still many of the surgically relevant cortical bone structures of the spine could be identified, with some limitations at the sacrum. As expected, image quality was dependent on the size and mass of the torso. Inherent registration was found to be sufficient for direct matching-free surgical navigation.

Conclusions: For the first time, the system provides fast and affordable 3D intraoperative updates to the surgeon. The easy handling, stable calibration, and comparably low radiation exposure of the device hold promise for its effective future clinical use. Fast intraoperative 3D updates with co-registered tracking systems will open new horizons in orthopaedic surgery.

A Pre- and Intraoperative Computer Assisted Tool for Reduction of Acetabular and Pelvic Fractures
Tarte S., Hüfner T., Bächler R., Langlotz F., Pohlemann T., and Nolte L.-P.

The most important planning task for successful reduction of pelvic fractures is the accurate definition of the fracture lines. Together with an accurate execution of the surgery, this is the main requirement for a good reconstruction of the pelvis' geometry and a prerequisite for realistic simulation in a CAS system. Currently available CAS systems cannot display the movements of several bone fragments simultaneously. To provide a reasonable navigation aid, it is necessary to provide not only three-dimensional (3-D) information pre- and intraoperatively, but also to allow active planning, and real-time feedback of intraoperative fragment movements. The planning software currently being developed allows the execution of different tasks required for the final planning step, the so-called virtual reduction. First, 3-D objects are created for all the relevant fragments. Next, the surgeon defines fracture lines and surfaces on the different fragments. To achieve the virtual reduction, the individual fragments can be moved into the desired location by using the mouse. As this might be difficult to achieve unaided, a method to automatically position the fragments is being developed. The surgeon then can refine the positions to achieve the desired reduction. For the intraoperative part, two main challenges remain to be solved. The registration of the fragments to be tracked and visualized needs to be facilitated. Although the current registration algorithm is highly accurate and convenient for standard use, e.g., in spinal surgery, the definition of landmarks for every fragment and the subsequent capturing of these points on the fragment would be rather cumbersome. Therefore, new strategies are being tested to enable an easy, surface based registration for the smaller fragments. The second challenge is the development of an adequate interface to assist during the fracture reduction phase. Using the results of the virtual reduction, the planned position of each fragment is known and the deviation of the current position can be measured. However, these values might not be easily understandable, and therefore an interface is being developed that aims at being as intuitive as possible.

Reality Augmented Virtual Fluoroscopy with Radiation Free Updates of In-Situ Surgical Fluoroscopic Images
Zheng G., Kowal J., Grützner P. and Nolte L.-P.

Intra-operative fluoroscopy is a valuable tool for monitoring underlying bone and surgical tool positions in orthopedics. Disadvantages of this technology include the need for continued radiation exposure for visual control with cumbersome verification image updates. The purpose of this paper is to highlight a reality augmented virtual fluoroscopy based on a novel virtual cylinder representation of bone fragment. It is used not only to provide a 3D image of the fracture but also to track fragments' spatial and projection position changes and further to achieve radiation free updates of in-situ surgical fluoroscopic images in a computer

assisted fluoroscopy based navigation system. In practice, a virtual cylinder is reconstructed from multiple registered fluoroscopic images and its projection is used to define the image area for bone fragments in each image plane. With opto-tracking of the spatial position changes of the virtual cylinder, its projection can be calculated by a mathmatical model of projection properties of the fluoroscope, which is obtained in a calibration procedure. Then, through a non-linear interpolation and warping techniques, the fragment image is repositioned in each image plane with no further image updates. With this new method, reality augmented virtual fluoroscopy is achieved without the use of multiple C-arm units in constant mode from different angles during the intervention, and without the associated high radiation exposure for the patient and the surgical staff. Although the novel concept can be applied in many situations which require fluoroscopic image updates, in this paper long bone procedures such as the reduction of femoral fractures are used to evaluate the effectiveness of the new concept.

Frameless Optical Computer Aided Microscopic Surgery System for ORL Surgery

Zheng G., Bächler R., Caversaccio M., Langlotz F., Häusler R. and Nolte L.-P

Objective: To integrate a digitally controlled operating microscope without a laser autofocus system to a frameless optical computer aided surgery (CAS) system and test the accuracy and usability of the computer aided microscopic surgery system in ORL surgery.

