The Many Faces of Osteoarthritis

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Preface

The conference "The Many Faces of Osteoarthritis", convened at Lake Tahoe, June 23–27, 2001, was held in my honor to acknowledge and to pay tribute to my contributions in the field and also to celebrate my birthday, which happened to fall in that time frame. The meeting was one of the happiest events in my professional life, and I am much indebted to the organizers and to all my colleagues and friends who contributed to its success. On a personal note, I was particularly pleased to meet again so many former trainees. The resulting book reflects the scientific presentations and discussions between a select group of invited investigators, all experts in this field. As will be evident, the meeting is a logical continuation of scientific workshops in the field, two of which were originally sponsored by Hoechst Pharmaceutical Company of Germany. This scientific meeting is now sponsored by two pharmaceutical companies, again Hoechst (now Aventis), and also Glaxo-SmithKline. The latter is a scientific partner for members of the Department of Biochemistry, which I have chaired since 1980 at Rush Medical College in Chicago.

In 1987, the Department of Biochemistry was awarded one of only three national grants in osteoarthritis as a Specialized Center of Research (SCOR) from the National Institute of Arthritis, Musculoskeletal and Skin Diseases of the National Institutes of Health. These Specialized Centers of Research support a cluster of individual, but interrelated, basic and clinical research projects. The SCOR at Rush entitled "Osteoarthritis: A Continuum (From Cartilage Metabolism to Early Detection and Treatment)" involved investigators from basic science and clinical departments, and I served as Program Director. In 1992, and again in 1997, Special Study Sections evaluated all SCOR grants in osteoarthritis and the program at Rush was approved each time for an additional five years, and is currently the only SCOR on osteoarthritis in the country.

To guarantee the best possible progress and research direction, the SCOR grant investigators are assessed and evaluated on an annual basis by a Scientific Advisory Committee composed of eight internationally renowned scientists (nicknamed "Scoriers") which not only came up with the idea of this meeting, but also put it together. In addition, they also evaluated the manuscripts for this book (not an easy task) and wrote a brief overview to reflect the general discussions during the meeting. The strength, however, lies in the fact that the meeting was set up in the familiar Gordon Research Conference style.

The conference "The Many Faces of Osteoarthritis" reflects the current state of knowledge and will help elucidate the etiopathology of osteoarthritis (OA), hope-

fully leading to early detection of the disease and novel treatment modalities. OA is the most common joint pathology and primarily affects the older population. Extended research, however, has shown substantial dissimilarities between OA and the aging processes. OA can be envisioned as a group of overlapping distinct diseases that may have different etiologies but show similar biologic, morphologic and clinical outcomes. The disease is characterized by unique pathological changes in some synovial joints, predominantly affecting the articular cartilage, but also the entire joint, including the synovial tissue and subchondral bone. It is only in later stages that it can be diagnosed indirectly by loss of articular cartilage as revealed in radiography, a method used to diagnose the disease in clinical practice and in epidemiological studies. Not all individuals with radiographic evidence of OA have clinical symptoms. However, the probability of symptoms increases with the severity of radiographic changes. It is hypothesized that both mechanical and biological events destabilize the normal coupling of synthesis and degradation of the matrix of the articular cartilage by its chondrocytes, with modulation also in the subchondral bone. The disease may be initiated by multiple factors including genetic, developmental, metabolic and especially traumatic ones that may have occurred much earlier in life.

In the early 1980s, when research in articular cartilage biochemistry was still in its infancy, I was asked, together with Dr. Vincent Hascall, to organize in September 1985 a Workshop Conference (sponsored by Hoechst-Werk Albert, Wiesbaden, Germany) entitled "Articular Cartilage Biochemistry." At this meeting, the results of ongoing research on the structure and metabolism, both of normal and osteoarthritic articular cartilage, and related arthritic disorders were presented. Through a detailed analysis of the matrix macromolecules, the biosynthesis and the normal and pathological metabolism of cartilage components by chondrocytes were reported. The questions asked were, for example: How do cells communicate in order to synchronize macromolecular synthesis and secretion with degradation in the different micro-regions of the extracellular matrix? What are the signals and the receptors in the intercellular transduction mechanisms? What are the critical interactions among intercellular macromolecules that infer tissue specificity upon extracellular processes? The participants of this meeting advanced the understanding of the mechanisms underlying cartilage degeneration in arthritic diseases. In 1986, the presentations and lively discussions of the workshop were published by Raven Press (New York) with Drs. Klaus Kuettner, Rudolf Schleyerbach and Vincent Hascall as co-editors.

