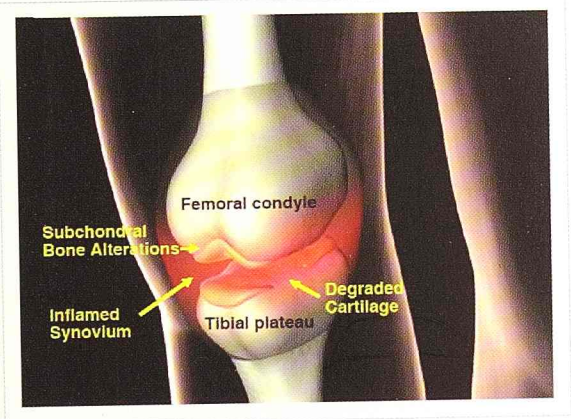
جائزة الملك فيصل العالمية
King Faisal International Prize



THE KING FAISAL MEMORIAL ARTICLES IN MEDICINE AND SCIENCE IX


بسم الله الرحمن الرحيم

King Abdullah Ibn Abd Al-Aziz

Custodian of the Two Holy Mosques
Supreme Chairman of King Faisal
Foundation

HRH Prince Sultan Ibn Abd Al-Aziz

Crown Prince, Deputy Premier
Minister of Defense and Aviation and
Inspector General

HRH Prince Nayef Ibn Abd Al-Aziz

Second Deputy Premier, Interior Minister

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INTRODUCTION

The King Faisal Foundation continues the traditions of Arabic and Islamic philanthropy, as they were revitalized in modern times by King Faisal. The life and work of the late King Faisal ibn Abd Al-Aziz, son of Saudi Arabia's founder and the Kingdom's third monarch, were commemorated by his eight sons through the establishment of the Foundation in 1976, the year following his death. Of the many philanthropic activities of the Foundation, the inception of King Faisal International Prizes for Medicine in 1981 and for Science in 1982 will be of particular interest to the reader of this book. These prizes were modeled on prizes for Service to Islam, Islamic Studies and Arabic Literature which were established in 1977. At present, the Prize in each of the five categories consists of a certificate summarizing the laureate's work that is hand-written in Diwani calligraphy; a commemorative 24-carat, 200 gram gold medal, uniquely cast for each Prize and bearing the likeness of the late King Faisal; and a cash endowment of SR750,000 (US$200,000). Co-winners in any category share the monetary award. The Prizes are awarded during a ceremony in Riyadh, Saudi Arabia, under the auspices of the Custodian of the Two Holy Mosques, the King of Saudi Arabia.

Nominations for the Prizes are accepted from academic institutions, research centers, professional organizations and other learned circles worldwide, as well as from previous laureatues. After preselection by expert reviewers, the short-listed nominations are submitted for further, detailed evaluation by carefully selected international referees. Autonomous, international specialist selection committees are then convened at the headquarters of the King Faisal Foundation in Riyadh each year in January to make the final decisions. The selections are based solely on merit, earning the King Faisal International Prize the distinction of being among the most prestigious of international awards to physicians and scientists who have made exceptionally outstanding advances which benefit all of humanity.

(Excerpt from Introduction to 'Articles in Medicine and Science 1"
by H.R.H. Khaled Al Faisal, Chairman of the Prize Board and Director General of King Faisal Foundation)

WINNERS OF THE 2010 KING FAISAL INTERNATIONAL PRIZE FOR MEDICINE

The 2010 King Faisal International Prize for Medicine (Topic: Non-Arthroplasty Management of Degenerative Joint Disease) has been awarded to: **Professors Reinhold Ganz** (Germany), **Jean-Pierre Pelletier** (Canada) **and Johanne Martel-Pelletier** (Canada)

Prof. Ganz dedicated his career to the study and treatment of diseases of the hip joint. He has carried out seminal anatomical research that contributed substantially to the understanding of the blood supply to the acetabulum and femoral head. He devised a new surgical strategy for treatment of the prearthritic hip. These achievements have led to his recognition as a leading authority on conservative hip surgery.

Professors Jean Pelletier and Martel-Pelletier have contributed substantially to translational research in the field of osteroarthritis. Their original work has led to major discoveries in the pathophysiology of osteoarthritis, particularly joint catabolism and repair. These studies have paved the way to identification of therapeutic targets. In addition they developed an innovative technology for the quantitative assessment of changes and alteration in cartilage and other articular tissues.

From better knowledge of vascular anatomy to new concepts in hip joint preservation

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Introduction

It is only one and a half decades ago, when Crock [1] in his atlas of the vascular anatomy of the Skeleton stated, that: "Theoretically a method is required by which the human hip joint can be dislocated atraumatically in the early phases of disease so that the blood supply of the upper end of the femur can be preserved. This would open the way for the use of new methods of surface replacement of articular cartilage based on developments in tissue culture and molecular biology. Rather than relying on prosthetic replacement of the hip to treat significant intra-articular pathology , a treatment philosophy based on biologic and physiologic principles could be more routinely used" .

Crock's statement was based on the fact that surgical hip dislocation was rarely executed and when it was undertaken, the notorious warning of potential danger to the vascularity of the femoral head was always linked to it. There was little information as to how this danger could be avoided. Although most of today's knowledge about the vascular supply of the proximal femur was available but fragmented in several publications [2, 3, 4, 5, 6] , important information, e.g. about the safe distance of dislocation and about variations of the vascular supply were lacking. Most articles were anatomic descriptions and not primarily undertaken with an interest in surgical solutions. Since meaningful conclusions could not be drawn, we decided to perform a new series of vascular dissections with special interest to describe the topographic neighborhood, to look for peripheral anastomoses for eventual compensation of the supply of the femoral head and to demonstrate the dynamics of the femoral head perfusion .

Vascular anatomy of the femoral head

Earlier studies have already shown that the main source for the femoral head perfusion is the medial femoral circumflex artery (MFCA) [3] and that the lateral circumflex artery, the artery of the round ligament and as well the intraosseous metaphyseal vessels do not substantially contribute to the perfusion of the femoral epiphysis [7] . Our first study demonstrated that the deep branch of the MFCA is sufficient to perfuse the entire femoral head; this vessel has a special topographic relation with the external rotator muscles and a constant peripheral anastomosis with the inferior gluteal artery, capable to perfuse the femoral head when the deep branch itself is interrupted (Fig. 1). Highly interesting was also the observation that the intact muscle-tendon complex of the obturator externus protects the deep branch from being streched or disrupted during dislocation

of the femoral head [8]. More recent studies confirmed these observations and showed in addition that the anastomosis with the inferior gluteal artery can have a substantially larger caliper than the deep branch and that capsular vessels do not contribute to the femoral head- or acetabular perfusion, when the overlying musculature is detached [9,10]. Finally, a dynamic confirmation of the described perfusion pattern was possible using laser-Doppler flowmetry with the probe placed in the bone of the epiphysis [11].

Surgical dislocation of the femoral head

The findings of our vascular studies have led to a number of surgical implications[8], by far the most important was the development of the technique for safe surgical dislocation of the human hip [12]. The procedure is executed with the patient in a lateral decubitus. It consists of a trochanteric flip approach [13], Z-shaped capsulotomy and anterior dislocation of the femoral head, while all external rotators remain attached to the stable portion of the greater trochanter. For dislocation of the femoral head , the hip is flexed, externally rotated and the leg brought over the front of the operating table and placed in a sterile bag. By manipulating the leg, the technique allows 360° access to the acetabulum and nearly 360° access to the femoral head (Fig. 2). The approach has found worldwide acceptance for its easy execution, excellent view of the entire joint and for its few complications.

Concept of femoroacetabular impingement

Femoroacetabular impingement (FAI) is not a disease per se but rather a pathomechanical process by which a hip can fail. A variety of abnormalities of the bony acetabulum and/or femur combined with terminal and/or rigorous hip motion can lead to repetitive collisions that damage the soft tissue structures at the acetabular rim. Today evidence has emerged sugesting that FAI may instigate osteoarthritis (OA) of the hip rather than axial loading as believed before. Furthermore there is increasing evidence that adolescents and active young adults with groin pain might be successfully treated by adressing FAI.

More than a century ago hip damage due to a femoroacetabular conflict was anecdotally described [14,15]. The first Swiss experience and the roots of the current FAI concept date back to the early 1990s with the recognition of impingement occuring after femoral neck fractures malunited in retroversion[16]. But it was not until the development of open surgical dislocation allowed direct observations[12], that the concept of FAI was introduced as a mechanical cause of OA. The distinction of this FAI concept[17] compared to previous work by Solomon and Schnitzler[18], Harris[19], Murray[20] and Stuhlberg et al.[21] referring OA secondary to

grossly visble deformities (acetabular dysplasia, pistol grip deformity), is that subtle, often unrecognized developmental alterations and spatial malorientation of the hip in the absence of overt childhood disease might instigate OA[17].

Two distinct types of FAI have been identified (Fig. 3). The first is characterized by the linear impact of the acetabular rim against the head-neck junction in a local (acetabular retroversion) or global (protrusio) overcoverage of the acetabulum; it is therefore named pincer FAI. The second type occurs with the jamming of a nonspherical extension of the femoral head into the acetabular cavity; it is therefore namend cam FAI[17]. Both morphologies are frequent and often combined, reaching 25 % in young males and 50% when internal rotation of the hip in flexion is reduced[22].

The concept of FAI applies to both the subtle and larger deformities of the acetabular and femoral side, compromising the clearance of the hip. The described damages produced by impingement are early stages of an extensive, generalized arthritic process of the joint. Hips with cam FAI fail toward an antero-superior OA, while hips with pincer FAI fail toward a postero-inferior or central OA.

New generation of hip preserving surgery

While classic procedures to preserve the native hip, such as intertrochanteric and pelvic osteotomies continue to have an indication, new and powerful techniques have emerged. Increased knowledge of the femoral head perfusion but also the new understanding about the onset of OA of the hip played a pivotal role in the development of such procedures. Beyond this, the impingement concept has served as stimulus to move hip arthroscopy from a diagnostic to a science based interventional procedure with increasing indication [23].In contrast to the older, mostly extracapsular interventions, the new approaches are intracapsular and allow at this level more direct corrections.

The new procedures are based on surgical dislocation of the hip as described above [12]. This aproach is expanded into the extended retinacular soft tissue flap, in its full dissection allowing access to the circumference of the neck without disturbing the blood supply to the epiphysis[24]. **The extended retinacular soft tissue flap** increases the safety against stretching or even rupture of the vessels by its length reaching from the area of vessel perforation into the epiphysis to the level of the lesser trochanter. To make the dissection of the flap easy and strictly subperiosteal, the stable trochanter is first taken down to the level of the neck using a piecemeal resection technique (Fig. 4). **Relative lengthening of the femoral neck** is the most frequent procedure using this technique. It may be indicated as an isolated procedure or combined with an osteotomy of the neck; it increases

joint mobility without ongoing impingement and results in an optimal muscle lever arm without the risk of necrosis of the femoral head(Fig. 5). **Anatomic subcapital reorientation** may be indicated in slipped capital femoral epiphysis with major degree of slippage. Here the fully extended retinacular soft tissue flap including the medial dissection is applied and helps to avoid avascular necrosis of the epiphysis[25]. **Femoral neck osteotomy** requires an identical flap dissection as the subcapital reorientation, however in the adult the periosteum is slightly thinner and therefore the dissection of the periosteum is more demanding. Femoral neck osteotomy is mainly indicated as a varus osteotomy; leading to much less leg shortening compared with an intertrochanteric osteotomy, it is especially indicated in unilateral problems (Fig. 6). **Femoral head reduction osteotomy** is a challanging operation based on the fact that the medial portion of the epiphysis is perfused by a separate branch of the MFCA, while the lateral sector of the head receives its blood supply by the retinacular vessels. This vascular pattern allows to resect a middle segment of the head in cases with a large head, central necrosis and substantial extrusion, morphologies which are not uncommon in late Perthes disease. To stabilize the smaller head within the socket with its secondary deformation a routine periacetabular osteotomy is necessary[24].

Summary

Evaluation and nonarthroplasty surgical options for hip diseases in the young are continually evolving. Accurate diagnosis of subtle anatomic abnormalities is crucial. Management should be directed toward recreating normal anatomy when possible, provided that articular degeneration is not too advanced. Profound knowledge of the vascular anatomy of the hip is the basis for modern joint preserving surgery of which surgical dislocation and the extended retinacular soft tissue flap are the working horses. Arthroscopy will be used more commonly in the future, however the corrections have to be executed with the same precision as it is possible with the open technique.

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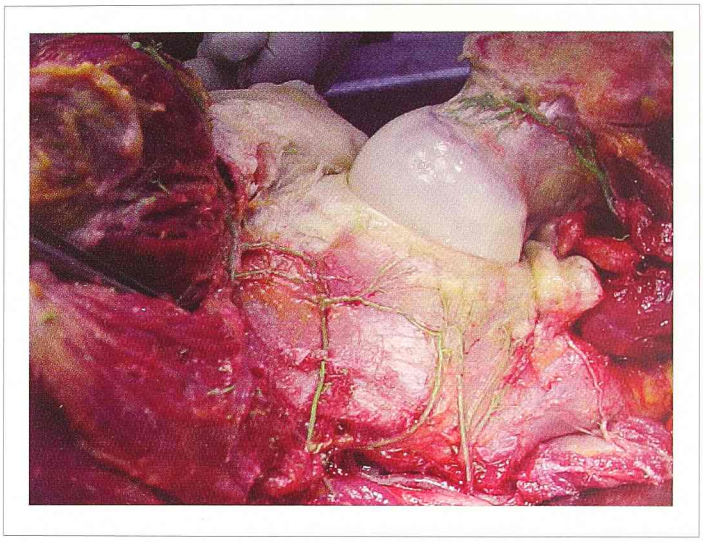


Fig.1 Overview of the deep branch of the MFCA and its ramifications in the retinaculum at the postero-superior neck. The penetration into bone is 3-5mm away from the cartilage border.

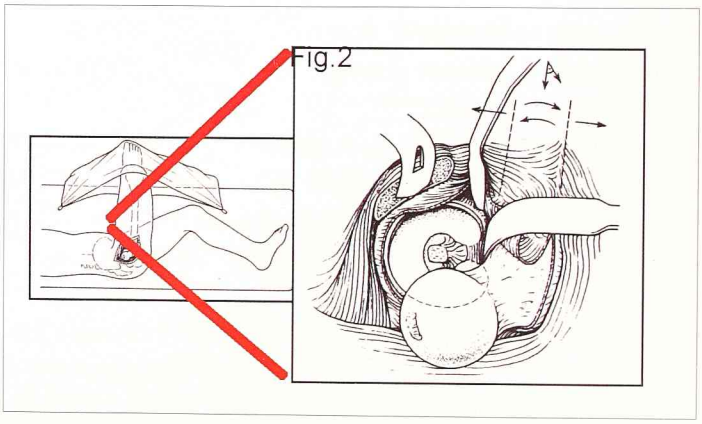


Fig.2 For dislocation of the hip the leg is put into a sterile bag on the opposite side of the table. Good view on acetabulum and femoral head after dislocation of the head, which can be further optimized by manipulation of the leg (arrows).