Background: Today, most of the demanding procedures in ORL surgery require the aid of the operating microscope. In microsurgery, in which the use of a specially designed operating microsocpe allows for the performance of controlled tissue removal under improved lighting and magnification, there is a great need for on-line information about both patient anatomy and the orientation and position of surgical tool. Unfortunately, the microscope and hand-held navigation instruments can not be used at the same time. The microscope has to be used as a localizing instrument itself.

Methods: A shield with four light emitted diodes (LEDs) is attached to the microscope and a specially designed calibration tool is used to precisely calibrate the microscope's focal point. During surgery, a client/server communication mode between the microscope module and CAS main application makes it possible to track the focal point and trajectory of the microscope in real time, and the information is correlated to the preoperative scan images and updated interactively.

Results: The practical accuracy of the navigation microscope on lateral side of a cadaver skull is 2.345±0.601 mm, and on the anterior side is 2.072±0.354 mm. In all eight cases of computer aided microscopy surgery, no complications occurred.

Conclusions: Our computer aided microscopic surgery system has proved its accuracy and usability in ORL surgery. Surgeons feel very comfortable with the

system, which offers the ability to combine the precise optics of an operating microscope with the localization power of a computer aided system.

2.2.2 Basic and Clinical Biomechanics (BCB)

Primary Stability of Anatomic Uncemented Femoral Stems
Berey S., Beutler T., Nolte L.-P. and Orr T.E.

Stability of a femoral stem prosthesis is a critical factor in its long-term clinical success. In non-cemented stems, the immediate post-operative, or primary, stability is important because it allows osseointegration, creating secondary, long-term stability. A previous study developed a protocol to compare the in vitro primary stability of rectangular and conical press-fit stem designs using custom-designed micromotion sensors. The purpose of the current study was to compare the micromotion characteristics of another category of cementless prosthesis - the anatomic stem, where the proximal part is designed to fit the proximal area of the femur. Three anatomic stem designs were compared. Stems were implanted in eight pairs of contra-lateral human femurs. Holes were drilled in the anterior cortex of the femurs corresponding to proximal, middle and distal locations on the stems. Custom-made three-dimensional micromotion sensors were mounted in these holes. The proximal and distal sensors defined the implant axis, and the middle sensor was mounted medially to analyze torsional stability. The specimens were mounted in a biaxial mechanical testing machine and loaded cyclically in simulated one-leg stance. The load consisted of a distally directed force applied to the head of the implant at 1Hz, varying between 200N and up to 4x BW. Three-dimensional motions were measured at each of the three locations. Measured motions were characterized as range of total motion (TM), the amount the stem migrates under a static load, and dynamic motion (DM), the amount of stem toggle under cyclic loads. The dynamic motions were comparable for all designs, and also demonstrated that the anatomical prostheses derive their fixation primarily from the proximal section. The amplitude of the dynamic motions at the proximal and the middle measurement locations were smaller than the smallest motion values which have been reported to inhibit solid bone ingrowth. However, the dynamic motions observed at the distal end of the prosthesis may exceed the limits for bone ingrowth.

Glenohumeral Range of Motion: In-Vitro Comparison of Two Prosthetic Designs
Beutler T., Berey S., Mason M.D., Orr T.E. and Nolte L.-P.

The goal of glenohumeral prosthesis design is to restore the functional and structural properties of the joint to their normal state. The design rationale for a dual-radius humeral head is to improve soft tissue balance, while allowing a greater range of motion (ROM) than a conventional single-radius humeral head.

In this study, the ROM of a dual- radius humeral prosthesis, with and without a glenoid component, was measured and compared to that of a conventional prosthesis. Nine cadaveric human shoulder joints with no signs of degeneration were prepared. To minimize capsular ligament length alterations during implantation, a modified procedure was performed using a split humerus for prosthesis insertion. The scapula was fixed in PMMA and attached to a rigid testing frame. Using an optoelectronic motion tracking system, the maximum passive ROM of the joint was measured in abduction, flexion-extension, and internal-external rotation. The center of rotation was calculated by tracking a single point on the humerus as it was moved manually over a wide range of motion and using the Levenberg-Marquard algorithm. Force and moment data were collected during testing.
For prostheses implanted with a glenoid component, the ROM of the dual-radius humeral prosthesis was 8% greater in flexion-extension ($p=0.02$), but there were no differences for abduction or rotation. The addition of a glenoid component decreased the ROM for both prosthesis designs in rotation by approximately 12% ($p=0.01$), and for the conventional prosthesis only in flexion-extension by 6% ($p=0.03$) and in abduction by 10% ($p=0.01$). The passive ROM measured in this study agreed well with previous studies. The results demonstrated an increase of ROM in flexion with the dual-radius humeral head compared to the conventional heads but not in the other directions. Further analysis of force and moment data is required to evaluate the possible role of the dual-radius head in soft-tissue balancing and joint stability.