The rapid growth of knowledge and methodologies in cartilage research resulted in an increase in diverse methods used to study cartilage biology and biochemistry. Therefore, in order to achieve a standardization of methods, I was asked by Dr. Alice Maroudas to conjointly organize an international seminar entitled "The Bat-Sheva Seminar on Methods Used in Research on Cartilaginous Tissues", which was held at the Nof Ginossar Kibbutz, Israel, in March 1989. This seminar was sponsored by the Bat-Sheva de Rothschild Foundation for the Advancement for Sci-

ence in Israel. The proceedings of the meeting were published in a book by Academic Press (London and San Diego) in 1990 under the title "Methods in Cartilage Research" with Drs. Alice Maroudas and Klaus Kuettner as co-editors. The time was right for assembling the various methodologies into a single volume that reflected the sophistication of each aspect in this field and also provided a comprehensive source for investigators from other disciplines. The book describes for example: Qualitative and quantitation techniques for the tissue specimens, extraction methods, chondrocyte and explant cultures, and the tissue composition and organization. Furthermore, physical and mechanical properties as well as their relevance to physiological processes were delineated. Different approaches were described, compared, discussed and assessed. The major aim was to show investigators the various choices and possibilities in research and to discuss the appropriateness of study designs without ignoring their inherent shortcomings, limitations and difficulties.

Three years later another workshop conference (again sponsored by Hoechst-Werk Albert) entitled "Articular Cartilage and Osteoarthritis" highlighted current basic scientific and clinical research efforts to further advance the understanding of articular cartilage physiology and pathophysiology and also the etiopathology of osteoarthritis. Among the questions asked were: How does the microenvironment, containing collagens and proteoglycans, serve as a prerequisite for the maintenance of cell differentiation? What regulates the biosynthesis of proteoglycans and glycosaminoglycans? Does secretion and diffusion of recently identified "morphogens" play a role in remodeling and/or repair? What are the influences of mechanical stresses upon the biosynthesis of extracellular macromolecules? What is the role of non-collagenous macromolecules upon extracellular matrix specificity? How does a degradation enzyme contact a collagen fibril (in the case of collagenolysis) when the latter is normally encased in a matrix of other macromolecules? Clinical research findings on potential diagnostic markers of early OA and investigational, potential therapeutic interventions were presented. They provided invaluable sources of information, illuminating observations and promising new approaches for all orthopedic surgeons, rheumatologists and basic research scientists investigating joint diseases. This workshop symposium was afterwards published, again by Ravens Press (New York) in 1992, with Drs. Klaus Kuettner, Rudolf Schleyerbach, Jacques Peyron and Vincent Hascall as co-editors.

In April 1994, Dr. Victor Goldberg and I were asked to organize a workshop entitled "New Horizons in Osteoarthritis." Our task was to bring together an international, interdisciplinary group of leading scientists and clinicians to define the present knowledge and delineate future research directions on the etiopathogenesis of OA, as well as to develop new strategies in research for the understanding of the etiopathology of OA. This workshop was sponsored by the American Academy of Orthopedic Surgeons, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, the National Arthritis Foundation, and the Orthopedic Research and Education Foundation. During this workshop,