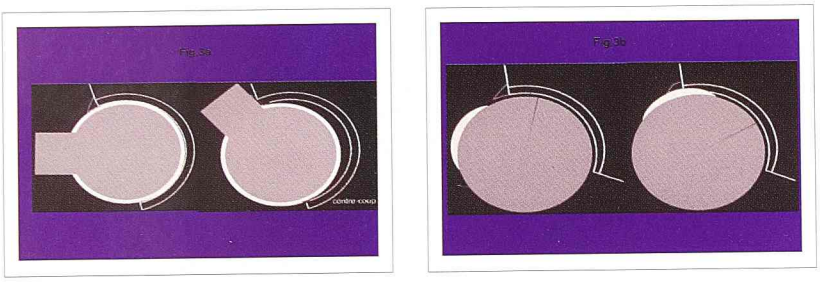


Fig.3 a) Diagram of pincer FAI as seen in acetabular retroversion (local) and in coxa profunda/ protrusio (global). Linear impact with the labrum as first structure to be hit. Contre coup lesion due to leverage.

b) Diagram of cam FAI. The nonspherical extension of the head is jammed into the acetabulum, destroying the cartilage. The labrum remains intact over a long time.

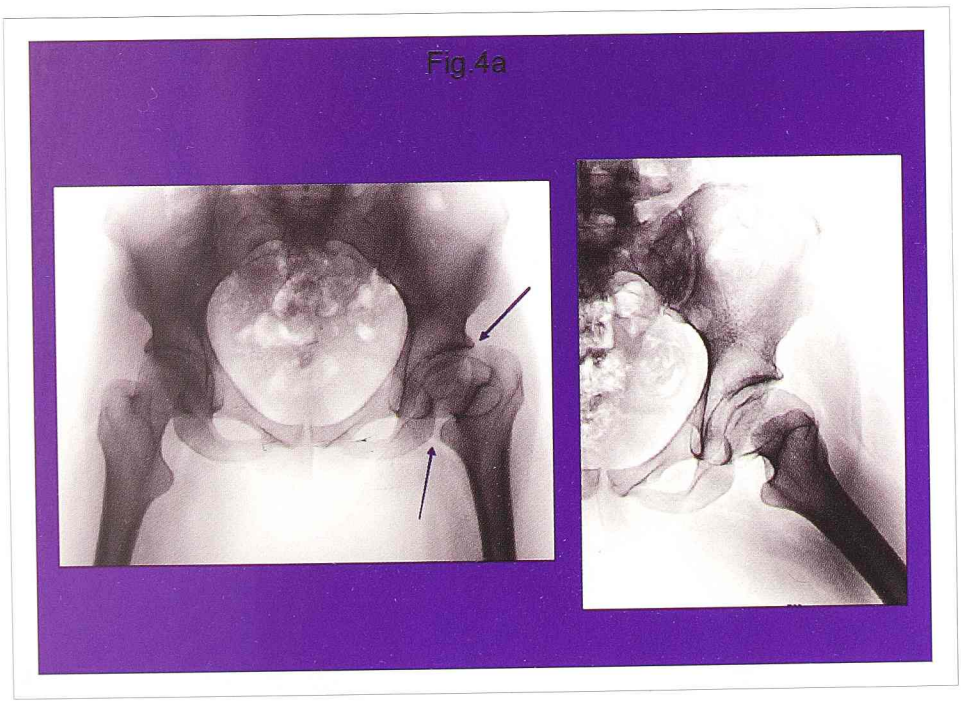
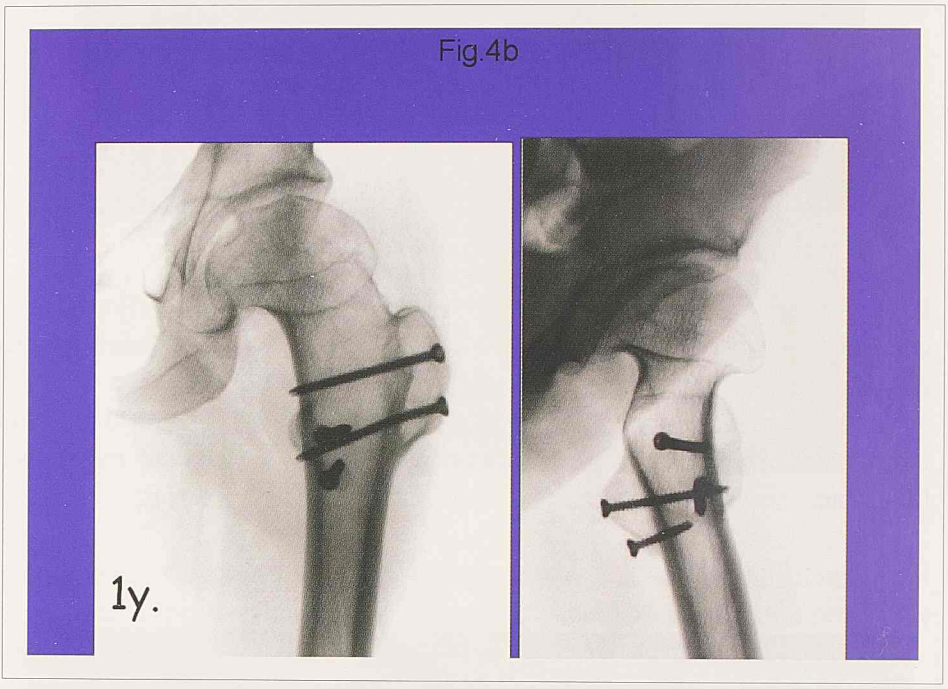


Fig.4 a) Sequelae of Perthes disease with only slightly deformed head, short neck and high riding trochanter leading to intra- and extra-articlar impingement.



b) Improved hip morphology and mobility without impingement after relative lengthening of the neck and distal advancement of greater and lesser trochanter.

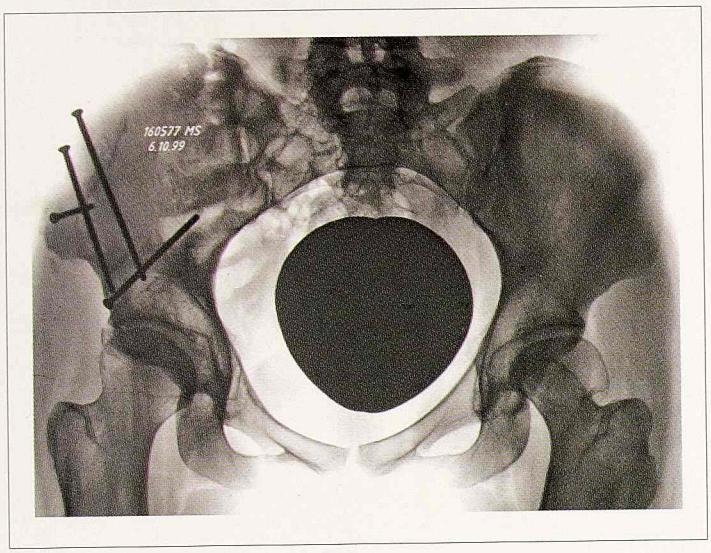
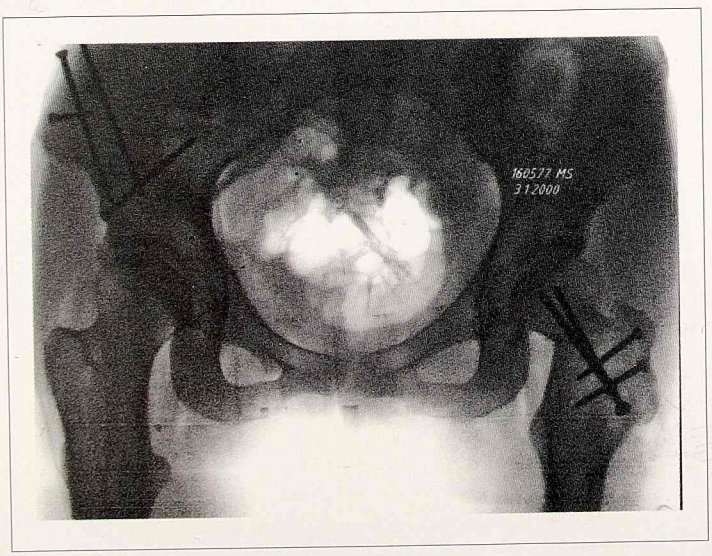


Fig.5 a) Radiography of the pelvis after periacetabular osteotomy on the right side. The left leg is 2 cm shorter. Treatment for the "head in the neck" deformity on the left side was planed as 30° varus osteotomy of the neck to avoid leg shortening as to be expected with intertrochanteric osteotomy .



b) Improved congruency and containment after varus neck osteotomy of 30° followed by minimal additional leg shortening.

The development of novel strategies for disease-modifying treatment of osteoarthritis: from molecular concept to clinic

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Over twenty-nine years ago, when I began my career as a rheumatologist and a researcher at the Medical School of the University of Montreal, Montreal, Quebec, Canada, treatment options for osteoarthritis (OA) were limited and consisted of lifestyle modification, patient education and functional training, symptomatic medications such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), and total joint replacement. Today, additional NSAIDs are available as well as coxibs, opioid analgesics for severe pain, topical analgesics, some nutraceuticals, intra-articular therapies (glucocorticoids and viscosupplementation), and surgical treatments involving arthroscopic procedures (Figure 1).

My goal was to discover therapeutics that would prevent the disease from progressing, which are now known as disease-modifying OA drugs (DMOADs). At the time, basic information about the disease was lacking and fundamental research was extremely limited and focused mainly on clinical trials with new analgesics and NSAIDs. Although DMOADs are not yet commercially available, I am convinced that now that appropriate targets have been identified and the right imaging technologies have been developed for the objective and quantitative evaluation of joint structural changes, such drugs will soon be available for the treatment of OA patients.

My involvement in arthritis began during my residency when I joined the Rheumatology Division at the University of Montreal. Yet, my love affair with the field of OA began when I first met Professor David Howell, a rheumatologist who was a pioneer and world leader in the field. Professor Howell, who passed away recently, was my fellowship mentor. His enthusiasm and innovative perspective of the disease, not only on the clinical side but also with fundamental research, made it easy for me to want to follow in his footsteps.

My plan for research in OA aimed at combining my clinical skills in rheumatology with my research expertise. Effort was made to develop the full-spectrum of translational investigation of this disease. I thus strived to include the broadest spectrum of scientific strategies ranging from molecular pathogenesis to *in vivo* studies using experimental animal models and clinical trials and more recently developed with our team imaging systems that reliably assess the disease at an early stage, its progression, and effects of treatment over time.

Osteoarthritis is the most common type of musculoskeletal disorder among

the contemporary population, and a leading cause of chronic disability. The etiology of this disease is multifactorial and is related to gender, body weight, and physical activity as well as to genetic factors (Figure 2). Primary OA is an idiopathic chronic degenerative disease related to aging, while secondary OA, which often occurs in relatively young individuals, results from a variety of predisposing conditions. Osteoarthritis most commonly affects the hands, feet, spine, and the large weight-bearing joints (hips and knees). Clinical manifestations may include deep joint ache (worsened by use), tenderness, reduced range of motion, crepitus, and local inflammation.

In vivo osteoarthritis target assessment: use of experimental animal models

With the use of pre-clinical studies in animal models of knee OA, my laboratory has helped to develop innovative therapeutic concepts. Indeed, the evolution of structural changes in OA occurs over an extended period which makes it very difficult to study the etiopathogenesis of the disease process. Hence, in addition to *in vitro* means, I decided to use animal models to test, *in vivo*, putative targets (Figure 3). At the time of my fellowship, there were only a few OA models, one of which had been recently developed and named the Pond-Nuki model of OA. I therefore first established and documented this model and contrasted the data with the *in vitro* findings from human specimens. Our data convincingly showed that this model reproduced the evolution of joint structural changes that occur during the human disease and mimicked the different pathophysiological mechanisms responsible for those changes [1-5]. This model presents significant advantages for the exploration of the different aspects of the changes that occur in this disease as it allows the study of the alterations in a time-wise fashion with the possibility of sequential evaluation of the disease lesions. Over the years, I have also used other experimental models. These models provide important information on the therapeutic benefits of drugs/agents and their potential as DMOADs as well as the possible extrapolation of data to the human clinical arena.

Data from *in vitro* experiments have shown that one proinflammatory cytokine, interleukin (IL)-1β is a key player in the progression of OA and tissue destruction. I therefore looked for agents that could control or limit the deleterious effects of this cytokine. A control mechanism unique to the IL-1 system, a physiological inhibitor of IL-1 receptors known as the IL-1 receptor antagonist (IL-1Ra), had been shown *in vitro* to specifically block the activity of IL-1β leading to the hypothesis that IL-1Ra would protect against structural tissue changes in

OA. Data first demonstrated that intra-articular injections of recombinant IL-1Ra in an animal model of OA reduced the disease progression [6]. Since the administration of proteins is a major weakness for drug delivery, I pursued by using gene therapy. Studies using two experimental animal models and two different strategies were conducted [7,8]. The first employed an indirect or *ex vivo* approach in which the IL-1Ra gene was transferred *in vitro* into the synoviocytes with the use of an adenovirus vector, and the transfected cells reintroduced into the joint. The second used a direct *in vivo* gene transfer utilizing a liposome complexed with a DNA plasmid encoding the IL-1Ra gene. The data collectively demonstrated that the IL-1Ra gene can be transfected into OA cells and produce the IL-1Ra protein resulting in a significant reduction in the progression of the disease. Results from these studies have led to clinical trials exploring the effectiveness of IL-1Ra in OA patients.

My research has also ascertained that other inflammatory mediators suggested by *in vitro* studies play major roles in the OA process; the principals being nitric oxide (NO) and the enzyme responsible for its inducibility, iNOS, and the eicosanoids including prostaglandins and leukotrienes.

Nitric oxide is an extremely important element with regard to the pathophysiology of OA (Figure 4). Firstly, we showed that there is excess production of NO in OA cartilage, which is generated via an increase in the iNOS level, and that it induces many of the catabolic pathways responsible for OA cartilage degradation, such as the reduction in IL-1Ra. Very importantly, we were the first to demonstrate *in vivo* the potential of the selective inhibition of iNOS to reduce the progression of OA in an animal model [9-11]. By using oral administration of therapeutic dosages of a specific inhibitor of iNOS, data demonstrated positive therapeutic benefits on the progression of lesions. In brief, inhibition of iNOS reduced the severity of joint tissue structural changes, which was associated with a reduction in metalloproteases and chondrocyte apoptosis in articular tissues, as well as a reduction in the levels of IL-1β and prostaglandin (PG)E_2 in synovial fluid. We further demonstrated that exogenous PGE_2 may sensitize human OA chondrocytes to cell death induced by NO [12,13]. This knowledge pointed to the possible therapeutic value of iNOS inhibitors in the treatment of OA as chondroprotective, anti-inflammatory and analgesic drugs. Such an inhibitor was therefore considered a very attractive target in OA, because reducing the excess production of NO may not only slow the disease progression, but is also likely to reduce the symptoms, making it possible to

attain two goals simultaneously. Our results were convincing enough to justify the initiation of a Phase III clinical trial testing a specific iNOS inhibitor.