In Vitro Stability Testing of Tuberositi Fixation in Humeral Hemioarthroplasty for Traumatic Indications

Beutler T., Frei H.P., Schatzmann L., Müllner T., Hertel R., Orr, T.E. and Nolte L.-P.

Obtaining consolidation of the humeral tuberosities in traumatic and postraumatic conditions requiring hemiarthroplasty remains a clinically relevant problem. It has been shown that the greater tuberosity was either dislocated and/or resorbed in as many as 50% of clinical cases, and that dislocation always precedes resorption. The present study was designed to biomechanically assess two alternative methods to the standard Neer method of stabilization of the tuberosity in hemiarthroplasty. Paired cadaver shoulder joints with intact rotator cuff ($n = 12$ pairs) were tested. Neer's recommended technique was compared with the tension band technique, using 5-0 braided polyester fiber in both cases ($n = 6$ pairs), and the tension band technique using 1mm steel cable was compared with the same technique using 5-0 braided polyester fiber ($n = 6$ pairs). The specimens were mounted to a material testing machine and the rotator cuff was attached to a special loading jig simulating moments present for active abduction-external rotation. The kinematic response of the tuberosities was measured using an optoelectronic camera. The measured load and rotations were used to calculate the rotational stiffness of the construct. The absolute rotation angles at 100, 200 and 300N load were also compared within the groups. No significant difference

was found between the Neer vs. tension band technique using nylon suture. However, the tension band technique allows the use of steel cable, which is precluded by the Neer technique. The tension band technique with steel cables was, however, significantly stiffer than the tension band technique with sutures, which leads to the conclusion hat the tension band technique using steel cables provides more rigid fixation than Neer's standard technique.

Biomechanical Analysis of Intrapedicular vs. Extrapedicular Thoracic Pedicle Screw Placement

Brentnall M., Berey S., Ferguson S.J., Bear S., Morgenstern W. and Orr T.E.

The use of pedicle screws for rigid fixation of instabilities in the lumbar and lumbosacral spine has become a routine procedure for the past ten years. Anatomical considerations of the thoracic spine and the potential risk for neurological complications is the main reason for many spine surgeons to hesitate using pedicle screws in the thoracic spine. Previously, the anatomy and morphology of the thoracic vertebra and the pedicle in particular have been investigated in order to define a safer and reliable insertion technique. All but one study evaluated an intrapedicular pathway. In the one study on extrapedicular screws, it was concluded that the anatomy of posterior elements is too variable to allow for a standardized technique. In a previous study by one of the principle investigators, landmarks were defined in order to facilitate extrapedicular screw insertion. The advantage of this technique is the possibility to utilize screws with increased length and diameter. Insertion is safer due to an increased distance to the spinal canal. The aim of this study was to compare the biomechanical properties of both the intra- and the extrapedicular technique in a nondestructive mode (using motion analysis). Ten human thoracic spines (five intra-, five extrapedicular) were instrumented with the AO Universal Spine System in a specified pattern and tested in flexion/extension, torsion, compression and lateral bending. The range of motion of the noninstrumented and the instrumented construct was measured using an optoelectronic system. The ratio of spine motion before and after instrumentation was calculated to quantify the stabilizing effect of the implant, and was also compared before and after cyclic fatigue loading of the implants. It was found that the decrease of flexibility of the extrapedicular group was equal to that of the intrapedicular group. It can be concluded from these results that the extrapedicular technique offers a safer insertion of pedicle screws, while maintaining the mechanical stability of the standard intrapedicular technique.

Mobility of the L5-S1 Spinal Unit: A Comparative Study Between an Unconstrained and a Semi-Constrained System

Charrière E., Beutler T., Caride M., Mordasini P., Dutoit M., Orr T.E. and Zysset P.