groups of investigators developed concepts and specific plans on various topics, which were presented, modified and endorsed by all participants. A book entitled "Osteoarthritic Disorders" was published by the American Academy of Orthopaedic Surgeons (Rosemont) in 1995, edited by Drs. Klaus Kuettner and Victor Goldberg. It contains invited summary manuscripts describing the current state of research in specific areas. Each summary is followed by a recapitulation of the extensive discussions. This covers the definition (including epidemiology) and classification of OA, cartilage changes in aging and changes in the osteoarthritic joint as an organ, role of mediators and inflammation in the degradative mechanisms, repair of cartilage, and the monitoring of preclinical and clinical progression and treatment of OA. At the time of the workshop the group identified gaps in factual knowledge and stated that more information was needed before questions addressed during the meeting could be answered. The book also contains selected reports, descriptions of the brainstorming discussions of future investigations, an overview, and consensus opinions and recommendations for new research directions in OA.

The group of investigators in the field of cartilage and osteoarthritis research is relatively small. Thus, most of the "Scoriers" were present at the four meeting/workshops/symposiums, mentioned above. Thus, the meeting in Lake Tahoe was a logical consequence of the numerous interactions that we had at these scientific "state-of-the-art" meetings. The remarkable growth of the field and the rapid increase in diversity of advancements, including the application of novel molecular biological approaches and new imaging techniques, was certainly reflected at this meeting at Lake Tahoe. The progress made since the first meeting about 16 years ago is enormous. Investigators now focus on receptors, transduction mechanisms, and specific cytokines that may regulate both the degradation and the repair/regeneration of the tissue. Still, significant research will be necessary in defining and clarifying questions about the basic etiopathology of OA. Clinical and epidemiological investigators will have to continue to interact with the basic scientists to identify the pathogenic characteristics of OA, in order to develop and assess new therapeutic interventions.

Special recognition is due to Dr. Hari Reddi, who was the local organizer of the meeting, and together with his administrative and well experienced staff (most of all Ms. Lana Rich), were responsible for inducing and maintaining an interaction between the scientists. Their time, energy and effort is highly appreciated. Special thanks go to Dr. Vincent Hascall, who was "volunteered" by his "Co-Scoriers" to be the "mastermind" of the scientific program of this meeting at Granlibakken/Lake Tahoe. His commitment and pursuit guaranteed its success. In this task he was invaluably supported by his secretary Ms. Kathy Vukovich. The meeting was dedicated, by Vince, to the friendship among scientists.

Spring 2002 Klaus E. Kuettner

The life of Klaus E. Kuettner

Introduction

Klaus E. Kuettner, Chairman of the Department of Biochemistry, Rush Medical School in Chicago, is one of a handful of especially gifted individuals in osteoarthritis research, who through the last two decades has raised the perception of this field in the eyes of important power structures, such as NIH, the Arthritis Foundation, multiple research journals, Gordon Conferences, ORS forums, Food and Drug Administration Agency, and European structures, including the World Health Organization. The latter has recognized these efforts by designating him to be their distinguished research center leader in osteoarthritis. On his 68th birthday, Klaus was honored at this symposium, and pending his resignation from his chairmanship, a glimpse of his life should interest the readership, including the many scientists whose careers he has influenced.

Childhood

Klaus was born in 1933 in Bunzlau, Silesia, an eastern province in Prussia, Germany. At the time, Bunzlau was a town of about 25,000 in which his family had lived for several generations. His great-grandfather was a potter; his grandfather started a company to use such building materials for making large commercial pipes; and his father expanded the company. Indeed, his father's factories manufactured stoneware fixtures for most of the German railways in the 1920–30s. From the earliest age on, Klaus felt an especially close relationship to his father, who encouraged him in scholastic endeavors and outdoor activities, thereby, inspiring him to pursue lofty goals. During World War II, the family, deeply opposed to the Third Reich, was able to survive. Toward the end of the war, the family escaped to Saxonia, central Germany and lived under Russian occupancy until 1949.

