RECENT ADVANCES IN RHEUMATOLOGY

EDITED BY

W. WATSON BUCHANAN
W. CARSON DICK

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RECENT ADVANCES IN RHEUMATOLOGY

（内部交流）

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PREFACE

Rheumatology within the last decade has emerged from being the Cinderella of medicine to one of the most exciting and challenging specialties within internal medicine. At least ten new diseases have been described in the last decade and since almost one-third of patients presenting to rheumatologists in 1975 still remain undiagnosed and uncategorised, this indicates that there is scope as yet for the description of at least as many diseases in the next ten years. This is a particular challenge to the clinical rheumatologist working in the field of day-to-day patient care. The rapid advance in rheumatology in the last decade owes a great deal to the contributions of pharmacologists, immunologists, biorheologists and other basic scientists and of course to orthopaedic surgeons. Perhaps the keynote of the success of research into rheumatology has been collaboration, and this is focused in such mutually educational conferences as the W.H.O. Symposium on Pathogenetic Mechanisms in Rheumatology in London and the Future Trends in Inflammation conference first held in Verona and more recently in Paris. At these meetings experts from widely disparate fields contributed to the corpus of knowledge which hopefully will ultimately be applicable to patients with rheumatoid arthritis.

Any book on recent advances in rheumatology written at the moment suffers from the inevitable drawback that it will be out of date very quickly. Furthermore, it would be absolutely impossible to attempt to cover every aspect of this burgeoning field and accordingly we have chosen to select those topics in which advances are to an extent at least becoming solidified or topics which are of particular relevance to clinical rheumatology.

The first section is devoted in the main to subjects of a pathogenetic nature and the second section is devoted to subjects which have direct relevance to clinical practice. This is of course not a complete division by any means but does provide some balance.

In Chapter 1 of Part I, a subject which has been rather left behind in the headlong rush towards immunological frontiers, namely osteoarthrosis, is given a new lease of life with provocative discussion by Dr

Radin. Chapter 2 is devoted to amyloidosis, a subject whose relevance to rheumatology is at present contentious. What is not in doubt is that the disease is of great interest to rheumatologists and the pathogenesis of amyloidosis is reviewed by Dr Cohen. Chapter 3 is addressed to dermatomyositis and polymyositis and is written from the UCLA rheumatology unit which has more experience with these diseases than any other unit in the world. In that chapter a proposed new classification and diagnostic criteria for these diseases is suggested. Systemic lupus erythematosus is one of the diseases which is particularly exciting to clinical rheumatologists today in view of recent research findings into its pathogenesis. Both the pathogenesis and the clinical features of this disease are reviewed by Drs Whaley, Hughes and Webb. In recent years there has been increasing interest in the role of immunosuppressive and cytotoxic drugs in the management of connective tissue disease and Drs Levy and Whitehouse review in Chapter 5 some laboratory and clinical test situations which may be relevant to the production of less toxic congeners of the presently used drugs. The possibility of producing 'soft immunosuppressants' or Zog (Zeloberflächengifte) was first suggested by Dr Whitehouse. Drs Fudenberg and Wells summarize some of the more recent concepts of the pathogenesis of 'autoimmune' disease and discuss the possible role of suppressor T cells, whereas in Chapter 7 the role of biogenic amines, kinins, complement and prostaglandins are reviewed by Drs Zeitlin and Grennan.

The flood of proposed new anti-rheumatic drugs, any or none of which may ultimately be proven to have activity in the disease, poses the clinician with a major problem of assessment. Currently used methods of assessment are reviewed in Chapter 1 of Part II* and the drugs themselves are reviewed in the current management of rheumatoid arthritis in Chapter 2.

The role of orthopaedic surgery, in particular of replacement of the hip joint in osteoarthrosis, is unchallenged as the major therapeutic advance in medicine in the last decade and the more recent developments in the surgery of the joints of the upper and of the lower limb joints are reviewed in Chapters 3 and 4. Possibly no other medical speciality has been so involved with the departments of ophthalmology in our hospitals and in Chapters 5 and 6 the ocular hazards in connective tissue diseases and scleritis and episcleritis are reviewed. Clinical rheumatologists are grateful for the involvement of their ophthalmological colleagues since complications occurring in the eye are of a particularly frightening nature.

No book on recent advances in rheumatology would be complete

*In separate volume

today without a mention of the present status of tissue typing with relevance to the seronegative arthritides. Professor Wright has conducted large scale family studies in these diseases and the final chapter is devoted to a summary of the present position of HLA typing and the implications of genetic factors to the seronegative arthritides.