Biomechanical testing of functional spinal units (FSU) has been used to better understand the kinematics of the intact and instrumented spines. There are many different testing set-ups among researchers and there is some controversy about the most appropriate method. The purpose of this study was to compare the kinematic behavior of the lumbosacral FSU in a semi-constrained system with an unconstrained system. Seven fresh human cadaveric L5-S1 FSU were tested in flexion-extension, bilateral lateral bending and bilateral axial torsion using an unconstrained (custom designed) and a semi-constrained system (MTS, Minneapolis, MN). The former involved the application of unconstrained pure moments (6 DOF). In the latter, rotations were applied to specimens and torque was measured on a multiaxial servohydraulic test machine; a maximum of 3 DOF were left free. Motions of the vertebrae were measured using an optoelectronic camera. Results of both systems did not show significant differences for the principal motion response. The directions of coupled motions were similar for both tests, but their magnitudes were smaller in the semi-constrained configuration, especially in axial torsion. An unconstrained system is today a "gold standard" for the characterization of FSU motion. The use of a semi-constrained method seems to be an appropriate way to characterize a FSU's main motion behaviour, but care should be taken using these methods if the determination of coupled motions measurements is important.

Adjacent Vertebral Failure Following Vertebroplasty: A Biomechanical Investigation

Ferguson S.J., Berlemann U., Nolte L.-P. and Heini P.F.

Vertebroplasty, the percutaneous injection of bone cement into vertebral bodies, has recently been used to treat painful osteoporotic compression fractures. Early clinical results are encouraging, as pain relief is immediate and reliable, and the complication rate is low. Therefore, vertebroplasty is gaining increasing popularity for the treatment of osteoporotic spine patients. However, very little is known about the consequences of cement augmentation for the adjacent, non-augmented level. Fresh compression fractures observed in adjacent levels soon after PMMA injection into lower levels could be an expression of the natural course of the disease, but theoretically additional fractures may be provoked by an adjacent rigid reinforcement. To test this hypothesis, the overall failure strength and structural stiffness were measured for paired osteoporotic functional spine units (FSUs). One FSU of each pair was augmented with PMMA at the caudal level, while the other served as an untreated control. Twenty FSUs (T9-T10 and T11-T12) from ten spines were tested. For augmentation, cement was injected bipedicularly under fluoroscopic control. Mechanical testing was carried out on a servo-hydraulic testing machine. Specimens were subjected to a non-destructive cyclic sinusoidal dynamic compression before and after treatment by vertebroplasty. Following cement augmentation, the FSU was compressed to failure at a constant displacement rate of 0.5 mm/s. The overall stiffness and failure load of the FSU were determined. Comparison of the load versus displacement curves before and after vertebroplasty revealed no differences in

segment stiffness. The ultimate failure load for FSUs treated by cement injection was on average 17.8% lower than that of the adjacent, untreated FSU ($p = 0.01$). For all FSUs, there was a significant correlation between increasing BMD and increasing failure load ($r2 = 0.402$, $p = 0.001$). For treated FSUs, there was a trend towards lower failure load with increasing degree of cement filling ($r2 = 0.262$, $p = 0.13$). While vertebroplasty greatly increases the strength of individual vertebrae, the decreased failure load measured in treated FSUs in the current study provides evidence that the presence of rigid cement augmentation may facilitate the subsequent collapse of adjacent vertebrae. The mechanism for such a failure is not clear, but it is possible that the increased stiffness of augmented vertebrae alters the load transfer across the disc / endplate interface. To better understand the subtle changes in spine biomechanics following vertebroplasty, further studies are planned to directly measure bone strains under load in augmented and adjacent vertebrae, before and after treatment.

Quantification of Pedicle Screw Toggle Movements during Cyclic Bending Loads

Jensen L.M., Szirtes B.G., Mason M.D., Nolte L.-P. and Orr T.E.

Pedicle screws in vivo are subject to various dynamic loading conditions that can eventually cause the bone/screw interface to fail. Previous studies have used pullout tests to quantify the differences between conical screws and traditional cylindrical screws. However, clinically screws do not fail in pullout. The goal of this study was to use a more physiological test of force controlled cyclic bending loading, as well as the traditional pullout test, to quantify the differences between two screw designs. Six human cadavaric lumbar vertebrae were implanted with two screw designs: 6.5 mm x 40 mm conical screws (Osteonics Inc., Allendale, NJ) and 6.5 mm x 40 mm cylindrical screws (Sofamor Danek). Computer assisted surgery software was used to ensure ideal placement of each screw. Force controlled cyclic bending load tests were performed over 5000 cycles and the 3D movements were recorded with an Optotrak camera. Rigid body kinematics were used to determine movement of the screw with respect to the vertebral body. Pullout tests of each screw were performed at 0.5 mm/sec to measure the strength after cyclic loading. There were no significant differences found between screw designs for pivot point location, pivot point migration or translation of the screw ends. The tests after cycling did not show a significant difference in mean pullout strength between screw designs although the conical screw was higher (1082N vs.962 N). The different screw designs did not produce distinct movement patterns. However, the measurement technique used in this study is a tool for future studies since it enables 3D analysis of screw movement and can identify how the screw moves inside the bone. It was able to demonstrate and quantify a pivot point and screw tip movement inside the vertebral pedicle. In future studies, it can be used to analyze geometrical and morphological effects in screw movement.