One of the signalling pathways mediating the effect of proinflammatory cytokines including IL-1β and other inflammatory factors is the mitogen-activated protein kinase (MAPK), MAPK kinase 1/2 (MEK1/2). MEKs are substrates for several protein kinases that act at an integration point for multiple biochemical signals. Data from one of the major studies aiming at *in vivo* effects of a synthetic inhibitor of MEK 1/2 showed that this drug reduced the development of cartilage lesions, osteophyte formation, and synovial hyperplasia, as well as the synthesis of major proteolytic enzymes and other OA catabolic pathways [14].

Moreover, recent literature including work by our group suggests that the activation of a nuclear receptor, the peroxisome proliferator-activated receptor (PPAR)γ, could be an attractive target. PPARγ belongs to the family of ligand-activated nuclear factors and in addition to its classical role in lipid and glucose homeostasis, *in vitro* experiments have shown its ability to suppress IL-1β-induced NO, metalloproteases and cyclooxgenase (COX)-2 production, and IL-1β-induced decrease in some cartilage matrix macromolecule (proteoglycan) synthesis. Using two experimental models of OA, we explored the *in vivo* effects of pioglitazone, a synthetic agonist of PPARγ [15,16]. Data showed that this drug reduced the development of OA lesions, the effect of which is mediated by inhibition of the MEK pathway, which we reported earlier [14] to be a very important one in mediating the catabolic responses in OA tissues (Figure 5).

In brief, OA is mediated by a multitude of factors that act on the articular tissue cells resulting in alterations in the cell metabolism. The end result is the production of proinflammatory cytokines, of which the central role of IL-1β has been established, as well as other inflammatory mediators. Data from our studies thus suggest that therapies targeting any of these factors, both upstream and downstream, may prove to be beneficial on the disease process.

Therapeutic intervention in humans

Following the data from basic research, we further explored the DMOAD effects of some relevant compounds/agents in human clinical trials.

Firstly, we investigated, *in vitro* and *in vivo* in animal models, the effects of glucocorticoids on the articular tissues/cells [17-27]. Corticosteroids are considered to be the most potent anti-inflammatory drugs. Even though

glucocorticoid injections have been used successfully for decades to relieve OA symptoms and restore function, there is still a debate about whether this drug has a significant effect on disease progression. *In vivo* proof of concept data [17,18,24,25] showed that the oral or intra-articular administration of steroids in an OA animal model reduces the development of joint tissue structural changes. We therefore conducted a two-year, double-blind, placebo controlled study on knee OA patients, evaluating the effect of steroids on the disease symptoms, quality of life and, importantly, on disease progression [28]. Data revealed that repeated steroid injections were effective for the long-term symptomatic treatment of knee OA without having any deleterious effects on the anatomical structure of the joint. The knee X-rays taken during this study to evaluate disease progression were not able to adequately detect structural changes, even in the placebo group. This finding led to questions about the sensitivity and accuracy of this imaging method for the assessment of the progression of joint structural changes in OA pathways, an issue which we then began to address (see below, *Imaging*).

Other major inflammatory factors involved in OA pathophysiology are the prostaglandins and leukotrienes. Prostaglandins are synthesized from arachidonic acid via the actions of the COX enzymes. The most abundant prostanoid in the human body is PGE_2. Depending on the context, PGE_2 exerts either a homeostatic or inflammatory effect. Inhibition of PGE_2 synthesis by NSAIDs has been an important anti-inflammatory strategy for more than a century. A recent study has shown that the use of NSAIDs or COX-2 selective inhibitors alone does not delay the natural progression of OA [29].

Arachidonic acid is a substrate that gives origin to, in addition to prostaglandins, many other lipid mediators including leukotrienes. Leukotrienes themselves play a major role in the development and persistence of the inflammatory process. Thus, the failure of NSAIDs to impact OA progression could be due to the fact that inhibiting only the COX pathways leads to a shunt to leukotriene production in these tissues. This concept introduced the hypothesis that blocking the production of both leukotrienes and prostaglandins could have a synergistic effect of achieving optimal or a wider spectrum of anti-inflammatory activity (Figure 6). Further to studies *in vitro* and *in vivo* in animal models [30-42] showing that the leukotrienes are an extremely important element during the progression of OA, we investigated the potential of a dual inhibitor of lipoxygenase and COX as a DMOAD in a Phase III clinical trial in human knee OA patients [43]. In this study, two imaging technologies, X-rays and a magnetic

resonance imaging (MRI) system developed by our team (see below, *Imaging*), were used. Importantly, data showed that treatment with such a dual inhibitor protected the articular tissues, in which a reduction in cartilage loss was found over time. Other findings from this study were also of major interest. Data demonstrated firstly the superiority of MRI over X-rays at detecting DMOAD effects of a drug and, secondly, validation and translation of the results from the pre-clinical *in vivo* animal studies to humans.

Imaging

Diagnosis of OA can usually be made with reasonable certainty upon clinical examination from patient history and physical examination, and the diagnosis can be confirmed by X-rays. However, the above parameters may appear normal in the early stages of the disease. In addition, it is well known that plain radiographs often do not correlate well with physical examination findings and, most importantly, usually cannot directly detect alterations in the three major joint tissues (cartilage, subchondral bone, and synovial membrane) during the disease process. It was obvious that the existing methods, although useful, were imperfect for DMOAD trials and required several thousand patients and long study periods (2 to 3 years). Hence, there was an urgent need to evaluate joint tissue structural changes in a time-wise fashion and with fewer patients included in the studies in order to assess therapeutic efficacy of a compound. Although qualitative alterations in structure can be identified with MRI, the real challenge has been the sensitive and reliable quantification of the cartilage changes. We thus embarked upon the development of innovative joint tissue imaging systems assessing cartilage volume quantification in the human knee (Figure 7) and hip (Figure 8) using MRI with non-invasive methodologies [44-49]. Data showed that the developed quantitative MRI system was not only very reliable in a multicentre clinical trial but that it could also estimate the differences between drug treatments as early as 6 months into the trial [43]. This level of sensitivity can never be attained with X-rays. Interestingly, MRI also provides relevant information on the other knee tissues surrounding the cartilage, such as meniscal damage, subchondral bone (bone marrow) lesions, synovial inflammation, and synovial fluid, which are now considered important risk factors of OA progression in addition to clinical factors. We therefore pursued by developing MRI systems to investigate changes in menisci, subchondral bone, synovial membrane, and synovial fluid [47,48,50-53]. In brief, data from these advanced imaging technologies using MRI support the hypothesis that alterations occur in these tissues during the disease process and,

importantly, that they are interdependent. Clinical trials are currently underway using these MRI systems.

The implications of the MRI findings on cartilage and surrounding tissues gathered from OA patients should have an important impact on clinical DMOAD trials, as these MRI technologies reduce the number of patients needed for these studies, improve patient retention, and reduce the overall length of trial required to evaluate treatment response. They may also help to redefine primary OA. The criteria for defining primary knee OA are currently based on clinical and/or X-ray findings. Since the cartilage is not vascularized or innervated, the pain experienced in this disease is likely to originate from other tissues. The criteria to define primary OA could be cartilage loss over time, which may not be reflected by the symptoms but will considerably precede radiological changes. Consequently, patients could be assessed at an earlier stage of the disease and, therefore, receive appropriate treatment.

Finally, we also recently developed similar MRI systems for studies in animals with OA [54,55]. Indeed, the use of animal models in DMOAD development programs is recommended to study long term effects of a drug and to ensure that the effects seen in the early stages of the disease are predictive of those observed at a later stage. Non-invasive joint imaging such as MRI thus represents a significant advantage in following the disease process and the effects of DMOAD treatment, as the same animals can be followed at different times and also over an extended period.

Conclusion

In conclusion, our work has been instrumental in providing and documenting new concepts of the pathophysiological process of OA to such an extent that many of the development programs for DMOADs have originated from results of our research. Work from our group has brought new knowledge of this disease from the bench to the bedside. Moreover, the development of new imaging technologies for the evaluation of joint tissue structural changes will dramatically change the way that OA clinical trials are conducted and perhaps also help to improve the concept supporting the diagnosis of primary OA. Therefore, in addition to the work on target molecules/tissues, these technologies will stimulate drug development and hopefully a breakthrough in the development of curative treatment, which is urgently needed as the population ages and the frequency of the disease increases.

Acknowledgements

I would first like to thank the members of the King Faisal Foundation and International Prize committee for bestowing upon me this prestigious award. I also wish to thank the supervisors of my fellowship, Professors D.S. Howell, R.D. Altman and J.F. Woessner (University of Miami, Miami, Florida, USA), who were sources of great inspiration, not only during but also after my internship. I also would like to thank the rheumatologists, researchers, and all the personnel of our Unit at Notre-Dame Hospital, University of Montreal Research Center for their confidence, valuable assistance, collaboration and enthusiasm throughout the years; I greatly appreciate their support. Many other collaborators (too numerous to list here) have assisted in the development of our ideas and research, and I thank them all. Finally, I would like to acknowledge the governmental organizations (Canadian Institutes of Health Research, formerly Medical Research Council of Canada, and the Fonds de la Recherche en Santé du Québec), the private organizations (e.g. The Canadian Arthritis Society), foundations (e.g. Foundation JA de Sève), and pharmaceutical and biotechnological companies, who have believed in our research and provided grants or donations that have allowed the continuation of our projects.

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FIGURE LEGENDS

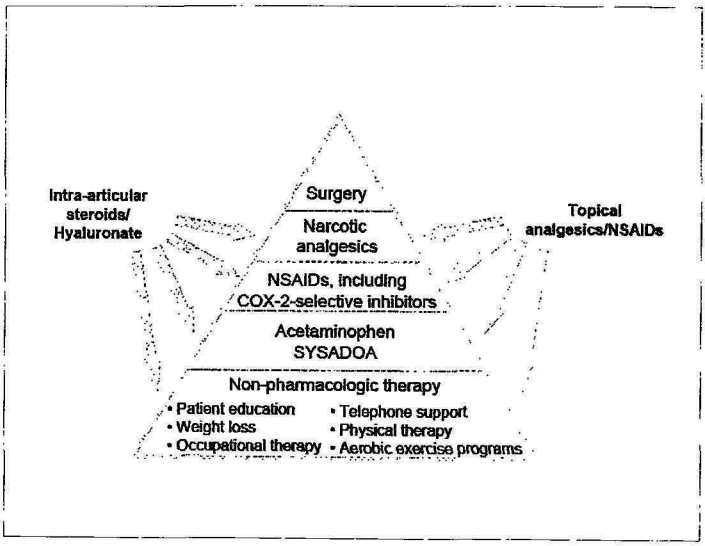

Figure 1

Overview of pain management in osteoarthritis of the knee.

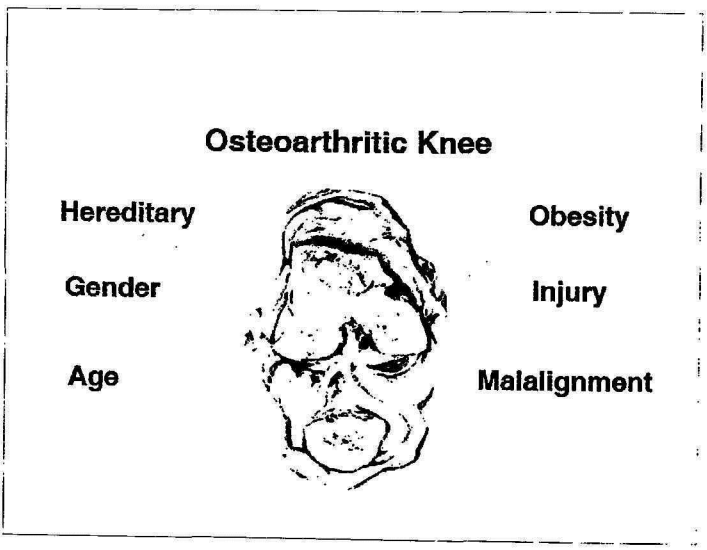

Figure 2

Schematic representation of osteoarthritis risk factors.

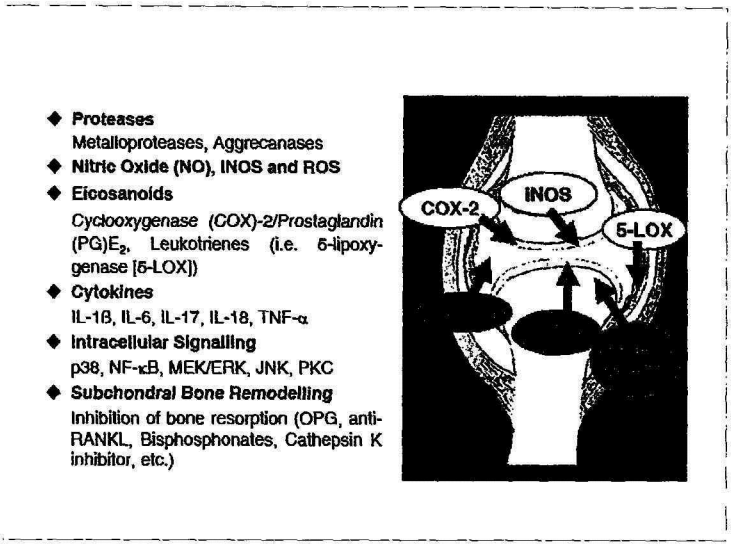

Figure 3
Putative targets for disease modifying osteoarthritis drugs (DMOADs).

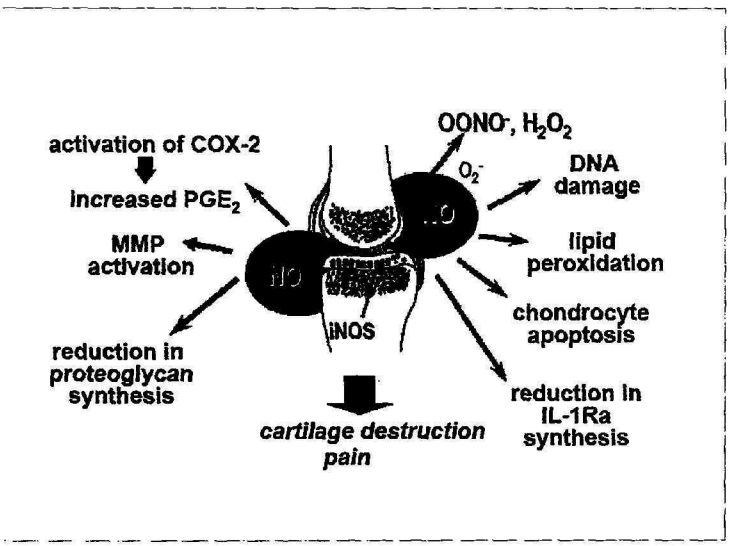

Figure 4
Mechanisms of nitric oxide (NO) mediated tissue damage in osteoarthritis.