Training for science

After Klaus attended high school in Leipzig, the entire family escaped again to Minden, West Germany. There Klaus trained at The Pharmacy School and received his B.S.-equivalent in pharmacy in 1955. His interests widened from the initial goal of a career in the business of running a pharmacy, leading to his subsequent studies first at the University of Freiburg, where he gained an MS in pharmaceutical science in 1958. He then became a Ciba Fellow (Basel, Switzerland) and studied at the University of Berne (Switzerland), where he was awarded a Ph.D. degree in 1961. This predoctoral period set the stage for his future interests.

His Ph.D. thesis studied the release of histamine and other biological amines from mast cell granules, and their interactions with macroanions. Studies with ion-exchangers bearing sulfate and carboxylic groups made a good foundation for later studies of proteoglycans. His closeness to the Ciba group gave him valuable friendships with scientists and administrators of the Ciba company. It also gave him a glimpse of the pharmaceutical slant toward basic research, which helped later to initiate research and academic training opportunities with industrial partners.

In 1962, Klaus received a post-doctoral fellowship at Argonne National Laboratory in Chicago to study plutonium binding in cartilage. There, Dr. Arthur Lindenbaum was his assigned mentor. They were fascinated with the subject of metals binding to macroanions, such as glycosaminoglycans (GAGs), and at Argonne, they showed that plutonium bound selectively at the calcifying front in growth plate cartilage.

Starting on the academic ladder

Although Klaus had intended to return after 2 years to Ciba at Basel for further industrial biochemistry training, a turning point in his life occurred. Prof. Richard Winzler, Ph.D., offered him an instructorship in the Department of Biochemistry at the University of Illinois in Chicago with a secondary affiliation in the Department of Orthopaedics at Rush Presbyterian St. Luke's Medical Center in 1964 (at the time of the portrait in Fig. 1).

Lysozome and anti-invasion factor (AIF) research

Klaus' original research investigated the biochemical alterations in the matrix of the epiphyseal growth plate that occur during the differentiation, hypertrophy and calcification of cartilage, and its ultimate replacement by bone. He focused mainly on a study of the molecular arrangement of proteoglycans and lysozyme, and their role in regulating calcification.

Figure 1
Intense work ethic may be reflected in the pallid features and worried expression consistent with this stage of his career.

Twenty-one papers evolved, with many well-known scientists in the field collaborating in this work, notably Reuben Eisenstein and Nino Sorgente, and other long-term friends. Notably, collaboration with Julio C. Pita showed that mammalian lysozyme, but not egg white lysozyme, could reduce the size of proteoglycan aggregates in dilute solution by altering its conformation and interacting with link protein. Although naturally occurring overexpression and underexpression of this protein have failed to indicate gross interference with mineralization mechanisms, it remains likely that lysozyme plays an adjunctive role to reduce aggregate size to improve conditions for mineralization.

In the meantime, starting about 1975 and extending over the next 10 years, Klaus and his research colleagues opened the field of regulation of capillary invasion of growth cartilage. His dramatic presentation of this phenomenon was shown when growth cartilage was grafted to chick allantoic membrane with an active capillary bed. Chick capillaries failed to invade various intact cartilages, but did invade cartilage that had been extracted with 1.0 M NaCl or guanidine HCl. This provided an explanation for why bone tumors during their invasion circumvented growth plate and epiphyseal cartilages. This phenomenon was expanded into many papers showing the presence of anti-invasion factor(s) (AIF) in NaCl extracts of bone, aorta, articular cartilage, urinary bladder, and enamel matrix.

Indeed, important scientists across the USA (including the host of the current symposium, Hari Reddi) became involved collaboratively in multiple studies of AIF. By 1980, it was clear that the AIF consisted minimally of an endothelial cell antiproliferative agent, an anti-elastase, and an anti-MMP factor, all of low molecular

weight. F. Suzuki's chondromodulin and Moses Folkman's TIMP-like factor, both of which inhibit angiogenesis in growth plates, now help explain how avascularity of hyaline cartilage is mediated! Although his work flourished along with good NIH RO1 support, life is what happens to one while making other plans.