Factors Affecting the Behaviour of Interbody Cages in the Lumbar Spine: Finite Element Analyses

Polikeit A., Orr T.E. and Nolte L.-P.

Interbody cages in the lumbar spine have been a promising advancement in spinal fusion to relieve lower back pain. Experimental studies have investigated the influence of factors such as cage design, and vertebral bone density using three dimensional flexibility studies and compressive strength tests. The conclusions from these studies have shown that cage design is not as important a factor as the bone density of the adjacent vertebra. The objective of this study is to use the finite element method to investigate what factors have the greatest influence on the stresses in the vertebra. Three-dimensional finite element models of a L2-L3 functional spinal unit (FSU) with and without an intervertebral cage were developed. The geometry of the model was based on reconstructed CT scans from a healthy cadaver specimen and consisted of 31716 elements for the intact case. This intact, ligamentous FSU model was validated by comparing resultant forces and strains to previously reported experimental studies. The design of the cage was based on the SynCage (Mathys Medical, Bettlach, Switzerland), but did not have such features as holes and teeth on the plates. Therefore, the elastic modulus of the material was reduced. An anterior approach was modelled. Contact elements with friction were used at the facet joints and the surfaces between the cage and the bone. Parametric analyses were performed varying the material properties of the cage (titanium, PEEK), the material properties of the adjacent bone (cortical, cancellous, endplate, posterior elements), and the loading conditions (pure compression, off-axis loading). The material properties were obtained from the literature of previous finite element studies. The material property of cancellous bone was varied to represent those values of bone mineral density measured in previous spine studies. All models were compared with the corresponding intact model. The insertion of the cage increased the maximum von Mises stress in all models and changed the load transfer in the adjacent structures. The variation of the cage material had much smaller influence than varying the properties of the underlying endplate and trabecular bone. In all cases, the stress in the trabecular bone on the periphery was less than in its corresponding intact model. The denser the cancellous bone, the more the stress was distributed underneath the cage while the peripheral structures were unloaded. The finite element model in this study was based on physiological geometry, ligaments and material properties; however, there were some limitations. The homogenous, isotropic material properties simplified the real situation. Additionally, no annular tension due to the insertion was modelled, what might represent a worse case scenario. The altered load distribution may lead to bone remodelling of the vertebral structures and explain damage of the underlying bone. The results of this study agreed with previous experimental studies that suggest that density of the bone underneath the cage is one of the most important factors in determining the behaviour of the caged vertebra.

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3.2 Division of Orthopaedic Biomechanics

Original Articles

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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.

* * *

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Chiquet M.: Regulation of extracellular matrix protein expression by mechanical stress. Swiss National Science Foundation, Bern. 1.4.1999-31.3.2002

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Nolte L.-P.: A Novel Approach for the Percutaneous Location of Bone Structure by Ultrasound; Towards New Minimally Invasive Computer Assisted Surgery, Swiss National Science Foundation, Switzerland. 1.10.99-1.10.2002

Nolte L.-P.: Dental Navigation, Institut Straumann, Waldenburg, Switzerland. 1.1.2000-31.3.2002

Nolte L.-P. and Langlotz F.: VŒU - A virtual orthopaedic European University, 5th Research Framework Program of the European Union, 1.5.2000-30.04.2003

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Orr T.E. and Beutler T.: The effect of Facet Joint Geometry on Axial Rotation, Stryker, Inc., Raubling, Germany, 1.6.1999-1.4.2000

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Orr T.E., Berey S. and Beutler T.: The range of motion of the humeral head: Solar dual radius vs. conventional humeral head, Osteonics (Stryker/Howmedica), Allendale, NJ, USA, 1.4.2000-1.10.2000