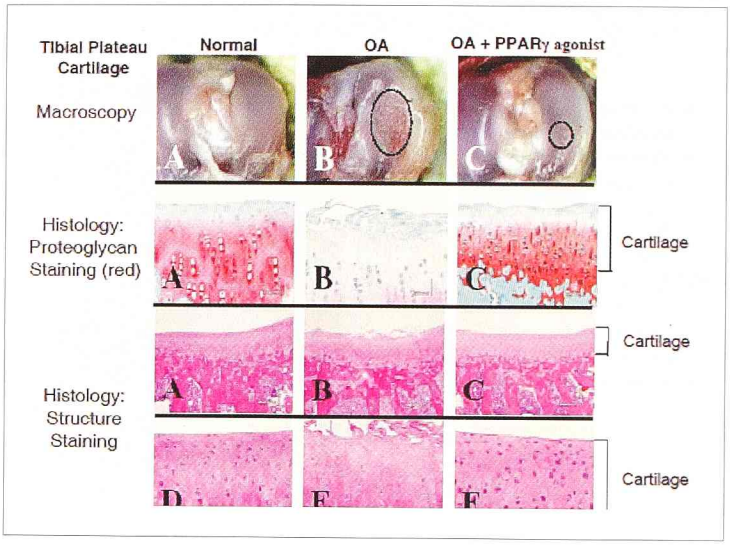

Figure 5
Disease-modifying effects of a PPARγ agonist in an osteoarthritis (OA) animal model.

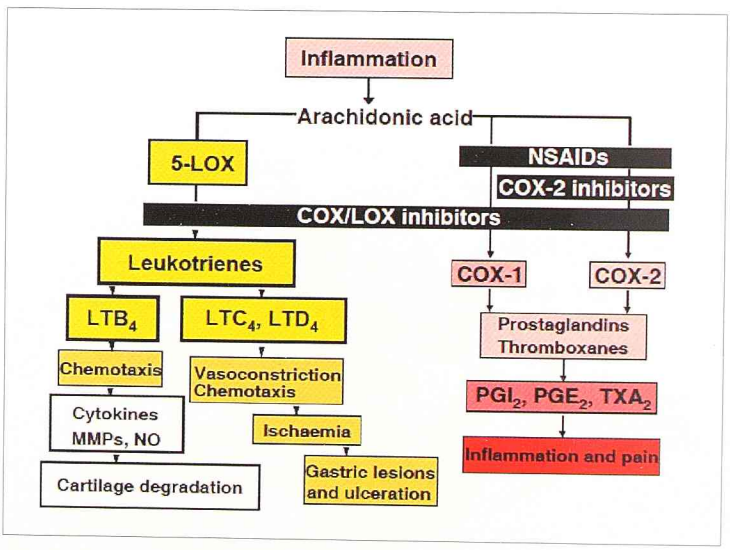

Figure 6
Schematic representation of two important arachidonic acid metabolite pathways: leukotrienes and cyclooxygenases. Black rectangles indicate inhibition.

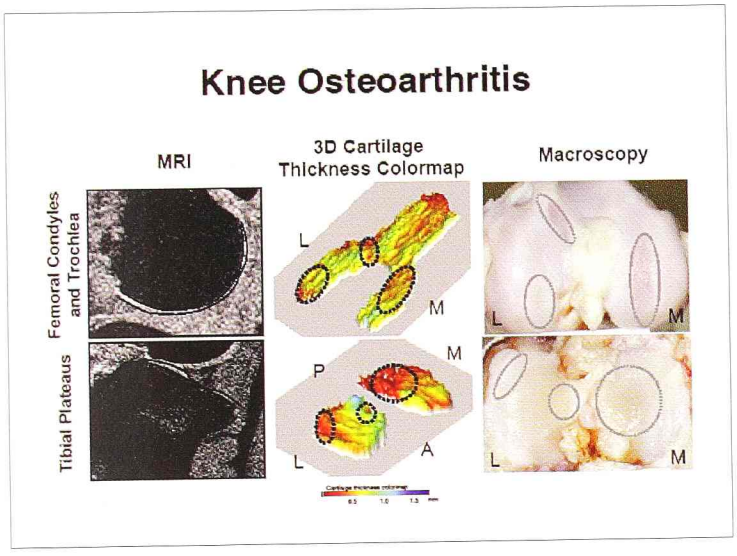

Figure 7
Comparative evaluation of osteoarthritic lesions using macroscopy and quantitative magnetic resonance imaging (MRI). L = lateral, M = medial, P = posterior, A = anterior. Circles indicate lesional areas.

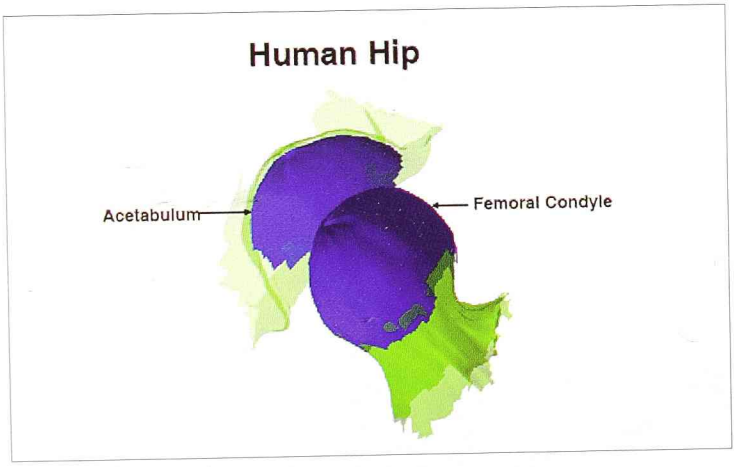

Figure 8
3D reconstruction of a human hip following magnetic resonance imaging. The cartilage is represented by the color blue and the bone by green.

The story behind the discovery of key pathophysiological mechanisms in osteoarthritis: a step toward finding a cure

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It is with the greatest pleasure that I share with two other recipients the 2010 King Faisal International Prize in Medicine. The seminal experience of my PhD in physiology at the University of Montreal in Montreal, Quebec, Canada and further training in rheumatology in the USA, launched my research in osteoarthritis in the Department of Medicine at the University of Montreal where I jointly established with Professor Jean-Pierre Pelletier, the Osteoarthritis Research Unit.
Interestingly, in the 1980s very few researchers in basic science studied osteoarthritis, as this disease was viewed as an inevitable outcome of aging and it was thought that nothing could be done but treat the symptoms of pain. It should be remembered that at that time, research in rheumatology, both basic and clinical, focused mainly on immune-mediated diseases. We knew that osteoarthritis was not an autoimmune disease, but my view was that it was linked to abnormal molecular pathways in joint tissues/cells, which if identified, could be targeted to improve therapeutic approaches and lead to the development of treatments that can reduce or stop the progression of the disease. Over the years, my work has not been limited to the cartilage, the only tissue originally thought to be involved in the disease process, but has demonstrated the global involvement of all the major tissues of the joint, namely the cartilage, synovial membrane, and subchondral bone (Figure 1). Our group has developed new and innovative concepts pertaining to the pathophysiology of osteoarthritis, which have assisted and will continue to assist in the development of new therapeutic approaches aimed at protecting the joint tissues from the structural changes that occur during the course of this disease.

Before briefly outlining the most significant concepts that have originated from my laboratories, let me first summarize this disease. Osteoarthritis is the most common form of arthritis and the leading cause of activity limitation and physical disability in developed countries worldwide. While arthritis is the most frequently diagnosed chronic medical condition in the world, osteoarthritis accounts for 40% to 60% of degenerative illnesses of the musculoskeletal system. On the whole, approximately 15% of the population suffers from this disease; however its frequency increases with the aging of the population and approximately 63% of the population 60 years of age and over has osteoarthritis (Figure 2). Current treatments are palliative and provide symptomatic relief without preventing the progression of the disease.

My research interests lie in understanding the mechanisms involved in articular tissue degradation and repair, as well as in investigating new therapeutic targets for the treatment of the disease. In short, the data have contributed to deciphering the roles of, and the links between, inflammation, cytokines, proteases, growth factors, and eicosanoids in osteoarthritic tissues. Below is a brief outline (by

subject, not in chronological order) of the most significant achievements that have originated from my research.

Proteases/inhibitors (Figure 3)

Firstly, I identified several enzymatic pathways that are intimately related to the development of this disease. More specifically, our group demonstrated that the metalloprotease (MMP) family is of pivotal importance in the degradation of osteoarthritic cartilage but that the involvement of serine- and cysteine-dependent proteases also plays a significant role. These studies were among the first to introduce and demonstrate the importance of an imbalance in enzyme/specific inhibitors (MMP/TIMP, cathepsin B/inhibitors and plasminogen activator (PA)-plasmin/PA inhibitor-1) in osteoarthritic tissues [1-14]. This concept has since become well recognized as an intimate element in the pathogenesis of osteoarthritis, and strategies to increasing TIMP in the joint have since been investigated as a therapeutic avenue for this disease.

In recent years, we were the first group to demonstrate the involvement of a new collagenase, collagenase-3 (MMP-13), in cartilage and its contribution to the osteoarthritis process [15]. Further work undertaken in our laboratory demonstrated that various factors are able to modulate this enzyme [16-19] and a study suggests [20] that collagenase-3 was involved in the cartilage remodelling phase in osteoarthritis, which was in contrast to the data from another collagenase, collagenase-1 (MMP-1), which appears to be preferentially involved during the inflammatory phases of the disease. In addition, we were also the first group to clone the human collagenase-3 promoter, more specifically its 5' flanking region [21], and further discovered in its promoter region, a binding site modulating this enzyme's basal transcription [22] and identified some of the proteins that bind to this regulatory site [23,24]. Moreover, we identified different mRNA species of collagenase-3, potentially leading to the production of different enzymes [25]. Together, these data showed that collagenase-3 is subjected to different levels of regulation and constitutes a more complex system than originally thought. These findings, in addition to offering a better understanding of the regulation of collagenase-3 in human osteoarthritis, provide a new basis for the rationalization of a therapeutic strategy and open up potential avenues in strategies targeting this MMP. This is important, as one of the strategies of the pharmaceutical industry is to block MMPs as an effective way to prevent this disease from progressing, and this enzyme, collagenase-3, is among the preferred candidates.

Growth factors

Transforming growth factor (TGF)-β. We also investigated the growth

factor TGF-β in osteoarthritic cartilage and, more specifically, its effect on collagenase-3 modulation. Interestingly, our data revealed that although many cytokines and factors can enhance collagenase-3 production, TGF-β appears to be, in vivo, the factor responsible for its up-regulation in human osteoarthritic cartilage [17,20,26]. These data have introduced a new concept for a role played by this growth factor, i.e. a catabolic one, which has challenged the notion that it possesses only anabolic properties. In addition, we provided evidence of the extracellular activation of TGF-β in human osteoarthritic cartilage [27].

Insulin-like growth factor (IGF)-1. During the course of the disease, the synthesis of new cartilage matrix macromolecules may be insufficient as a consequence of deficient stimulation. Because of its properties, we chose to study the involvement of insulin-like growth factor-1 (IGF-1) in the osteoarthritis process.
Our studies identified in cartilage a metabolic disorder of the IGF-1 system that we believe is associated with the development of osteoarthritis. We showed that although more IGF-1 is secreted by the osteoarthritic cartilage cells, the chondrocytes, these cells are hypo-responsive to stimulation by this growth factor [28]. Moreover, IGF-1 presence in cartilage does not originate from systemic production but from local production by the chondrocytes [29]. The hypo-responsiveness of the chondrocytes to IGF-1 was found not to be related to a change in IGF-receptor expression but rather to an increase in some IGF binding proteins (IGFBP) that affect the bioavailability of IGF-1 [28,30]. Further studies showed that prostaglandin (PG)E_2 [31] and a miRNA [32] were, at least in part, responsible for the regulation of these binding proteins.

Moreover, it has been suggested that thickening of the subchondral bone during osteoarthritis contributes to this disease pathophysiology. Investigation showed that abnormal activation of IGF-1 and its intracellular signalling in the subchondral bone cells, the osteoblasts, may contribute to these changes [33,34].

Bone morphogenic protein (BMP) antagonist. Among the growth factors that are up-regulated in human osteoarthritis are the bone morphogenic proteins (BMPs) which belong to the TGF-β super-family. These factors play important roles during embryogenesis, the formation of cartilage and bone, and the tissue homeostasis of adult cartilage by promoting the production of cartilage macromolecules. BMP activities are controlled in part by specific antagonists, which prevent them from interacting with their specific receptors, thus preventing their effect. In order to find out if BMP are active and effective during the disease process, we investigated the presence and activity of some specific antagonists in human normal and osteoarthritic articular cartilage and synovial membrane, as we believe that in pathological tissues increased levels may lead to decreased

anabolic BMP activity, consequently affecting tissue repair and remodelling. Our data showed, for the first time, that the BMP antagonists follistatin, gremlin, and chordin are produced in human cartilage and synovial membrane with differential localization [35,36]. The levels of follistatin and gremlin are increased in the diseased tissues yet, interestingly, they are differentially regulated [35], which led us to hypothesize that production of these antagonists occurs at different stages of the disease, therefore suggesting different roles. Our data [37] showing that gremlin is associated with the remodelling found in the early phase of osteoarthritis, whereas follistatin is associated with the inflammatory process, further confirm this hypothesis. Thus, findings suggest that despite the constant presence of BMPs in osteoarthritic cartilage, these molecules may not be optimally effective due to the increased levels of specific antagonists resulting in decreased production of matrix macromolecules and a shift towards degradation rather than matrix synthesis and repair. Hence, these results on the potential interference of different BMP antagonists with BMP activity during osteoarthritis should be taken into consideration in the design of cartilage repair therapeutic strategies involving BMPs.

Synovial inflammation/interleukin (IL)-1β

As a result of the work on the enzymes and growth factors, it was clear that the enzymatic alterations combined with the deficit in stimulation of the matrix macromolecules could explain the exhaustive degradation of the joint tissues; however, this did not provide an explanation for the increased synthesis and expression of these enzymes/factors. Another hypothesis that represents a turning point in the understanding of the pathophysiology of osteoarthritis was the identification of the role of synovial membrane inflammation in the progression of structural changes leading to the development of clinical disease (Figure 4) [38,39], with the demonstration of the major role of the proinflammatory cytokine IL-1β [9,40,41]. We demonstrated the important role played by IL-1β in the abnormal metabolism of osteoarthritic tissues, the mechanisms by which it stimulates the diseased cells, and how this process is modulated. In brief, data showed that IL-1β was the major proinflammatory cytokine involved in the stimulation of the production of catabolic factors in the articular tissues. Moreover, one of this cytokine's receptors, type I IL-1R, was found responsible for an overstimulation of osteoarthritic cells by the cytokine [41-45]. We also found a relative deficit of the specific IL-1R antagonist (IL-1Ra) vis-à-vis IL-1β in the osteoarthritic synovial membrane and IL-1Ra reduced the IL-1-induced articular tissue degradation [46]. Work on this cytokine also led to the demonstration that the specific enzyme responsible for the extracellular release of active IL-1β, the IL-1β converting enzyme (ICE), was present in both human cartilage and synovial membrane, and its level significantly increased in these osteoarthritic tissues [47,48]. Moreover, we also showed that ICE specific inhibition in human osteoarthritic cartilage resulted

in a complete abrogation of active IL-1β formation [47]. Together, these findings support the notion that blocking this enzyme represents another interesting potential target for osteoarthritis therapy.