A new career

By 1980, when the portrait in Figure 2 was taken, Klaus had reached the next turning point. A dilemma arose about whether to continue as the leader of a small team of workers solely focused on individual research projects as described above, or to take the Dean's unexpected offer to become Chairman of the Department of Biochemistry! After the first wave of euphoria, Klaus confronted local realities. The Department had only an extramural research budget of $ 33,000, five elderly professors, and only one person able to teach biochemistry courses. The challenge was irresistible, and Klaus sank his teeth into the severe problems of departmental remodeling and building.

His past studies on polyanions impressed on him the importance of proteoglycans for normal function of articular cartilage and their likely role in the pathophysiology of osteoarthritis. This area, then, became the central focus for research in his enlarging department. Because of a wide acquaintanceship with academicians in this arena, over the next 20 years, Klaus was unbelievably successful in attracting diverse talent to the department while continuing his own research, as is apparent to the attendees at this conference.

To elaborate on this a little further, in the 1970s, Klaus collaborated with Vince Hascall, then at the University of Michigan, and later at the National Institute of Dental Research, and later with Helen Muir and Tim Hardingham, at the Kennedy Institute, and with Dick Heinegard at the University of Lund. This established a dynamic network of friends and collaborators with cartilage research interests. This network continued to expand in the 1980s as Klaus took proactive roles in promoting the Orthopaedic Research Society, and in organizing Gordon Conferences on bones and teeth, and later on proteoglycans. This network proved most advantageous in his efforts to recruit an excellent and productive faculty.

Faculty recruitment

In this recruitment, Klaus was careful not to duplicate subdisciplines, but to find outstanding independent investigators whose productivity and goals cover the most important bases. Eugene Thonar came first and was pivotal for proteoglycan structure and markers. Next was Margaret Aydelotte for new cell culture methods and cellular heterogeneity; followed by Linda Sandell, for molecular biology of chon-

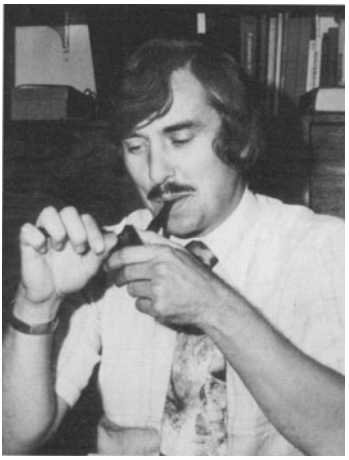

Figure 2
1980 – Now a debonair and confident academician.

drocytic matrix synthesis; Jim Kimura, for chondrocyte cell biology, Warren and Cheryl Knudson for hyaluronan cell biology; Tom Schmid for collagen chemistry; Gene Homandberg for fibronectin metabolism; Tibor Glant for autoimmune features of proteoglycans, Juergen Mollenhauer and H. Hauselmann in the 1990s for study of pericellular matrix metabolism in alginate beads; Koichi Masuda, who used these beads for tissue engineering of cartilage implants; Gabriella Cs-Szabo to study small proteoglycans, Susan Chubinskaya to explore the function of key anabolic mediators on articular cartilage, and Ada Cole to study profiles of MMPs and TIMP in knee and ankle cartilages. Jim Kimura and Linda Sandell very successfully made further career moves. Margaret Aydelotte retired in the late 1990s. A large number of scientists in other Departments (such as Richard Loeser, Joel Block, Carol Muehleman, and Jim H. Williams) were incorporated into the Department of Biochemistry programs to further their studies.

Klaus' philosophy has been to form a protective organization for this team of researchers, to offer a stable environment financially, and to make available educational and other types of opportunities.

Cartilage cells and matrix: the research program in osteoarthritis

Although the contributions from the team of independent researchers provide the bulk of the departmental output, Klaus retained certain areas of personal participation.