Pohlemann T. and Langlotz F.: Computer assisted pelvic ring fracture fixation, AO/ASIF-Foundation, Bern, 12.98-12.2000

Trueb B.: Transformation-sensitive Proteins of Tumor Cells. Swiss National Science Foundation, Bern. 1.10.97-30.9.2000

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Trueb B.: Structure and Function of Novel Cartilage Proteins. Swiss National Science Foundation, Bern. 1.10.2000-30.9.2003

Unser U. and Thévenaz Ph.: Fluoroscopy-Based 3D/2D Registration for Minimally-Invasive Approaches in Trauma and Spine Surgery, AO Research Commission, Switzerland, 1.10.2000 - 30.9.2002

Wong M., Hunziker E.B. and Hubbell J.: Regulation of matrix synthesis in tissue-engineered constructs for cartilage repair. Swiss National Science Foundation, Bern. 1.4.2000-31.3.2003

5 TEACHING ACTIVITIES

University of Basel:

- 2461 and 5515: New literature in extracellular matrix biology
- 7446: Extracellular matrix: from bone to brain

University of Bern:

- Cytologisch-Histologisches Praktikum für Medizin- und Tierarzt-Studenten im 1. Jahr.

- W4001: PBL (Problem Based Learning)-Curriculum, Medical Faculty: Tutorial (1. year, 4. rotation)

- W4001: PBL (Problem Based Learning)-Curriculum, Medical Faculty: Concept Lecture KV 28-2

- S7330: Applied Molecular Biology, interfakultäre Vorlesung für Vorgerückte an der Universität Bern

- W7337: Connective Tissue Research, Kolloquium für Studierende an der Universität Bern

- W7331.1: Uebungen in Immunologie II, Faculty for Natural Sciences

Inselspital Bern:

- Biomechanics for Physiotherapists

Federal Institute of Technology, Zürich:

- 01-319: Biochemie, Kolloquium für Studierende des Studiengangs 551 in Biologie an der ETH Zürich

6 FELLOWSHIPS, DISSERTATIONS AND MASTER THESES

6.1 Dissertations Completed

Bächler Richard, Ph.D., University of Bern, Bern, 2000
Registration techniques in CAS

Belluoccio Daniele, Dr. phil. II, Universität Basel, 3.5.2000:
Characterization of clones from a subtracted, cartilage-specific cDNA library: MGP and Matrilin-3

Imhof Martin, Dr. phil. II, Universität Bern, 27.4.2000:
Alternative splicing of collagen XIV: Structure and function of novel splice variants

Tannast Moritz, Dr. med., University of Bern, Bern, 2000
Die Berechnung von Anteversion und Inklination der Beckenfrontalebene

Trächslin Jonas, Dr. phil.II, Universität Basel, 17.2.2000
Regulation of collagen XII expression by mechanical stress

Wang Xuanhui, Dr. med., University of Bern, Bern, 2000
The Biosynthetic Activity of Chondrocytes in Alginate Cultures

Zulliger D., Dr. med., University of Bern, Bern, 2000
Computer unterstützte Navigationschirurgie der lateralen Schädelbasis (eine theoretische Studie zur optimalen Registrierung)

7 HONORS AND AWARDS

02.2000 Best Paper Award 5th & Millennium CAOS-Symposium, Davos, CH, "Computer -assisted placement of a double-bundle ACL through 3D fitting of a statistically-generated template into individual knee geometry":
Wymenga A.B, Sati M., Luites W.H., Bourquin Y., Blankevoort L., Venne van der R., Kooloos J.G.M., Stäubli H.-U.

02.2000 Nolte L.-P.: Founder and First President of the International Society for Computer Assisted Orthopaedic Surgery, with domicile in Zürich, CH

03.2000 to date, Hunziker E.B.: Member of the National Institutes of Health-review panel for tissue engineering and related bioengineering research partnership grant applications (NIH, Bethesda) USA

03.2000 to date, Hunziker E.B.: Member of the Special Review Panel of the German Ministry of Education and Science for Tissue Engineering Projects, Germany

06.2000 Nolte L.-P.: Member of the Advisory Board (Leitungsausschuss) of MedTech for the Commission for Technology and Innovation, Bern, CH

07.2000 to date, Hunziker E.B.: Chairman Elect for the Gordon Research Conference on Musculoskeletal Biology and Bioengineering, USA

11.2000 Ferguson S.J.: Scientific Prize of the Swiss Society for Biomedical Technology for his work "Biomechanics of the Acetabular Labrum"