Inflammatory factors

Changes in cartilage and synovial membrane are believed to be related to a complex network of biochemical pathways that implicate the diffusion of catabolic factors and cytokines between the different joint tissues (Figure 5). Such molecular cross-talk between the articular tissues is believed to be an integral part of the disease pathogenesis and progression. We therefore studied the roles of the most important inflammatory factors in the mediation of articular tissue destruction in human osteoarthritis using in vitro and ex vivo means. These include pro-inflammatory cytokines other than IL-1β, such as IL-6 [13,49], IL-17 [19,50-53], IL-18 [47,48], and tumour necrosis factor-α (TNF)-α [54-58], inflammatory mediators including nitric oxide [59-62], the eicosanoid PGE_2 [62-67] and the leukotriene LTB_4 [68-71], and the recently identified proteinase-activated receptors (PARs)-2 [72-74]. Moreover, we also showed that a nuclear receptor, the perosixome proliferator-activated receptor (PPAR)γ, upon activation plays a role as an anti-inflammatory factor and reduces some catabolic factors involved in osteoarthritic tissues [75-78]. In brief, we documented the presence/production of each of these factors as well as their implication and mechanism of action in the disease process. These works provides important information about the critical link between inflammation and articular tissue remodelling and destruction, and point toward these factors as therapeutic targets in osteoarthritis.

Subchondral bone

It was long believed that osteoarthritis was a rather focal process, involving only the destruction of articular cartilage. We proposed that the subchondral bone had a significant implication in this disease and elected to examine the causes of the abnormal cell metabolism in this tissue.

The subchondral bone plate is a tissue located at the base of the articular cartilage; it possesses an irregular surface into which the cartilage is keyed (Figure 6). In normal condition, the subchondral bone is thin and acts as a shock absorber which protects the cartilage against damage caused by excessive load.

Our work has provided new substantiated evidence of the concept that subchondral bone alterations are intimately related to the onset/progression of osteoarthritis rather than being merely consequential. Indeed, we showed that during the course of the disease, biological and morphological disturbances occur in the subchondral bone. We demonstrated the presence of increased abnormal metabolism in subchondral bone osteoblasts with altered production/activity of

local factors including alkaline phosphatase, osteocalcin [79], PA/plasmin [80], IGF-1 [66], osteoprotegerin and the receptor activator of nuclear factor κB ligand (OPG/RANKL) [81,82], EphB4 receptors/ephrin B2 ligand [83], proteases such as MMP-13 and cathepsin K [84], cytokines, TGF-β, PGE_2, leukotrienes [66,85-88], and the collagen α chains [89] leading to abnormal bone resorption or deposition (Figure 7). These data strengthen the notion that therapeutic interventions that specifically inhibit bone resorption have the potential to be used as disease-modifying osteoarthritis drugs. A first clinical trial directed at looking at such a drug was undertaken with the help, among others, of Professor J-P. Pelletier from our Unit [90]. Presently, other clinical trials with osteoarthritis patients are ongoing to investigate drugs that curb abnormal bone remodelling/resorption.

Conclusion

In summary, my research has provided major advancement in the knowledge of the mechanisms that lead to joint destruction in osteoarthritis at the same time as laying the groundwork for testing novel therapeutic interventions. Although we still do not completely understand what initiates the degradation and loss of articular tissues, data have shown that it results from increased catabolism due to elevated levels of cytokines and catabolic factors combined with the ineffectiveness of some growth factors' activities in osteoarthritis leading to an impairment in joint tissue repair. Importantly, we demonstrated that the alterations that take place during the disease process involve all of the three major articular tissues, the cartilage, synovial membrane, and subchondral bone, and that there is an interdependence between these tissues. These findings have challenged and changed the scientific community's view of the pathogenesis of osteoarthritis from being a disease solely of the cartilage to one in which there is a global involvement of all of the joint tissues (Figure 8). Moreover, data from our basic research have set the framework for the intimate process of this disease, which is now known to result from a complex system of interacting mechanical, biological, biochemical, molecular and enzymatic feedback loops. The final common pathway is joint tissue destruction resulting from failure of cells to maintain a homeostatic balance between matrix synthesis and degradation.

Acknowledgements

I would first like to thank the King Faisal Foundation and International Prize committee for bestowing upon me this prestigious award. I also wish to thank the directors of my post-doctoral training, Professors D.S. Howell and J.F. Woessner (University of Miami, Miami, Florida, USA), who were sources of great inspiration, not only during but also after my internship. I also would like to thank the rheumatologists, researchers, and all the personnel of our Unit at CHUM-Notre-Dame Hospital, University of Montreal Research Center (CRCHUM) for their confidence, valuable assistance, collaboration and enthusiasm throughout the years; I greatly appreciate their support.

Many other collaborators (too numerous to list here) have also assisted in the development of our ideas and research, and I thank them all. Finally, I would like to acknowledge the governmental organizations (Canadian Institutes of Health Research, formerly Medical Research Council of Canada, and the Fonds de la Recherche en Santé du Québec), the private organizations (e.g. The Canadian Arthritis Society), foundations (e.g. Foundation JA de Sève), and pharmaceutical and biotechnological companies, who have believed in our research and provided grants or donations that have allowed the continuation of our work.

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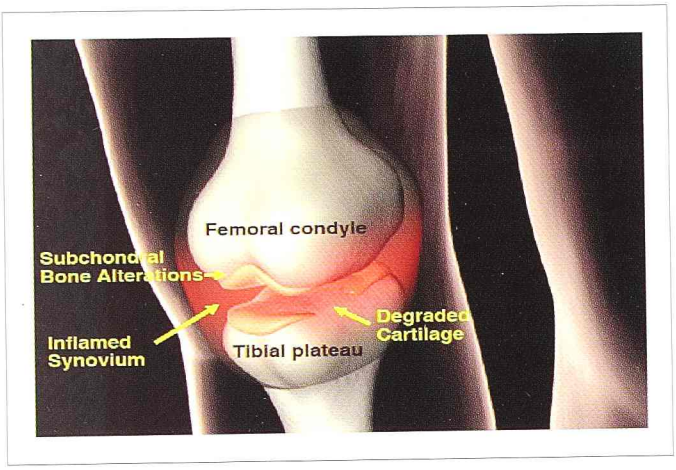


Figure 1
Reproduction of the osteoarthritic knee which shows the abnormal disease process in three major articular tissues: cartilage, synovial membrane and subchondral bone. Osteoarthritis is characterized by a degeneration of articular cartilage. At the clinical stage of the disease, this is associated with changes in the synovial membrane, where an inflammatory reaction is often seen. Osteophytes, not represented in the figure, also are often present. In addition, subchondral bone also demonstrates a remodelling process and a complex relationship between subchondral bone and cartilage is currently seen as a major pathophysiological factor in the progression of the disease.

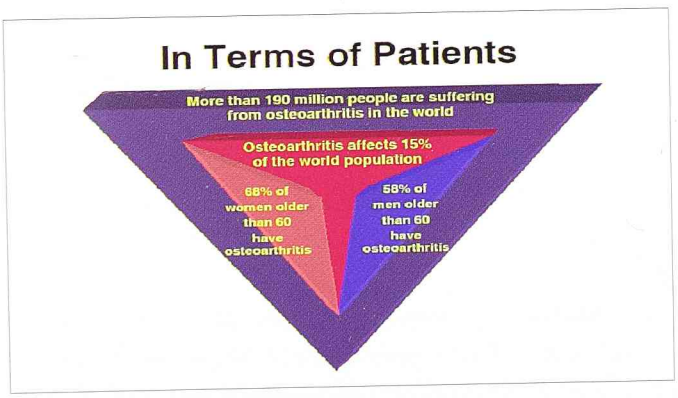


Figure 2
Numbers and percentage of patients affected with osteoarthritis.

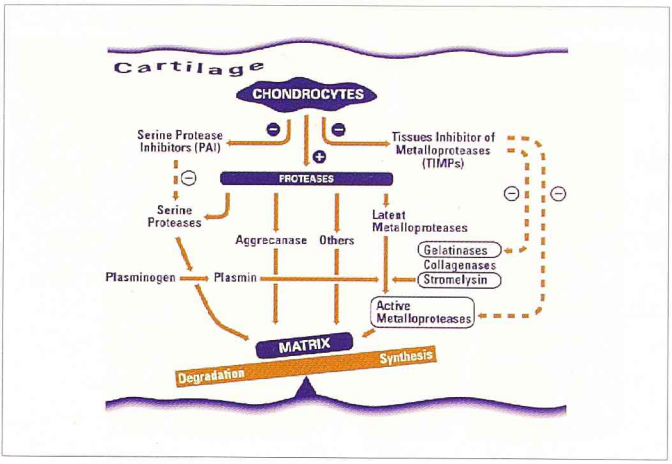


Figure 3
Schematic representation of the major local catabolic enzymes and their inhibitors regulating articular cartilage turnover. The minus sign (-) and broken lines indicates inhibition.

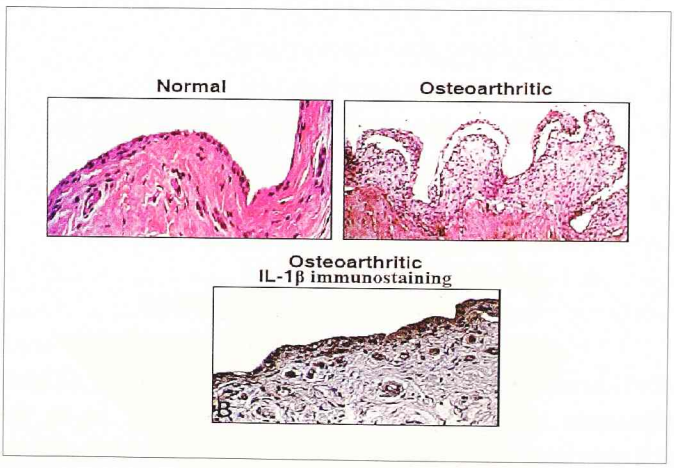


Figure 4
Representative section of synovial membrane from normal and osteoarthritic subjects. The upper panels show histological specimens and the lower panel an immunohistochemical staining demonstrating the presence of IL-1β in an osteoarthritic synovial membrane.

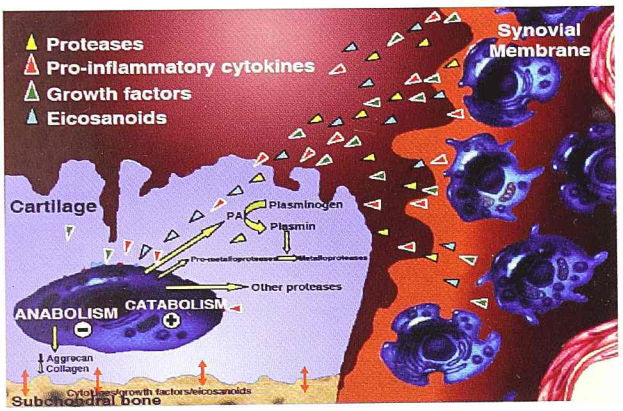


Figure 5

A schematic representation of the process involved in osteoarthritis pathophysiology at the clinical stage of the disease. As inflammation of the synovial membrane occurs, proteases, proinflammatory cytokines (of which IL-1β is the key cytokine responsible for the up-regulation of catabolic processes), growth factors, and eicosanoids are released and diffused through the synovial fluid into the cartilage. This induces additional breakdown of cartilage matrix macromolecules. At this stage, the chondrocytes are hyper-responsive to cytokine stimulation because of an increased level of cytokine cell receptors.

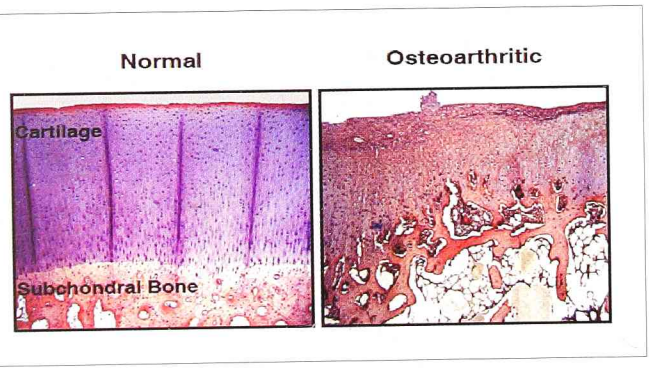


Figure 6

Representative sections of cartilage and subchondral bone from normal and osteoarthritic subjects. In normal, cartilage is thick and subchondral bone is thin. In osteoarthritis, there is a thinning of the cartilage, and the subchondral bone is the site of a number of active morphological and molecular changes which may vary during the evolution of the disease.

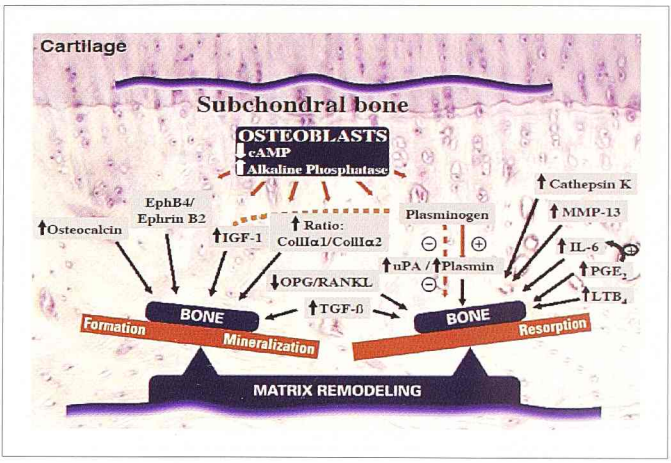


Figure 7
Schematic representation of the major local factors abnormally regulated in osteoarthritis.