In the early 1980s, a novel method was developed in his laboratory for culturing adult articular chondrocytes for extended periods of time while maintaining phenotypic stability in agarose and later in alginate gels. These chondrocytes elaborated an extracellular matrix very similar or identical to that synthesized in vivo. The cells could be stimulated by modulators to degrade this new matrix, in a manner resembling the accelerated tissue breakdown characteristic of degenerative joint disorders, such as in osteoarthritis. This approach was named "chondrocytic chondrolysis." It was used to investigate the biochemical mechanisms of cartilage destruction and to test disease-modifying agents that may have therapeutic value for patients suffering from the arthritides. Two publications by M. Aydelotte and K. Kuettner (*Connec Tiss Res* 18: 205–222 and 223–234 (1988)), report biochemical and morphological studies defining differences in chondrocytes isolated primarily from the superficial layer and from the mid- to deep zones of bovine articular cartilage after the cells were isolated and resuspended in an agarose matrix. These studies, carried out with Barbara Schumacher, show the ability of mid- to deep zone chondrocytes to reassemble an extracellular matrix with retention of proteoglycans, whereas those from the superficial layer did not organize a similar matrix. They then exploited and refined an earlier observation by Bill Jourdian and his colleagues at the University of Michigan that chondrocytes can be maintained with phenotype stability in alginate cultures. The advantage of this matrix was that it could be dissolved in low salt, calcium-binding solvents without disrupting the interactions between the matrix macromolecules. This system was described in three papers (*Connect Tiss Res* 28: 143–159 (1992); *Matrix* 12: 116–129; *J Cell Science* 107: 17–27 (1994)).

Work in progress now utilizes the alginate system to define the metabolic differences between proteoglycans that are retained in close association with the cells (territorial) after dissolution of the alginate and proteoglycans, and those that are further removed (interterritorial). These studies have obvious consequences for expanded cell biological investigations, with special reference to characterizing separate cell populations.

A unique facility for access to human cartilage

Over 10 years ago, Klaus began collaboration with Steven Gitelis, M.D., Department of Orthopedic Surgery, who was then and currently remains the Medical Director of the Regional Organ Bank of Illinois. To the author's knowledge, this is the only such bank worldwide that can provide a quantity of weight-bearing articular cartilage of high quality for a thorough pursuit of biochemical properties so badly needed. To date, more than 2,000 human cartilages have been studied, and nearly every researcher in the Department now investigates human articular cartilages, an important attribute of Klaus' foresight.

Figure 3
2001 – Enjoying the sun and fun at Granlibakken.

NIH approval for the Rush OA research program

In the early 1980s, the Department of Biochemistry was awarded one of only three national grants in osteoarthritis to support a Specialized Center of Research (SCOR) from the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH). The coordinated effort of a SCOR grant addresses a specific health area and provides a multidisciplinary approach to the problem investigated. Originally, there were nine centers established: three in rheumatoid arthritis, three in osteoarthritis, and three in osteoporosis. The one at Rush entitled "Osteoarthritis: A Continuum (from Cartilage Metabolism to Early Detection and Treatment)" involved 15 investigators from five departments (Biochemistry, Orthopedic Surgery, Medicine [Rheumatology], Pathology, and Anatomy) with Klaus as program director (Fig. 3).

All SCOR grants in osteoarthritis were peer reviewed by a Special Study Section in 1992 and again in 1997. The renewal program at Rush received both times a favorable evaluation and was approved to continue its research objectives. Currently, this is the only ongoing SCOR for osteoarthritis.

The Research Educational Program

Klaus was convinced that to be completely successful, his department critically needed a Ph.D. doctoral training program. The timing (early 1980s) for this was

unfortunate due to an overabundance of Ph.D. programs and training programs in the Chicago area at virtually every other medical school. Therefore, a novel and exciting program was necessary, and this was achieved through the focus on the single disease, osteoarthritis. The only other biochemistry program like it was that of Dennis Lowther at Monash University in Melbourne, Australia. Indeed, then, the Illinois Board of Higher Education approved the application for a Ph.D. degree teaching program at Rush Medical Center in 1984. This event led to an expansion of all phases of the Department's research and teaching programs.