11.2000 Trueb B.: Prize of the Department for Clinical Research DKF, University of Bern, for the best pre-clinical research work

12.2000 Wong M.: Venia docendi for Biomechanics of the University of Bern

12.2000 Trueb B.: Professorship for Biochemistry of the University of Bern

8 GUEST PRESENTATIONS

24.3.2000 - Dr.-Ing. Markus Wimmer: Wear of the Polyethylene Component Created by Rolling Motion of the Artificial Knee Joint. Joint Replacement Group AO Research Institute, Davos, Switzerland

3.4.2000 - Wolfgang Birkfellner, MSc: Computer-aided Navigation in Oral Implantology. Department of Biomedical Engineering and Physics, University of Vienna, Austria

17.7.2000 - Dr. Michael A.K. Liebschner: Numerical Simulation can improve the operative treatment of fractured spinal vertebrae. Orthopaedic Biomechanics Laboratory, University of California, Berkley, USA

31.8.2000 - Prof. Dennis R. Carter: The Mechanical Regulation of Cartilage Growth and Ossification. Biomechanical Engineering Division, Department of Mechanical Engineering, Stanford University Stanford, CA, USA

9 PERSONNEL

9.1 Faculty

Hunziker Ernst B., M.D., Prof.	Director.....11.89 -	
	* * *	
Nolte Lutz-Peter, Ph.D., Prof.	Division Head .....05.93 -	
Trueb Beat, Ph.D., Prof.	Deputy Division Head .....04.95 -	
Chiquet Matthias, Ph.D., PD	Research Group Head (80%)...05.95 -	
Bächler Richard, Ph.D.	Research Group Head.....06.96 -	
Ferguson Stephen, Ph.D.	Research Group Head.....02.00 -	
Langlotz Frank, Ph.D	Research Group Head.....05.93 -	
Orr Tracy, Ph.D.	Research Group Head.....10.97 -	09.00
Sati Marwan, Ph.D.	Research Group Head.....07.96 -	03.00
Studer Daniel, Ph.D.	Research Group Head (20%)...03.92 -	
Wong Marcy, Ph.D., PD	Research Group Head (80%)...02.92 -	

9.2 Research Associates

Amstutz Christoph, M.D.	Ph.D.-Student.....01.99 -

Baer Shiloe, dipl. Ing.	Exchange Student	07.00 -	12.00
Barbieri Carrera Roberto, dipl. Ing.	Assistant	08.00 -	
Bear Shiloe, dip. Ing.	Exchange Student	07.00 -	12.00
Belluoccio Daniele, dipl. Biol.	Ph.D.-Student	05.95 -	05.00
Berey Szilárd, M.D.	Assistant	10.99 -	09.00
Beutler Thomas, dipl. Ing. HTL	Assistant	05.99 -	
Bourquin Yvan, dipl. Ing. HTL	Assistant	11.95 -	05.00
Brentnall Mark, dipl. Ing.	Exchange Student	07.99 -	07.00
Bugnon Véronique, dipl. Phil. II	Ph.D.-Student	03.99 -	03.00
de Siebenthal Julien, dipl. Phys.	Ph.D.-Student	07.00 -	
Driesang Iris, Dr. med.vet.	Assistant	06.96 -	
Flück Martin, Dr. Phil Nat.	Postdoc	04.99 -	12.00
Giannoni Paolo, Dr. Phil.	Postdoc	04.99 -	10.00
Griessen Roland, dipl. Ing. HTL	Assistant	11.96 -	
Goodwin Kelly, M.S.	Assistant	06.00 -	
Hoigné Dominik, cand. med.	M.D.-Student	10.99 -	12.99
Hu Qingmao, Dr. Ing.	Postdoc	10.97 -	03.00
Hunenbart Stefan, dipl. Ing.	Ph.D.-Student	09.99 -	
Imhof Martin, dipl. Phil. II	Ph.D.-Student	01.96 -	02.00
Kouadri Mostéfaoui S., dipl. Inf.	Ph.D. Student	07.00 -	
Kowal Jens, dipl. Ing.	Ph.D.-Student	10.97 -	
Kubiak Monika, dipl. Inf.	Ph.D.-Student	11.99 -	
Kunz Manuela, dipl. Inf.	Ph.D.-Student	06.98 -	
Langlotz Ulrich, dipl. Ing..	Ph.D.-Student	07.96 -	02.00
Li Bo, dipl. Phil. II	Ph.D.-Student	06.99 -	
Long Gong, Ph.D.	Postdoc	11.97 -	04.00
Montanari Javier H., Biom. Ing.	Ph.D.-Student	10.00 -	
Nemec Bernhard, Inf.	Student	03.00 -	
Oetliker Martina, cand. med. vet.	Ph.D.-Student	11.95 -	01.00
Poggi Silvia, lic.Sc.Nat.	Ph.D.-Student	10.00 -	12.00
Polikeit Anne, dipl. Ing.	Ph.D.-Student	03.98 -	
Rojas González Maricio, dipl. Ing.	Assistant	03.99 -	01.00
Schild Christof, dipl. Phil. II	Ph.D.-Student	06.99 -	
Siegrist Mark, dipl. Phil. Nat.	Assistant	07.97 -	
Stern Andreas, cand. Ing.	Guest Student	09.00 -	
Sugimoto Masayuki, M.D.	Postdoc	03.00 -	
Tannast Moritz, cand. med.	Ph.D.-Student	08.99 -	12.99
Tarte Ségolène, dipl. Ing.	Ph.D.-Student	09.99 -	
Trächslin Jonas, dipl. Phil. II	Ph.D.-Student	06.96 -	04.00
Van Schrojenstein Esther, cand.Ing.	Exchange Student	09.00 -	
Wang Gongli, dipl. Ing.	Ph.D.-Student	04.00 -	
Wälti Heinz, dipl. Inf.	Assistant	12.96 -	
Wiedemann Markus, dipl. Phil. II	Ph.D. Student	03.97 -	
Yin Yunsheng, Prof. Dr. med.	Guest Professor	08.99 -	08.00
Zheng Guoyan, Dr. Ing.	Postdoc	03.99 -	