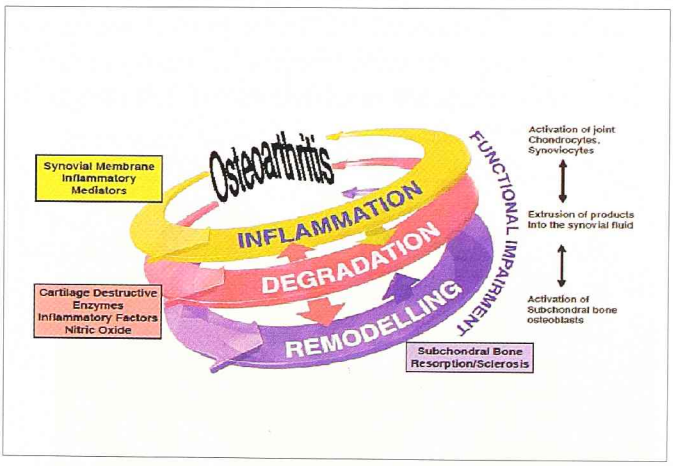


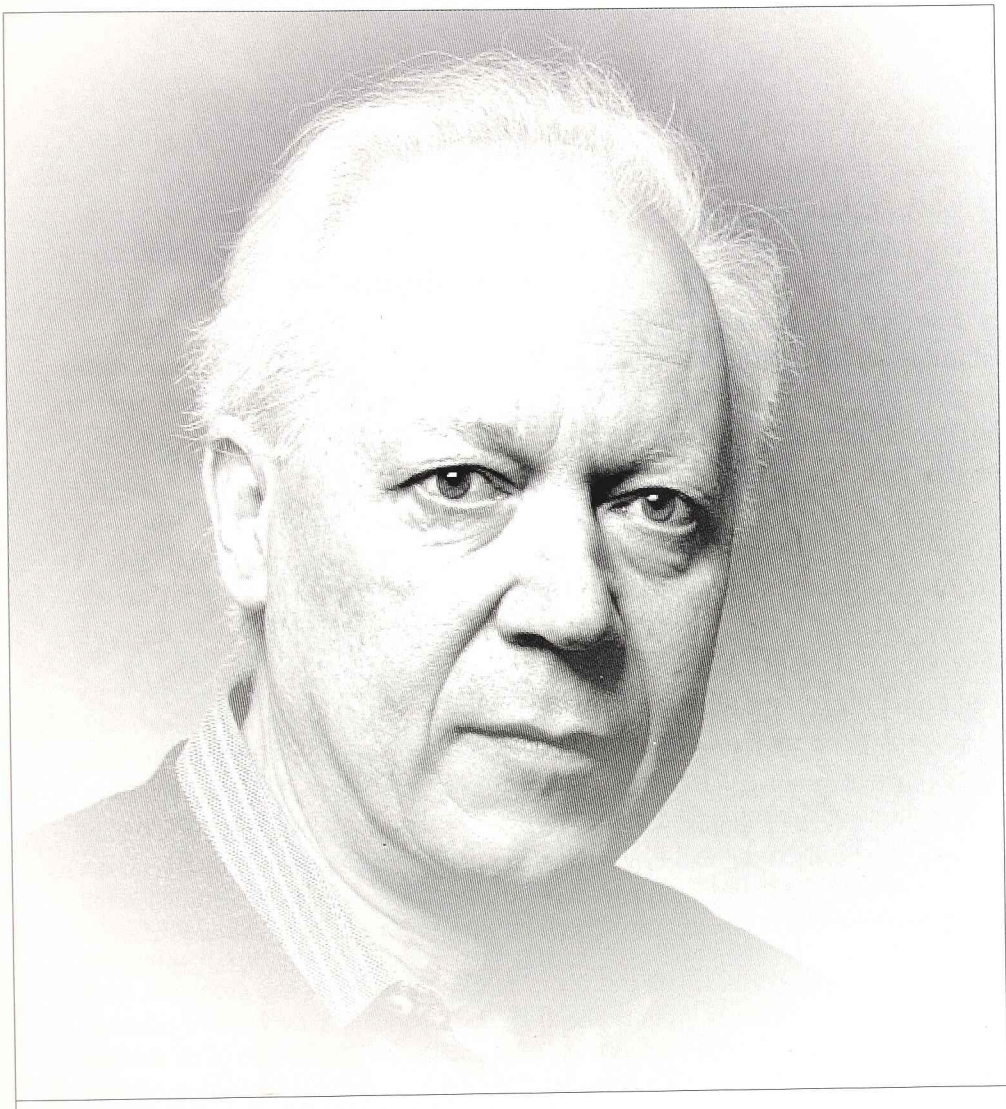
Figure 8
Suggested schematic representation of the pathophysiological events in osteoarthritis. There is now evidence of cross-talk between the joint tissues with diffusion of catabolic factors from the synovial membrane and subchondral bone to cartilage.

WINNERS OF THE 2010 KING FAISAL INTERNATIONAL PRIZE FOR SCIENCE (MATHEMATICS)

The Prize for Science (Topic: Mathematics) has been jointly awarded to: Professors Enrico Bombieri (USA) and Terence Tao (Australia)

Professor Bombieri has made pioneering contributions to various branches of mathematics. His work is characterized by originality, power, and clarity of exposition, addressing fundamental and difficult problems in number theory, algebraic geometry, complex analysis, and minimal surfaces.

Professor Tao is a world-renowned mathematician working in a number of branches of mathematics including harmonic analysis, partial differential equations, combinatorics, number theory, and signal processing. He is known for his highly original solutions of very difficult and important problems and for his technical brilliance in the use of the necessary mathematical machinery.



My journey in the world of mathematics

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Enrico Bombieri

My journey in the world of mathematics

1. The beginning

Often I have been asked the question how to do mathematics and how I became a mathematician. This is a difficult question to answer because there will be as many answers as there are mathematicians in the world. So I will not attempt to set my answer in a general frame but rather I will tell you my personal story, how and why I was attracted to mathematics and what has been my path into it.

We all encounter arithmetic for the first time in elementary school. At the beginning I was struggling with numbers. A note by my teacher in elementary school informed my parents that I was a kid with good behavior in the class, with good profit in everything except that I was "Weak in arithmetic." Well, some time has gone by and today a large part of my mathematical work is in number theory, so I must conclude that there is hope for everyone and that learning mathematics may well be a task not as difficult as one may think.

Things improved when I found at home two books dealing with geometry and mathematics and I started reading them. These books belonged to my father, who was a banker but had always liked mathematics. The first book was a popular exposition by Lancelot Hogben of many interesting concepts and problems, from antiquity to recent times, from explaining Zeno's paradox to the birth of calculus. The second book, by the engineer and mathematician Italo Ghersi, with the title "Entertaining and curious mathematics", was a very readable collection of facts and stories about numbers and geometry, all very accessible to the novice.

The big turning point occurred when my father, during a business trip to London, saw in the window of the University bookstore a book with the title "An Introduction to the Theory of Numbers", by the British mathematicians Hardy and Wright. We started reading it together but my father did not have much time for it, so I took the book, read it from beginning to end and started thinking about prime numbers and diophantine equations. The Pythagorean equation determining right-angle triangles with integer sides, like the famous triangle, known to the Babilonian mathematicians, with sides 3, 4, 5 satisfying $3^2 + 4^2 = 5^2$, is probably the most famous example of diophantine equation. Of course, Fermat's Last Theorem also attracted my attention and I wrote for myself, first a paper on an

extension of Fermat's equation for exponent 5 and then another short paper showing that the equation $m^4 - 5n^4 = 1$ in positive integers has the unique solution $(m, n) = (3, 2)$.

At this point my father thought that it was a good idea to get an expert opinion on what I was doing and Giovanni Ricci, professor of mathematics at the University of Milan, read my papers and asked for an interview. After a thorough exam of my very uneven knowledge of mathematics, he decided to help me to get a thorough preparation in mathematics. So he became my mentor, making sure that I would not miss a basic preparation in algebra, geometry, and analysis. After finishing high school I started my study at the University of Milan with Ricci, having already published a couple of mathematical papers.

2. First encounter: Prime numbers

Number theory and complex analysis were my first interest, especially the theory of prime numbers and of functions of a complex variable.

Prime numbers are the building blocks of integers, with respect to multiplication. Their distribution is very irregular and a superficial look at a table of prime numbers shows no special patterns except for the fact that their density gets thinner and thinner as their size increases. The precise rate at which this phenomenon happens was conjectured by Gauss around 1792 when he was a teenager, namely the number $\pi(N)$ of primes up to N is about

$$\pi(N) = \frac{1}{\log 2} + \frac{1}{\log 3} + \frac{1}{\log 4} + \cdots + \frac{1}{\log N} \asymp \frac{N}{\log N}.$$

It took over a century to obtain the first proof of this statement, the so-called Prime Number Theorem, by Hadamard and De la Vallée Poussin in 1996. The methods of Hadamard and De la Vallée Poussin were entirely based on complex function theory and dependent in an essential way from the fact, not entirely easy to prove, that the solutions of the Riemann equation $\zeta(s) = 0$ always had real part $\sigma < 1$. Successive improvements dealt with the quality of the approximation, although all of them remain very far from the conjecture that the error in the approximation should be not much larger than the square root of the main term. The 'square-root' conjecture is well supported by numerical evidence, as seen in the following table up to a trillion

N	$\pi(N)$	$\pi(N) - \mathrm{li}(N)$	$\sqrt{\pi(N)}$
10	4	−2.2	2.0
100	25	−5.2	5.0
1000	168	−9.7	13.0
10000	1229	−17.2	35.1
100000	9592	−37.9	98.0
10^6	78498	−129.6	280.2
10^7	664579	−339.5	815.3
10^8	5761455	−754.4	2400.3
10^9	50847534	−1701.0	7130.8
10^{12}	37607912018	−38262.9	193927.6

However, the conjecture is equivalent to Riemann's conjecture about the solutions of the equation $\zeta(s) = 0$, where the Riemann zeta function $\zeta(s)$ is a function of a complex variable $s = \sigma + \sqrt{-1}t$ which has a relatively simple definition:

$$\zeta(s) = 1 + \frac{1}{2^s} + \frac{1}{3^s} + \frac{1}{4^s} + \ldots \qquad (\sigma > 1)$$

and defined by analytic continuation for arbitrary s.

This is the celebrated Riemann Hypothesis, formulated by Riemann 150 years ago, that all solutions of the equation $\zeta(s) = 0$ consist of the negative even numbers and an infinite sequence of numbers all of them with real part exactly 0.5. The hard part of the conjecture is the one regarding the complex solutions of the Riemann equation. Even one failure of the conjecture would create huge oscillations of the remainder in the Gauss approximation. Numerical calculations with a network of computers has shown today that the Riemann Hypothesis holds for the first ten trillion solutions of the Riemann equation, a fact that by usual standards should be hugely in favor of the Riemann Hypothesis. However, mathematicians are a fickle bunch of scientists and some still remain skeptical of this evidence. By now, thousands of papers have been written on the assumption that the Riemann Hypothesis is true and the outcome of all this hypothetical work is a coherent web of results, fitting together in a beautiful fabric. So if the Riemann Hypothesis is true it has a lot of significance, while if it is false it means that the world of numbers is not at all what it appears to be.

For this reason, it is the opinion of many mathematicians, including myself, that the Riemann Hypothesis is the most important open question in all of number theory. When I learned for the first time about the zeta function and the Riemann Hypothesis, I, like many other mathematicians, fell under its magic mysterious spell and started studying prime numbers.

The Prime Number Theorem is not easy to prove and a direct elementary proof of it had to wait until 1949, when Erdős and Selberg found it. Selberg's approach in [22] was based on an entirely new ideas and it was natural to see how far one could go studying prime numbers along Selberg's lines. I started working along this path and after a few months I showed in [2] that Selberg's method could be refined to a point which was sufficient for most applications to arithmetical questions. In this paper I introduced a new class of Selberg-type formulas and a sort of calculus for them and this probably was the most interesting part of my work. The real significance of the new ideas introduced came to the surface only later, when in 1977 I applied them to the study of sieves in number theory, in what is called today Bombieri's sieve [3].

Prime number theory, always considered a very abstract part of mathematics has found unexpected practical applications in real life. Today, almost all encripted information on the Internet is provided by security software based on rather subtle properties of prime numbers. It is a good example of what the physicist Wigner called "The irrational usefulness of mathematics".

3. First explorations: Complex analysis

In my early studies I had to learn functions of a complex variable and complex analysis, one of the pillars of modern mathematics. The topic of my Ph.D. thesis was in this field, the Bieberbach conjecture in conformal mapping. A conformal map preserves angles but not necessarily lengths; its historical origin is in making geographical maps for nautical use.

The statement of the conjecture is simple enough: If $w = f(z)$ is a one-to-one conformal map of the unit disk $|z| < 1$ of the complex plane to the complex plane, normalized so that the origin $z = 0$ is mapped to $w = 0$ and has no distorsion at the origin, then the coefficients a_n of its expansion in Taylor series

$$f(z) = z + a_2 z^2 + a_3 z^3 + a_4 z^4 + \dots$$

satisfy the bound $|a_n| \leq n$ for all n; equality holds for

$$f(z) = \frac{z}{(1-z)^2} = z + 2z^2 + 3z^3 + 4z^4 + \dots .$$

Such functions are called univalent. In my thesis I studied univalent functions 'near' the suspected extremal $z/(1-z)^2$ and found a new approximate formula for the coefficients a_n. From this, I proved that $|a_6| \leq 6$ for these univalent functions, thus a 'local' version of the Bieberbach conjecture for the sixth coefficient.

Three years later in 1966, I was able to complete this program and proved in [4] the validity of the 'local' Bieberbach conjecture for all coefficients. The original Bieberbach conjecture remained open for quite a while, but at last was solved in the affirmative by de Branges in 1985, using an entirely new original method.

4. The Cambridge year: Moving to geometry and number theory

Although I continued to work on a few other questions in complex function theory, my interests in mathematics had shifted in other directions. After attending a mathematical conference I was invited by Harold Davenport to come to Cambridge to study with him for a year. Ricci simply said "Go. He is the best!" Davenport was very much interested in the arithmetic over finite fields, which is simpler than ordinary arithmetic but which has important applications in various fields of mathematics, ranging from number theory to geometry to probability and, today, even to computer science and communication theory. The tools needed come from geometry and p-adic analysis, where p is a prime number. In p-adic analysis the distance between two rational numbers is small if their difference has numerator divisible by a high power of p. So for example the 5-adic distance between 0 and 5 is $1/5 = 0.2$, between 0 and 25 is $1/25 = 0.04$, but between 0 and 6 it is 1. The p-adic geometry is also weird in some respect and for example any point inside a circle (not on the boundary) is a center of that circle. It is a remarkable fact that one can develop a notion of continuous and differentiable functions and calculus working with this unusual type of distance, but the consequences are equally remarkable.

In Cambridge, under the guide of Davenport and Swinnerton-Dyer I learned a lot of algebraic geometry, of arithmetic over finite fields, and of p-adic analysis. Starting with a paper by Dwork [19] that proved the rationality of the Zeta functions associated to algebraic varieties of any dimension over finite fields, in [5] I extended the results to the larger class of L-functions. This proved to be very useful for arithmetic applications.

My stint in Cambridge was very important, firstly because I found this overall area of research to be like a virgin territory to be explored and secondly because of another event. At that time I attended a number theory conference in France and gave a presentation of my work extending Dwork's results. In the audience there was Jean-Pierre Serre, one of the greatest mathematicians of all times, who that year had given a whole course of his own on Dwork's theory. Serre did not say anything after my presentation but instead took me for a walk and asked many

questions. (Now I understand it was to check how much algebra and geometry I knew.) Two months later I received a letter from the mathematician Zariski of Harvard, to join an elite Summer School in Algebraic Geometry in Woods Hole, Massachusetts, which was going to be held in July 1964. This event changed my approach to mathematics, since afterwards geometry became a very big part of my thinking.

Only many years later I learned that it was Serre who worked to include me, at the very last minute, in the list of invitees.

5. Back to number theory: The large sieve

In 1965 Davenport came to Milan to give a series of lectures about his new work on cubic equations in many variables. We decided to work together on a difficult problem of arithmetic, namely to show that there were many consecutive prime numbers with a small difference. By the Prime Number Theorem, the average gap between the nth prime p_n and the next prime p_{n+1} is about $\log p_n$. Probability considerations lead to conjecture that the density of gaps such that

$$p_{n+1} - p_n < a \log p_n$$

is precisely $1 - e^{-a}$. Thus the prime gaps sequence is very irregular but still is expected to follow what is called a Cauchy–Poisson probability distribution.