In April 1991, Klaus' Department of Biochemistry was designated the first World Health Organization (WHO) Collaborating Center in the Field of Osteoarthritis (Rheumatology). One of the major "assignments" of this designation has been to train young, new, as well as experienced investigators in the area of cartilage/osteoarthritis research with the aim to transfer the knowledge to other laboratories and to the practice of medicine in the field of orthopaedic surgery/rheumatology. During the past 11 years, more than 60 young investigators (postdoctoral fellows) from around the globe have worked within the research laboratories of this department and collaborating departments. Over half of them held an M.D. (mostly in orthopedics) and after leaving, were able to incorporate their knowledge of basic biochemistry into the practice of academic-investigative medicine. At any one time, there are between five to ten postdoctoral fellows in the department.

At the time of this writing, there were 24 graduate students (Ph.D. candidates) in the department, and most of them chose research projects in cartilage biochemistry for their Ph.D. thesis work. In 1996, and again in 2001, the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) awarded the department a training grant entitled "Training in Cartilage Research," which supports the education of three graduate students and two postdoctoral fellows.

Industrial academic interactions

Klaus instituted a program for industry-academia interactions by providing a select group of graduate students to work on their thesis projects, with apprenticeships in large international pharmaceutical corporations. In this setting, the students learn modern research techniques and are educated in the application of basic knowledge to goal-directed research. This allows an intellectually productive interaction between academic teachers, investigators, and students with industrial research activities.

In 1987, Ciba-Geigy created an endowed chair for the Department of Biochemistry directed toward basic research in osteoarthritis and cartilage metabolism. Klaus was able to obtain two additional endowed chairs. All of these have the proviso that the income is applied to investigations and training in the field of Orthopaedic Sciences, especially osteoarthritis research.

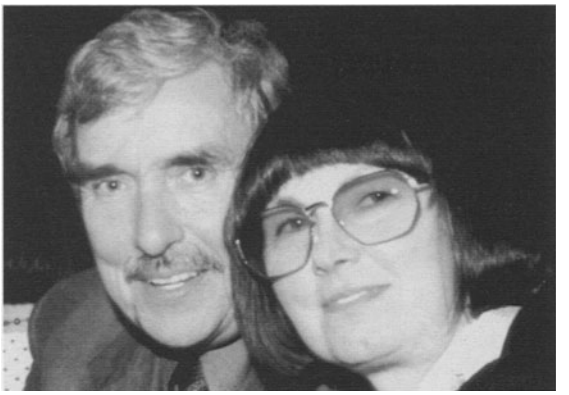

Figure 4
The most important factor in the life of Klaus Kuettner has been the 11 years of his marriage to Erzsi, whom he met on a visit to the Center of Rheuma Pathology (WHO Center) in Mainz, Germany. She was the personal assistant to Professor Hans Georg Fassbender. The latter is a lifelong friend of Klaus, and a "father" of research in rheumatoid arthritis pathology.

More recently, Klaus's department entered into a unique relationship with the pharmaceutical company, Glaxo Wellcome of North Carolina. A contract was signed entitled "Osteoarthritic Changes in Human Cartilage: Research for the Development of New Medicines." The basic agreement focuses on methodology transfer combined with an exchange and specific interaction between research scientists at both locations, as well as to provide a program for academic research fellows to experience industrial research methods and, for some, to explore opportunities for careers in this arena. Significant funding and resultant career learning opportunities ensued. After the merger with Smith-Kline the program is continuing under new management.

At the conference, Klaus clearly enunciated his intent to continue to provide a leadership role in the SCOR project and to participate in the ebb and flow of the exciting research developments in the osteoarthritis and articular cartilage biology arena. Thus, we can look forward to new adventures and achievements in addition to those highlighted in the tables.

Thus, it is very fitting that these proceedings from a Conference honoring Klaus's contributions, celebrate not only his past achievements, but also anticipate those that remain to be accomplished. Some of these adventures and achievements are listed in Tables 1 and 2, and each listing could be greatly expanded upon. Leading the list in importance is his marriage to Erzsi (Fig. 4).