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 (70%)	12.90 -	
Haller Manuela	Secretary (50%)	11.00 -	
Hutzli Walter	Aid Lab. Technician	11.89 -	
Kapfinger Eva	Res. Technologist (75%)	11.89 -	
Lüthi Marc	Apprentice in Fine Mechanics	08.99 -	08.00
Mathys Isabelle	Res. Technologist	08.00 -	
Mühlheim Erland	Mechanicien (60%)	01.92 -	
Neseli Güler	Res. Technologist	08.96 -	
Neuenschwander Annelies	Secretary (35%)	04.95 -	
Nüssli Simon	Res. Technologist	12.00 -	
Perumbuli Prasanna	Res. Technologist	08.96 -	02.00
Reist David	Res. Technologist	07.97 -	
Rohrer Urs	Head Mech. Workshop	07.91 -	
Schenker Thomas	Chief Technician	04.95 -	
Täschler Sara	Res. Technologist	08.00 -	
Tunc-Civelek Vildan	Res. Technologist (80%)	09.99 -	

9.4 Scientific Consultant

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

9.5 Guest Scientists

Dr. Thomas M. Quinn, Biomedical Engineering Laboratory, Department of Applied Physics, Swiss Federal Institute of Technology, Lausanne, Switzerland

Dr. Pierre Mainil-Varlet, Institute of Pathology, University of Bern, Bern, Switzerland

10 MISCELLANEOUS

10.1 Conferences Organized

5th International CAOS Symposium, Davos, Switzerland February 17-19, 2000

10th Swiss Cytomeet, Bern, March 22, 2000 (Chiquet M.: Co-Chairman)

3rd ICRS Symposium, Gothenburg, Sweden, April 27-29, 2000 (Hunziker E.B.: Co-Organizer)

CAOS/USA 2000 – Fourth Annual North American Program on Computer Assisted Orthopaedic Surgery (Nolte L.-P.: Co-Chairman), Pittsburgh, PN, USA, June 15-17, 2000

Live Surgery Symposium in Minimally Invasive Spine Surgery (Nolte L.-P.: Co-Chairman), Bern, Switzerland, Dezember 8-9, 2000

11 MEMBERS OF THE SCIENTIFIC ADVISORY BOARD (KURATORIUM)

- Prof. Dr. R. Häusler, (President), Director HNO-Klinik, Inselspital, Bern
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- Prof. Dr. H. Reuter, Dept. of Pharmacology, University of Bern, Bern
- Prof. Dr. E.R. Weibel (Secretary and Vice President), M.E. Müller Foundation, Bern
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