Finally, we would like to express our appreciation to all of the authors involved and to the publishers for their contribution to this text. Publication of medical textbooks is becoming a more and more difficult task year by year as costs rise and the publication of this edition of Recent Advances has been particularly complicated by the fact that the authors are drawn from centres of rheumatology on the West and East coasts of America as well as the United Kingdom and Australasia. From our point of view we think that the exercise has been well worth while and we hope that the readers will derive as much enjoyment out of reading the text as we did from editing it.

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OSTEOARTHROSIS AS A STATE OF ALTERED PHYSIOLOGY*

Eric L. Radin *Michael M. Ehrlich*
Charles A. Weiss *Howard G. Parker*

The joint changes of osteoarthrosis are a well defined process distinct from the basic inflammatory arthritities such as rheumatoid arthritis and gout. Osteoarthrosis is characterized by an apparent wearing out of the joints, associated with a sometimes acute but mainly chronic inflammatory reaction, and is characterized pathologically by an attempt at healing which is unsuccessful. Frequently there are obvious causes—any process which leads to an incongruity or a deficiency of the mechanical properties of the joint tissue (trauma, infection, certain metabolic diseases and inherited disorders) will eventually lead to joint degeneration. However, in the majority of cases there is no obvious cause. Because of the increased incidence of both clinically apparent and silent joint degeneration with age it was assumed, until recently, that joint degeneration was simply an ageing phenomenon. Considerable research has been carried out to attempt to define ageing changes in articular cartilage that might lead to wear. Several decades of such research lead to the inescapable conclusions that joint degeneration is not naturally a process of ageing (Sokoloff, 1969). Although a clear occupational incidence of specific joint degeneration has been established, the lack of a correlation with life-long physical activity is striking and the distribution of the joint involvement, with almost total sparing of certain joints, is puzzling (Radin, Paul and Rose, 1972).

Considerable effort has recently been expended to attempt to relate joint degeneration to some metabolic aberration of chondrocytes. Such efforts reflect the great interest in molecular biology, especially since the mid-part of this century, and have demonstrated a molecular aberration in several other arthritic disorders. Although considerable information has been accumulated as to the subsequent inflammatory, chemical and enzymatic destruction of articular cartilage in osteoarthrosis, no information as to the inciting cause of these processes from a molecular or chemical standpoint has been forthcoming

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(Sokoloff, 1969). Cellular activity in degenerating cartilage has also been studied and demonstrates both reparative and degenerative activity (Makin et al, 1971).

Since the joints clearly function as articulating mechanical bearings it is logical to presume that an increased stress might come from a failure of lubrication, which could be on the basis of some altered synovial metabolism. Although joint lubrication had been studied in the 1930's, it was not until 1967 that direct coefficient of friction measurements could be made on animal joints at all times in an oscillatory cycle (Linn, 1967). In the past such measurements were only averages of many cycles or were calculated from the decay of a pendulum and this made distinguishing the various lubrication mechanisms extremely difficult. Improved measurement ability came along shortly after Charnley had repopularized the concept that synovial fluid acts in joints in a chemical way, as a surface or boundary lubricant (Charnley, 1959) much as does teflon in a frying pan, and after the experiments of McCutchen, which suggested the importance of cartilage interstitial water in maintaining separation of loaded cartilage surfaces (McCutchen, 1962). The last several years have seen a plethora of lubrication modalities suggested for joints and it is only now that enough new evidence has been accumulated to allow a clear picture of joint lubrication to emerge.

Animal diarthrodial joints are amazingly resistant to wear from rubbing. Animal joints subjected to in vitro simulated oscillation, under the maximal loads that the subchondral bone can support, have shown themselves to be wear-free (Radin and Paul, 1971). The diarthrodial joint has an enviable low frictional resistance by engineering standards (Table 1). It is obvious that the joint surfaces must be kept separated, even under the rigors of heavy loading, for the cartilage not to wear. There is now almost universal agreement that joints are

Table 1 Comparative coefficients of friction

	Lubricant	Coefficients of Friction	
Steel on steel bearing	oil	0·210	
All metal total hip replacement	synovial fluid	0·120	(Weightman, et al, 1972)
Bronze on steel bearing	oil	0·072	
Plastic on metal total hip replacement	synovial fluid	0·060	(Weightman, et al, 1972)
Teflon on teflon bearing	none	0·050	
Metal femoral head replacement on acetabular cartilage	synovial fluid	0·032	(Rydell, 1966)
Ice skate on ice	none	0·030	
Rubber on steel bearing	water	0·004	
Articular cartilage on articular cartilage	synovial fluid	0·002	(Radin and Paul, 1971)

lubricated by a fluid film and small amounts of cartilagenous interstitial fluid. This fluid is squeezed out of the cartilage under compression in the areas peripheral to the zone of impending contact (Radin and Paul, 1972) (Fig. 1). This self-pressurized lubrication is of extreme importance because its efficiency increases as the pressure