We attacked the problem assuming at the beginning a generalized Riemann Hypothesis for Dirichlet L-functions and showed that there was a positive percentage of gaps smaller than $0.5 \log p_n$, which was far better than what was previously known. Davenport then made the key observation that the full force of the generalized Riemann Hypothesis was not needed; it was sufficient to show that the expected approximation consequence of the generalized Riemann Hypothesis, held on average. The large sieve, a technique invented by Linnik and Rényi in the 40's, was the tool to use.

The difficulty of the large sieve is in obtaining a good estimate of the size of the error term. I noticed that the structure of the error term itself was reminiscent of the main term and wondered whether one could study it in the same way. After thinking about this crazy idea for a few minutes I found a trick that would do exactly what I wanted! It then dawned on me that the problem of estimating the error term had been solved. In [6] this gave a sharp form large sieve, far more general than before, and directly applicable to many other questions.

Although I was not aware of this at the time, Roth [21] a little before me had obtained an improvement of the large sieve of similar strenght but less flexible for

applications, and the Russian mathematician Vinogradov [23] at about the same time also had proved a slightly weaker result for the distribution of primes in progressions. Nowadays, the main theorem about the distribution of primes in the average in arithmetic progressions is called the Bombieri–Vinogradov Theorem. Undoubtedly, the subject was ripe for progress. Since then, much more work has been done by many mathematicians in extending the large sieve method. The all-important extension to modular forms was obtained by Deshouillers and Iwaniec [18] in 1982.

The joint paper with Davenport [8] on differences of prime numbers also was the starting point for further research. The best result was obtained two years ago when Goldston, Pintz, and Yildirim [20] were able to prove that the gap between consecutive primes infinitely often becomes smaller than $a \log p_n$, no matter how small the positive constant a is. The Bombieri-Vinogradov Theorem is essential for the proof.

This is not the end of the problem and much more work needs to be done. I worked with John Friedlander and Henryk Iwaniec for some time with the goal of extending the range of the Bombieri–Vinogradov Theorem, in a series of papers starting with [11]. The extension of the large sieve to deal with modular forms as in Deshouillers and Iwaniec [18] plays a big role here. There are new interesting applications of these deeper results, but as yet one has to put restriction on the type of arithmetic progression one can control, so the range of applications is not as general as in the original Bombieri–Vinogradov Theorem.

Obtaining such an extension without restrictions is an important problem. For example, even a small improvement of the original form of the Bombieri–Davenport Theorem implies, after the work of Goldston, Pintz, and Yildirim, that the difference of consecutive primes remains bounded infinitely often. This would be a spectacular result, but achieving it belongs to the number theory of tomorrow.

6. Analysis: Minimal surfaces

After Milan I moved to Pisa, Italy, where there was a flourishing mathematical school, led by Aldo Andreotti in geometry while Guido Stampacchia and Ennio de Giorgi were the leaders in partial differential equations. Partial differential equations are vital in modeling natural phenomena. A well-known example is the Laplace equation for minimum kinetic energy:

$$\operatorname{div}(\nabla f) = \frac{\partial^2 f}{\partial x_1^2} + \frac{\partial^2 f}{\partial x_2^2} + \cdots + \frac{\partial^2 f}{\partial x_n^2} = 0,$$

first encountered by Laplace in his study of Saturn's rings. Equations of this type always arise when we have an unconstrained physical system in stable equilibrium; they can be derived from the fundamental principle that total energy reaches a minimum whenever stable equilibrium has been reached.

However, gravitational and kinetic energy are not the only ones that drive physical phenomena and another classic example arises when we considered surface tension. Surface tension occurs at the interface of different media and the associated minimal surface equation

$$\operatorname{div}\Big(\frac{\nabla f}{\sqrt{1+|\nabla f|^2}}\Big) = 0$$

is a very interesting equation. In dimension 2 it describes a surface $y = f(x_1, x_2)$ of minimum area with a prescribed fixed boundary. Physically, the surface of a soap film is of minimum area and follows an equation of this type. Not unexpectedly, the minimal surfece equation is important in the study of foams.

Of course, mathematicians study such equations in greater generality, also in space of arbitrary dimension. This equation is quite difficult to study because of its non-linearity: the solution affects the behaviour of the equation. Fortunately for mathematics, de Giorgi in [17] had already developed the basic tools needed to study equations of this type.

I became part of de Giorgi's team and with him and Mario Miranda [10] we solved the first main problem of the theory, showing that all solutions of the minimal surface equation, in any dimension, were smooth, withouts pits or wrinkles.

It was known that a solution of the minimal surface equation extending everywhere in every direction had to be a hyperplane if the dimension was 2 (Bernstein and others) or 3 (de Giorgi [16]) and it had been conjectured that this might be true in any dimension. The question was related to another one, namely whether there existed cones of minimal area. One evening, during a casual conversation with de Giorgi the subject switched to the problem of minimal cones and in the early morning an idea for attacking the problem surfaced. This took form in the next few days, with Enrico Giusti joining forces, and eventually we found the surprising solution detailed in [9]. There were no singular minimal cones in Euclidean space of dimension at most 7, but there were singular ones in space of dimension 8 or more. The hyperplane conjecture was true in Euclidean space up to dimension 8, but false in dimension 9 or more, a totally unexpected result.

Minimal surface theory remains today a very active area of mathematics.

7. The Institute years

In 1977 I joined the Faculty at the Institute for Advanced Study. Besides continuing my preceding studies, I got interested in new questions at the interface between arithmetic and geometry. In algebraic geometry, I worked on classification problems and in algebra I contributed to the classification of finite simple groups by completing the proof of the uniqueness of simple finite groups of Ree type in [15].

The discovery of irrational numbers goes back to Pythagoras, who showed that the diagonal of a square is not commensurable with the side. The proof by Lindemann in 1982 that the number π (the ratio of the area of a circle to the square of the radius) cannot be the solution of an algebraic equation with rational coefficients put an end to the quest, lasted for over 2000 years, of squaring the circle: There is no construction of π within Euclidean geometry. The theory of diophantine approximation and of transcendental numbers deals with questions of this type and in particular how well a given number can be approximated by rational numbers or algebraic numbers.

My main contribution to the field consists in a new method to obtain effective lower bounds for the approximation of algebraic irrationals by rational numbers. It is a famous theorem of Roth that if α is a real algebraic number of degree at least 3 (the simplest example is $\alpha = \sqrt[3]{2}$) then for any fixed $\varepsilon > 0$ the inequality

$$\left|\alpha - \frac{p}{q}\right| < \frac{1}{q^{2+\varepsilon}}$$

has only finitely many solutions. This result has many applications, not only to number theory but also to other areas of mathematics, for example to the study of dynamical systems. Unfortunately, Roth's method cannot determine the solutions of such an inequality and is 'ineffective' on this point. The problem of getting an 'effective' proof of Roth's theorem remains today one of the big outstanding problems of number theory. A deep method of Baker [1] was for a long time the only way to attack the problem of effectiveness. After a series of papers, in 1993 I finalized a completely different approach for reaching effectiveness [7], with results comparable with those obtained with Baker's method and even better in many cases. Rather than being mutually exclusive, sometimes the two methods can be combined together with good effect.

My most recent work at the Institute has been in the field of arithmetic geometry. Besides writing a substantial monograph on the subject with Walter Gubler [12], I have developed jointly with David Masser and Umberto Zannier [13], [14],

a new theory for multiplicative relations among solutions of diophantine equations. This theory is in full development at the present time.

8. Conclusion

In my career as a mathematician I have been lucky enough to find great mentors in Ricci, Davenport, Serre, Andreotti, and de Giorgi. Without them, my work would not have been possible.

Mathematics is a monolithic science, without revolutions, growing slowly through the contributions of many, year after year and century after century. Mathematics is a science with no boundaries, it is the science of logic and logical truth. I like to compare the work of a mathematician to the work of an artist, the only difference is that instead of working with paint, or bricks, or sounds, or words, he works with ideas using the tool of pure logic. The constructions of mathematics remain for ever.

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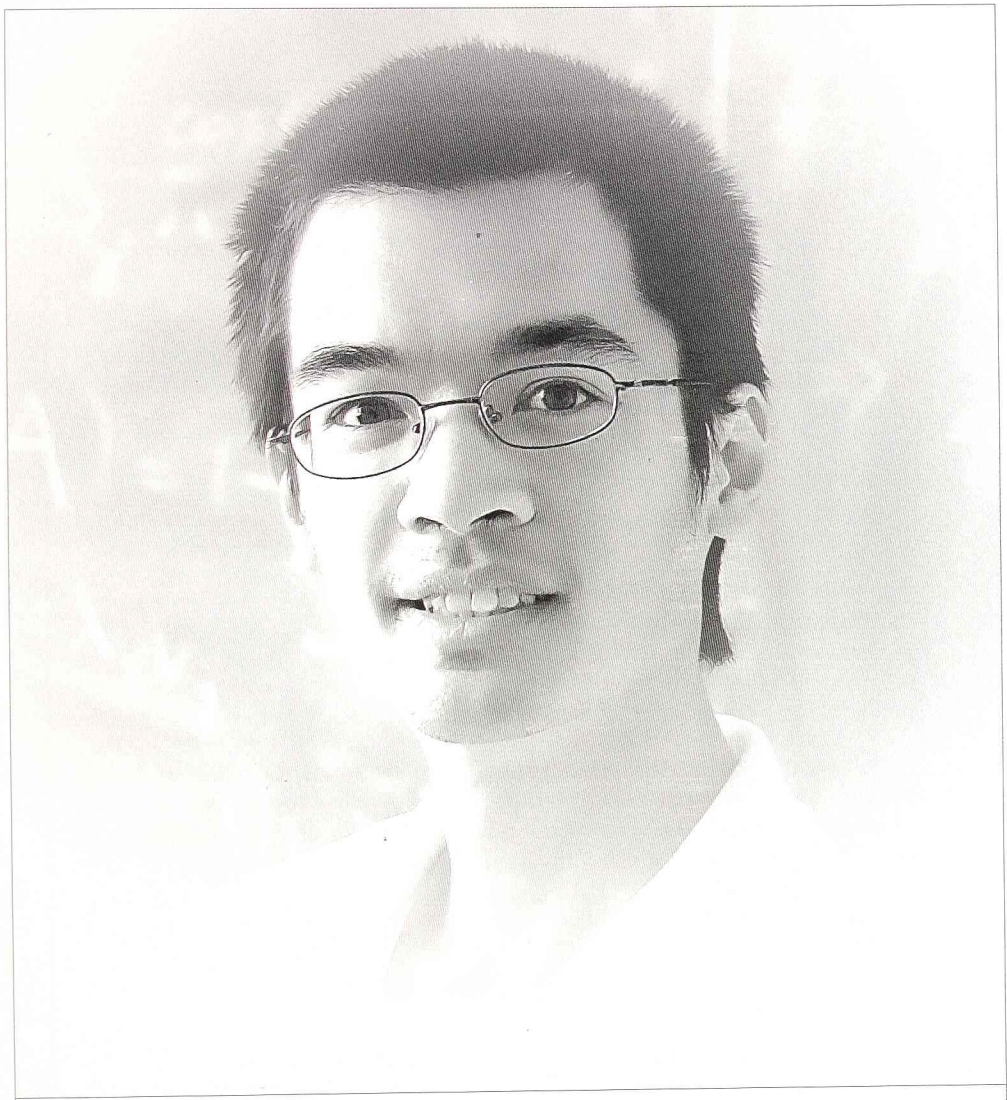

Universality in random matrix models

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UNIVERSALITY IN RANDOM MATRIX MODELS

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ABSTRACT. A survey of some recent progress on understanding the *universality phenomenon* in random matrix theory.

1. THE INVARIANCE PRINCIPLE

The world is a complex place, and so one would think that complex mathematical models, with many independent variables, are needed to describe it. However, it is a curious phenomenon that the cumulative effect of many independent variables in a system becomes *more* predictable as the number of variables increases, rather than less.

In fact, in many cases, the exact behaviour of each individual variable becomes essentially *irrelevant* (except perhaps for one or two key parameters); one gets the same observed behaviour for the system as a whole regardless of what the individual components are doing.

This phenomenon is sometimes referred to *universality*, or the *invarance principle*; it occurs in both the physical world and in mathematical theories. Here are two well-known examples of universality in the physical world:

Example 1.1 (Statistical mechanics). The behaviour of a system of N particles with respect to changes in energy, volume, etc., would seem almost impossible to compute precisely when N is huge, requiring precise knowledge of the system and its interactions. But, in fact, in the limit $N \to \infty$, the behaviour can be controlled by just a handful of key parameters, such as *temperature* and *entropy*.

Example 1.2 (Benford's law). 30% (or more precisely, $\log_{10} 2 \approx 30.1\%$) of all statistics start with the digit 1! For instance, 30% of all cities have populations beginning with 1, 30% of all word frequencies in a language begin with 1, 30% of all stock prices begin with 1, etc. This is despite the fact that different statistics are governed by completely different laws of nature.

And here are two well-known examples from probability theory:

Example 1.3 (The law of large numbers). If $X_1, \ldots, X_n$ are n random variables that are *independent and identically distributed* (iid), then the empirical average $\frac{X_1+\ldots+X_n}{n}$ converges (both in probability, and in the almost sure sense) to the mean μ of any one of the variables X_i in the limit $n \to \infty$.

Example 1.4 (The central limit theorem). Continuing the above example. the distribution of the normalised deviation $\sqrt{n} \times (\frac{X_1+\ldots+X_n}{n} - \mu)$ converges as $n \to \infty$ to the *normal distribution* $N(0, \sigma^2)$, where σ^2 is the *variance* of any of the X_i.

In the above two examples, we saw that the only two features of the random variables that are relevant in the limit $n \to \infty$ are the mean and variance; it does not matter, for instance, whether these variables are continuous or discrete.

This is a model case of a more general principle, which we may informally state as follows:

Principle 1.5 (Invariance principle). *In many cases, the behaviour of a combination $F(X_1, \ldots, X_n)$ of iid random variables $X_1, \ldots, X_n$ for n large does not depend very much on the actual distribution of the X_i, but only on some key parameters of that distribution, such as mean and variance.*

In the law of large numbers and central limit theorem, F was a *linear* combination of the X_i. But the principle also extends to some important *nonlinear* combinations as well, in particular to spectral statistics of random matrices, to which we now turn.

2. Random matrix models

We will consider a number of random matrix models, which can be either discrete or continuous:

- **iid random matrices** These are $n \times n$ matrices $A = (x_{ij})_{1 \leq i,j \leq n}$, where the x_{ij} are iid random variables, normalised to have mean zero and variance 1. Key examples include the *Bernoulli matrix ensemble* (random sign matrices), in which $x_{ij} = \pm 1$ with an equal probability of each, and the real and complex *gaussian matrix ensembles*, in which the x_{ij} have either the real or complex gaussian distribution with the indicated mean and variance.
- **Wigner symmetric matrices** These are similar to iid random matrices, but the coefficients x_{ij} are now assumed to be

real and symmetric ($x_{ij} = x_{ji}$). The x_{ij} are now iid just for $1 \leq i \leq j \leq n$. Examples include the *symmetric Bernoulli matrix ensemble* ($x_{ij} = \pm 1$) and the *gaussian orthonormal ensemble* (GOE) (x_{ij} are real gaussians, though for technical reasons we give the diagonal entries twice as much variance as the off-diagonal ones).