David Howell

Table 1 - Some of Klaus E. Kuettner's principal honors

1978	Chairman, 25th Gordon Research Conference on the Chemistry, Physiology and Structure of Bones and Teeth
1978	Kappa Delta Award for outstanding orthopedic research (AAOS and ORS)
1984	Chairman 1st Gordon Research Conference on Proteoglycans
1987	Recipient, International Carol Nachman Prize for advancement of clinical, therapeutic, and experimental research in rheumatology
1988	Recipient Pauwels Memorial Medal – German Society for Orthopedics and Traumatology for outstanding research in orthopedic sciences
2000	Co-recipient of Bristol-Myers Squibb/Zimmer Award for distinguished achievement in orthopedic research
1987–2002	Program director, NIH, Specialized Centers of Research (SCOR), "Osteoarthritis: A continuum (from Cartilage Metabolism to Early Detection and Treatment)". National Institute of Arthritis, Musculoskeletal, and Skin Diseases (funded for three consecutive 5-year periods).
1970	Personal NIH grant in Biochemistry of Bone and Connective Tissue (funded consecutively for 22 years)
2001	Honorary Degree in Medicine, University of Berne, Switzerland

Table 2 - Forums

1970s-90s	17 Midwest Connective Workshops host/co-chairman
1970s-90s	Participant 25 years Gordon Conference on Bones and Teeth, a session Chairman, selected each of 15 years
1989	Organizer/Chairman, International Conference on Articular Cartilage Biochemistry, Wiesbaden, Germany
1989	Co-Organizer – Bat Sheva Seminar-Methods Used in Research on Cartilaginous Tissues, Ginosar, Israel
1991	Organizer/Chairman, International Workshop on Articular Cartilage and Osteoarthritis, Wiesbaden, Germany
1994	Organizer/ Cochairman – NIH/American Academy of Orthopedic Surgeons/ National Arthritis Foundation Cosponsored Workshop "New Horizons in Osteoarthritis" and "WHO Satellite Meeting on Standardization of Methods for Assessment of Articular Cartilage Changes in Osteoarthritis of the Knee and Hip", Monterey, CA
1999	Organizing Committee International Symposium on Many Faces of Osteoarthritis, Granlibakken, Lake Tahoe

Acknowledgements

No conference such as "The Many Faces of Osteoarthritis" can be truly successful without the generous support of companies that have a genuine interest in the research area in question. We are most grateful to our corporate contributors listed below, both for their support and their participation. They have made it possible to invite outstanding investigators as speakers and to support talented younger investigators to participate. Special thanks go to Aventis Pharma Deutschland GMBH and Glaxo-Wellcome-SmithKline for additionally underwriting most of the expenses for publishing these Proceedings of the conference through the efforts of Ruth Raiss (Aventis Pharma Deutschland GMBH) and Steve Stimpson (Glaxo-Wellcome-SmithKline).

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Roche Bioscience
Seikagaku Corporation
Stryker Biotech

When conferences run so smoothly as ours did, it is the result of the tireless efforts of the local organizers. In this case all the credit and many thanks go to Hari Reddi and his conference consultant, Lana Rich. Their work made the conference a lot of fun as can be seen in the photo montages of many of the participants.

With the exception of the session organized by Hari Reddi, each session of the conference was organized by a member of the organizing committee, the Scoriers. This team comprises the External Advisory Board for the SCOR program at Rush Medical College at Rush-Presbyterian-St. Luke's Medical Center in Chicago. We thank them for putting together a state-of-the-art program that features the very latest research efforts in the arthritic diseases.

Finally, it is no exaggeration to say that it would have been impossible for us to organize the conference program and to handle all the endless details, such as transcribing and editing the discussions at the conference and corresponding with the contributors and publisher after the conference, without the help of our talented assistants, Kathy Vukovich (for VH) and Verhonda Hearon Eggleston (for KK). We thank them wholeheartedly for their efforts on our behalf.

Vincent Hascall
Klaus Kuettner