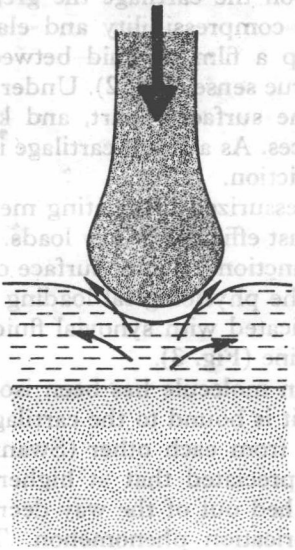

Figure 1 As cartilage is compressed, fluid tends to flow out of it. Fluid flow through cartilage is blocked by the relatively impervious subchondral plate and by cartilage's inherently low permeability.

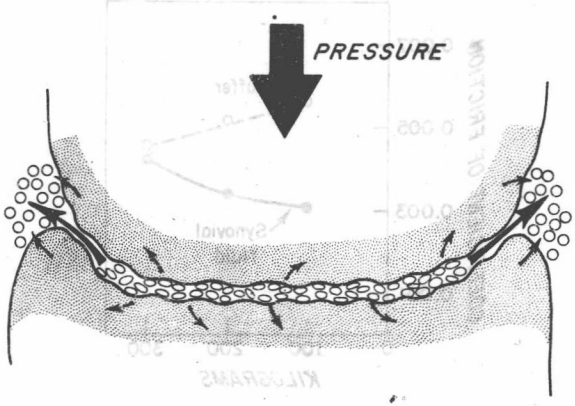

Figure 2 The joint lubricant is trapped in a 'squeeze film' between two loaded cartilage surfaces. Pressurization of the cartilagenous interstitial fluid caused by cartilage compression, keeps the lubricant from flowing into the cartilage. The elasticity of the cartilage in a moving joint causes stenosis at the edges of the contact zone. It is almost impossible to force the squeeze film out, even under high loads over prolonged periods of time.

increases. Articular cartilage is not very permeable; fluid flows through it with great difficulty (Edwards, 1967). The underlying subchondral plate is relatively impervious to fluid flow in the adult and thus when the cartilage is compressed its interstitial fluid is pressurized and much of the load on the cartilage is borne by this fluid attempting to escape. The greater the load on the cartilage the greater the pressure in its interstitial fluid. The compressibility and elasticity of the articular cartilage tends to trap a film of fluid between the two surfaces, a 'squeeze film' in the true sense (Fig. 2). Under high loads this trapped squeeze film keeps the surfaces apart, and keeps them from being subjected to shear forces. As a result cartilage in the presence of water does not wear from friction.

Because the self-pressurized lubricating mechanism depends upon pressurization, it is least efficient at low loads. Under such conditions another mechanism functions, that of surface or boundary lubrication. At the lower end of the physiological loading range the coefficient of friction of joints lubricated with synovial fluid is considerably below that obtained with saline (Fig. 3).

A large glycoprotein molecule has been isolated from the synovial fluid which acts as if it is bound to the cartilage surface and separates the articular surfaces from each other (Swann and Radin, 1972). It can be intuitively appreciated that at higher loads these molecules would tend to be pushed out of the way decreasing the effectiveness of the boundary lubrication phenomenon. Thus the advantage of having self-pressurized lubrication available to take over under such conditions.

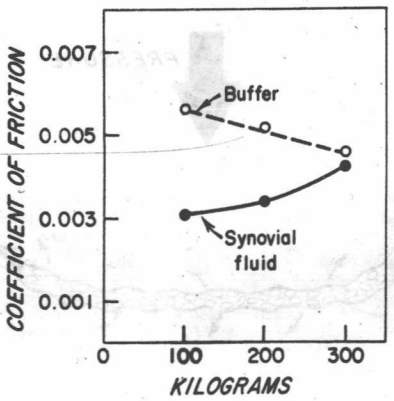

Figure 3 Coefficient of friction in bovine metatarsal phalangeal joints as a function of applied stress (40 cpm). Within the physiological range, note that the lubricating advantage of synovial fluid viz-a-viz buffer which exists at the lower stress values diminishes as the stress increases. This means that at low stress the boundary effect predominates. The diminution of the coefficient of friction with saline lubricant with load is typical of pressurized (hydrostatic) lubrication.