- **Wigner Hermitian matrices** These are similar to Wigner symmetric matrices, but now the coefficients x_{ij} are complex and Hermitian ($x_{ij} = \overline{x_{ji}}$). The x_{ij} are iid on the upper triangular region $1 \leq i < j \leq n$ and on the diagonal $1 \leq i = j \leq n$, but can have different distributions in the two regions. For instance, in the *gaussian unitary ensemble* (GUE), the x_{ij} are complex gaussian for $1 \leq i < j \leq n$ but real gaussian for $1 \leq i = j \leq n$. (In all cases, the coefficients have mean zero and variance 1.)

Many other random matrix models are of interest, but to focus the survey we shall only discuss these particular ones. In particular, we will not discuss the rich theory of invariant ensembles and their relation with orthogonal polynomials; for this we refer the reader to the recent text of Deift and Gioev.

Discrete random matrices arise naturally in numerical linear algebra (as a model for rounding errors), while continuous random models arise naturally in various physical settings (e.g. spectra of atoms).

The gaussian models are particularly tractable due to their *group invariance* properties. For instance, the GUE ensemble is invariant under conjugations by the unitary group $U(n)$, and GOE is similarly invariant under the orthogonal group $O(n)$.

Given an $n \times n$ random matrix A_n, we let $\lambda_1(A_n), \ldots, \lambda_n(A_n)$ be the n (generalised) *eigenvalues* of A_n. In symmetric or Hermitian models, these eigenvalues will be real, and we can order them: $\lambda_1(A_n) \leq \ldots \leq \lambda_n(A_n)$. In the iid random matrix model, the eigenvalues will be complex and unordered; but one can then define the *singular values* $0 \leq \sigma_n(A_n) \leq \ldots \leq \sigma_1(A_n)$ (the eigenvalues of $(A_n A_n^*)^{1/2}$).

Eigenvalues and singular values are related to many other important matrix quantities, such as the determinant

$$|\det(A_n)| = \prod_{i=1}^{n} |\lambda_i(A_n)| = \prod_{i=1}^{n} \sigma_i(A_n)$$

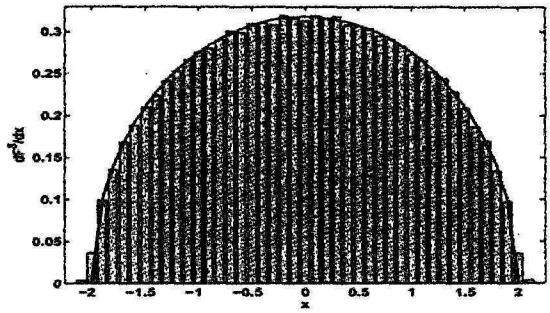

FIGURE 1. Normalised eigenvalue distribution of a random 100×100 GUE matrix. (Image by Alan Edelman.)

or the trace

$$\mathrm{tr}(A_n) = \sum_{i=1}^{n} \lambda_i(A_n).$$

For this and other reasons, it is of interest to understand the distribution of these numbers.

3. UNIVERSALITY

In accordance with the invariance principle, many facts about the distribution of eigenvalues and singular values of random matrices seem to be *universal* in the limit $n \to \infty$ - they do not depend on the precise matrix model used. Thus, for instance, continuous and discrete random matrices often have the same statistics in the high-dimensional limit.

This phenomenon has been observed numerically for many decades. More recently, rigorous explanations of this phenomenon have been found (and there is still work to be done in some cases).

Many distributions of empirically observed eigenvalues (e.g. atomic spectra) obey the same statistics as random matrix models. The universality phenomenon provides a partial explanation of this fact.

The most well-known example of universality is for the bulk distribution of eigenvalues of Wigner matrices:

Theorem 3.1 (Wigner's semicircular law). *For a Wigner symmetric or Hermitian random matrix A_n, the normalised eigenvalues $\frac{1}{\sqrt{n}}\lambda_1(A_n), \ldots, \frac{1}{\sqrt{n}}\lambda_n(A_n)$ are asymptotically distributed according to the* semicircular distribution $\frac{1}{2\pi}(4-x^2)_+^{1/2}\,dx$.

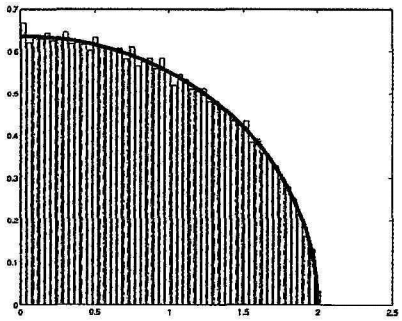

FIGURE 2. Normalised singular distribution of a 100×100 iid gaussian matrix. (Image by Antonio Tulino.)

This result is illustrated in Figure 1. It was first established in the special case of the GOE ensemble by Wigner[49], and then repeatedly generalised; for instance, the version above was established by Pastur[26]. There are now several important proofs of this result, as well as numerous variants, generalisations, and refinements.

There is an analogous law for bulk distribution of singular values of iid matrices:

Theorem 3.2 (Quarter-circle law). *For an iid random matrix A_n, the normalised singular values $\frac{1}{\sqrt{n}}\sigma_1(A_n), \ldots, \frac{1}{\sqrt{n}}\sigma_n(A_n)$ are asymptotically distributed according to the* quarter-circle distribution $\frac{1}{\pi}(4-x^2)^{1/2}1_{[0,2]}(x)\,dx$.

This result is illustrated in Figure 2. It is a special case of the *Marchenko-Pastur law*[23], which gives a universal law for the eigenvalues of covariance matrices such as Wishart random matrices. Again there are many proofs, variants, and generalisations of this basic result.

As for the bulk distribution of eigenvalues of iid matrices, we have

Theorem 3.3 (Circular law). *For an iid random matrix A_n, the normalised eigenvalues $\frac{1}{\sqrt{n}}\lambda_1(A_n), \ldots, \frac{1}{\sqrt{n}}\lambda_n(A_n)$ are asymptotically distributed according to the* circular law $\frac{1}{\pi}1_{x^2+y^2\leq 1}\,dxdy$.

This result is illustrated in Figure 3. It was established for gaussian matrices by Mehta[24]. For the general case, the initial breakthrough is due to Girko [15], which was then built upon by many authors [1], [2], [16], [17], [25], [18], [41], [4], [43]; the result as stated above is due to the author, Vu, and Krishnapur [43].

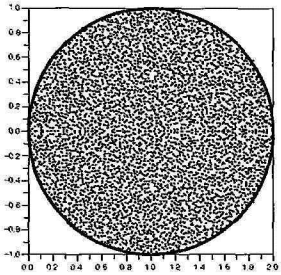

FIGURE 3. Normalised eigenvalue distribution of a 5000×5000 iid Bernoulli matrix. (Image by Phillip Wood.)

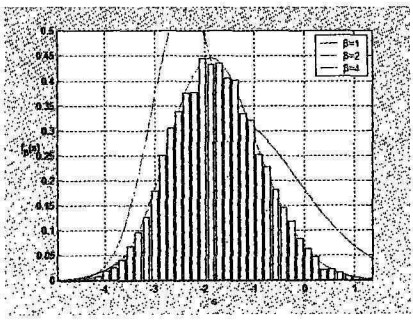

FIGURE 4. Normalised largest eigenvalue of GUE matrices. (Image by Alan Edelman et al..)

Instead of the bulk distribution, one can ask for finer information about individual eigenvalues, which is harder. A typical result in this direction is

Theorem 3.4 (Tracy-Widom law). *For a Wigner Hermitian matrix A_n with additional hypotheses, the normalised largest eigenvalue $(\lambda_n(A_n) - 2\sqrt{n})n^{1/6}$ is asymptotically distributed according to the* Tracy-Widom law $F_2(x)\,dx = \det(1-K)\,dx$, *where K is the integral operator with* Airy kernel $\frac{\mathrm{Ai}(x)\,\mathrm{Ai}'(y) - \mathrm{Ai}'(x)\,\mathrm{Ai}(y)}{x-y}$.

This result is illustrated in Figure 4. This law was established for GUE and GOE matrices by Tracy and Widom[47], [48]. It is not yet known what the minimal hypotheses on A_n need to be. However, the law has been established for symmetric decaying distributions [34], [35], [36], [37], [33], [21] and for decaying distributions with vanishing third moment [46].

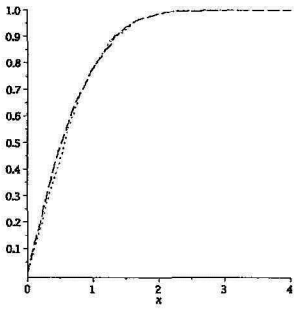

FIGURE 5. Cumulative distribution of normalised singular values of one thousand 100 × 100 Bernoulli and gaussian iid matrices. (Image by Phillip Wood.)

The Tracy-Widom law, which deals with the largest eigenvalue or singular value, is a result about the "soft" edge of the spectrum. More recently, universality results have begun appearing for the "hard" edge, and in particular for the least singular value:

Theorem 3.5 (Least singular value law). *For a real iid random matrix A_n with sufficiently many moments finite, the normalised least singular value $\sqrt{n}\sigma_n(A_n)$ is asymptotically distributed according to the law $(1+x)e^{-x-x^2}\,dx$.*

This law is illustrated in Figure 5. This law was first established for GOE by Edelman[6], and in the generality considered above by the author and Vu in [44], which builds upon work on bounding the least singular value in [29], [30], [31], [32], [40], [39], [42].

In addition to progress in understanding the hard and soft edges of the spectrum, there has been much recent progress in understanding the internal structure of the bulk of the spectrum also. For instance, we have

Theorem 3.6 (GUE spacing). *For a Wigner Hermitian matrix A_n with sufficiently many moments finite, the normalised gap $\sqrt{n}(\lambda_{i+1}(A_n)-\lambda_i(A_n))$ for a randomly chosen $1 \leq i \leq n$ is asymptotically distributed according to the* ***Gaudin distribution*** $\frac{d^2}{dx^2}\det(1-K)_{L^2([0,x])}$, *where K has the* sine kernel $\frac{\sin \pi(x-y)}{\pi(x-y)}$.

This law is illustrated in Figure 6. Established for GUE by Gaudin and Mehta[24]. Progress towards more general Wigner matrices began with a breakthrough of Johansson[19], which was followed by many further works [7], [8], [9], [10], [11], [12], [46], [13], [20], [45]; the result as stated above is established in [45].

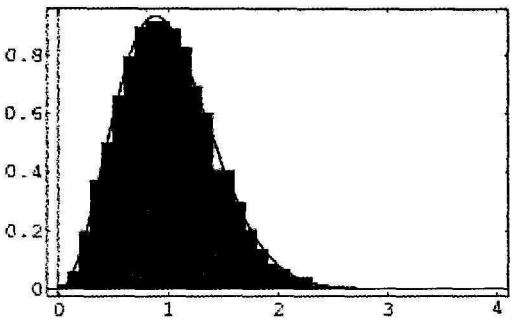

FIGURE 6. Cumulative distribution of eigenvalue spacings of five hundred 100×100 GUE matrices. (Image by Peter Kostelec.)

4. PROOF TECHNIQUES

A remarkably large number of techniques from a wide array of mathematical fields go into the proofs of these facts. We will primarily discuss just two key tools:

- **Linear algebra identities** that relate eigenvalues and singular values to more computable quantities, such as moments, resolvents, determinants, and distances.
- The **Lindeberg exchange strategy**, based on exchanging an arbitrary distribution with a gaussian one of the same mean and variance.

However, one should point out that many other tools are used too, such as

- Symmetry reductions and explicit formulae, Lie groups
- Asymptotics of orthogonal polynomials, Riemann-Hilbert problems
- Free probability
- Dyck paths, combinatorics
- Stieltjes transform, complex analysis
- Concentration of measure, high-dimensional geometry
- Inverse Littlewood-Offord theorems, additive combinatorics
- Estimation of eigenvalues by random sampling
- Dyson Brownian motion
- Ornstein-Uhlenbeck process
- Cauchy interlacing law
- ...

4.1. **Linear algebra identities.** A surprising amount of mileage can be gained from basic linear algebra identities such as

$$\operatorname{tr}(A^k) = \sum_{i=1}^n \lambda_i(A)^k$$

$$\operatorname{tr}((A^*A)^k) = \sum_{i=1}^n \sigma_i(A)^{2k}$$

$$\log|\det(A - zI)| = \sum_{i=1}^n \log|\lambda_i(A) - z| = \sum_{i=1}^n \log \sigma_i(A - zI)$$

$$\log|\det(A)| = \sum_{i=1}^n \log|\operatorname{dist}(X_i, \operatorname{span}(X_1, \ldots, X_{i-1}))|$$

To give a simple example, let $A = (x_{ij})_{1 \leq i,j \leq n}$ be an $n \times n$ symmetric Bernoulli matrix. Then

$$\operatorname{tr}(A^2) = \sum_{i=1}^n \sum_{j=1}^n |x_{ij}|^2 = n^2$$

and thus

$$\sum_{i=1}^n \lambda_i(A)^2 = n^2.$$

For non-Bernoulli matrices, one has to use the law of large numbers to obtain a similar conclusion; thus we see that linear universality results, such as the law of large numbers, can be used to deduce nonlinear universality results, such as moment bounds for spectral distributions.

4.2. **The Lindeberg strategy.** The Lindeberg strategy splits the task of proving a universal law into two distinct parts:

- **The gaussian case** Show that the law holds when all the underlying random variables are gaussian. This is usually achieved by algebraic means, using all the special properties of gaussians (e.g. the group symmetries of the gaussian ensembles).
- **Invariance** Show that the limiting distribution is unchanged when non-gaussian random variables are replaced by gaussian random variables. This is usually achieved by analytic means, showing that the error terms caused by this replacement are asymptotically negligible compared to the main terms.

We illustrate this with Lindeberg's classic proof[22] of the central limit theorem. Specifically, suppose one wants to prove the central limit theorem for the normalised average $S = \frac{X_1 + \ldots + X_n}{\sqrt{n}}$ of iid variables

$X_1, \ldots, X_n$ of mean zero and variance 1. We replace the X_i by gaussians Y_i of the same mean and variance, and consider the normalised average $T = \frac{Y_1+\ldots+Y_n}{\sqrt{n}}$.

Under mild decay assumptions on X (e.g. subgaussian decay), it will suffice to show that the moments $\mathbb{E}S^k$, $\mathbb{E}T^k$ asymptotically match as $n \to \infty$ for each $k = 0, 1, 2, \ldots$. (The decay assumptions can be removed afterwards by a truncation argument.)

When one expands out the moments $\mathbb{E}S^k$, one gets a linear combination of terms of the form $\mathbb{E}X_{i_1}^{a_1} \ldots X_{i_j}^{a_j}$. The corresponding moment $\mathbb{E}T^k$ has a similar expansion with the X_i replaced by Y_i.

When all the exponents $a_1, \ldots, a_j$ are at most 2, then the term for X and the term for Y are identical (because the X_i, Y_i are iid and have matching moments to second order).

The terms when one or more of the a_i exceed 2 can be shown to be asymptotically negligible. Putting all this together, one establishes the central limit theorem.

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