The glycoprotein lubrication fraction which acts on cartilage surfaces is hyaluronate-free (Swann and Radin, 1972). No lubricating function for hyaluronate in cartilage on cartilage lubrication has been established. Hyaluronate does act as the boundary lubricant for the synovial membrane, which in most joints makes up the largest moving surface area (Radin et al., 1971). Furthermore, from a clinical standpoint, it is probably the resistance of the soft tissues that is responsible for morning stiffness and most of the clinically apparent stiffness. This lubrication by hyaluronate of synovial tissue is molecular size and weight dependent. Rheumatoid hyaluronate falls well within the functional range the system requires (Swann et al, 1974). In recent experiments in our laboratories it has been impossible to detect an action of hyaluronate in protecting articular cartilage from wear. Hyaluronidase treated synovial fluid, whose viscosity is close to that of water, lubricates cartilage-on-cartilage systems just as effectively as does untreated viscous synovial fluid, and for equally long periods of time (Swann et al, 1974). Hyaluronate would appear to function purely as a soft-tissue lubricant.

The source of the non-hyaluronate glycoprotein lubricating fraction cartilage on cartilage system is under investigation in our laboratories in collaboration with David Swann. The similarity of this lubricating molecule to cartilagenous metabolites is intriguing and it may be that the articular cartilage itself provides at least a moiety of this lubricating fraction. It may turn out that synovial membrane is only metabolically responsible for producing hyaluronate, the substance necessary for its own lubrication.

As for the other proposed joint lubricating mechanisms, no evidence exists that cartilage acts as a filter for hyaluronate. Furthermore thick films of hyaluronate on the articular cartilage surfaces would not potentiate their lubrication. Thus no 'boosted' mechanisms (Longfield et al, 1969) are likely. Elastohydrodynamic effects (Dowson, 1967) would act to potentiate the squeeze film but can no longer be considered a major lubricating mechanism. 'Weeping lubrication' (McCutchen, 1962) is also no longer tenable as fluid cannot come out of cartilage into the zone of impending contact where the instantaneous pressure would be maximal.

While the frictional force that articular cartilage is subjected to is extremely low, the longitudinal load across articular surfaces is quite high. Most of this force is generated by contraction of the muscles spanning the joints (Meyer, 1849). For the joint the important consideration is force per unit area or stress. Since joints in the upper extremities have smaller contact areas than the weight-bearing lower extremity joints, which bear both body weight and muscular contraction, it is reasonable to assume that the joints in the upper extremities

are subjected to the same degrees of stress as those in the lower extremities.

In vivo the nature of joint loading is intermittent. Static loading is not a part of the physiological condition and all of our activities from picking up a pencil and writing to ambulating, from chewing to getting dressed, all intermittently load the joints. Very high impulsive loads (impacts) will fracture bone. This is an efficient way of absorbing energy and acts to protect the joints. It's of interest that patients with easily fractured bones (osteoporosis, osteopetrosis and osteomalacia) have a decreased incidence of degenerative joint disease (Foss and Byers, 1972; Kessel, 1974). The classical study of X-rays of the necks of the high divers of Acapulco (Schneider, Papu and Alvarez, 1962) showed that if the divers broke their plunge into the water with their thumbs locked over their heads, their cervical spines were within normal limits. If they did not break their fall in this manner, the radiographs showed multiple fractures. Arthritis can always develop secondary to incongruities caused by intra-articular or mal-united fractures but apparently in this group arthritis did not develop initially. There is a higher incidence of degeneration of the spine in coal miners who work in a stooped position rather than standing (Lawrence, 1955; Caplan, Freedman and Connelly, 1966), in the feet of ballet dancers and soccer players (Brodelius, 1961), in the elbows and shoulders of pneumatic drill operators (Hunter, McLaughlin and Perry, 1945) and in the elbows of baseball pitchers and boxers (Woods, Tullos and King, 1973).

Impulsive loads can cause cartilage to degenerate both in vitro and in vivo (Simon, Radin and Paul, 1972; Radin et al, 1973). In both instances the articular cartilage shows degenerative changes within a rather rapid period of time (Fig. 4 and). Since cartilage is obviously susceptable to repetitive impulsive loading, which constitutes the physiological norm for activities of daily living, mechanisms obviously exist to protect articular cartilage from impulsive loading. The shock absorbing mechanisms for diarthrodial joints are both active and passive. Passively gross fracture of bone is the most efficient mechanism, but does not occur in normal bone except under impact (very high loads delivered rapidly) conditions. In vitro cartilage is worn away within two–three days in rabbit knees subjected to continuous physiologically reasonable impulsive loading. Ultra microscopic signs of cartilage fibrillation can be detected within three days (Fig. 5a) in the knees of rabbits subjected in vivo to short daily periods of impulsive loading in which one leg of adult rabbits was impulsively loaded with a physiological load of $1\frac{1}{2}$ times the animal's body weight at 40 cycles per minute for 40 minutes each day. There is a significant increase in the number of chondrocytes at this time