

Title page

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A clinician's perspective on emerging concepts in Osteoarthritis

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ABSTRACT

Osteoarthritis as a disease that has been known since man assumed bipedal status. Superimposed on epidemic of obesity, it is expected to become the fourth most common cause of disability in elderly⁽¹⁾. For many years it has been classified under non-inflammatory conditions and was described as disease caused by 'wear and tear' until the recent research into genomics followed by proteomics, made it clear that OA is much more than a simple aging process^(1,2). It involves not only the cartilage, but also the bone, synovium, ligaments and muscles. There are three important steps in pathogenesis of OA. First step is the damage to cartilage which may occur due to an injury, mal alignment, overuse or obesity. Second step involves activation of inflammatory pathways following the injury. Various cytokines like IL-1, IL-6, IL-8, IL-12, TNF- α , prostaglandins, leukotrienes have been implicated in the pathogenesis of OA leading to increased activity of proteases like MMPs. The available inhibitors of proteases like TIMP-1, TIMP-2 are overwhelmed, resulting in net degradation. The third step is repair which tries to undo the damage but in the process, produces structurally altered joint which further perpetuates the process of damage and inflammation. Replacement of collagen 2 with collagen 1 and unregulated growth in form of osteophytes are some of the examples in this context.

Early diagnosis is a prominent agenda for a clinician. However, the diagnosis of OA remains delayed; because symptoms appear late, we have no reliable serological markers and x-rays remain insensitive tool apart from having poor co-relation with the severity of disease. A focused search for markers of damage to joint or that of

inflammation specific to OA may help. The stepwise and systematic targeting of proposed mediators of the disease is the logical next step. The first step is preventing damage to cartilage, which is already being taken care of and includes exercise to reduce weight & muscle strengthening exercises. The second step is to block the inflammatory pathways; we already have NSAIDs & steroids which block some aspects of inflammation. But none of them act as 'DMARDS' which can put a halt on never ending process of OA; they only give symptomatic relief. The cytokines targeted in animal models have been IL-1, TNF- α , and the results have been encouraging as far as IL-1 modulation is concerned⁽³⁻⁵⁾. The third step at which intervention can be done is to correct the abnormal repair. IGF-1 & TGF- β pathways have been targeted in animal models and results again have been encouraging. With better understanding of pathogenesis of OA, we can hope to be able to stop its relentless progression.

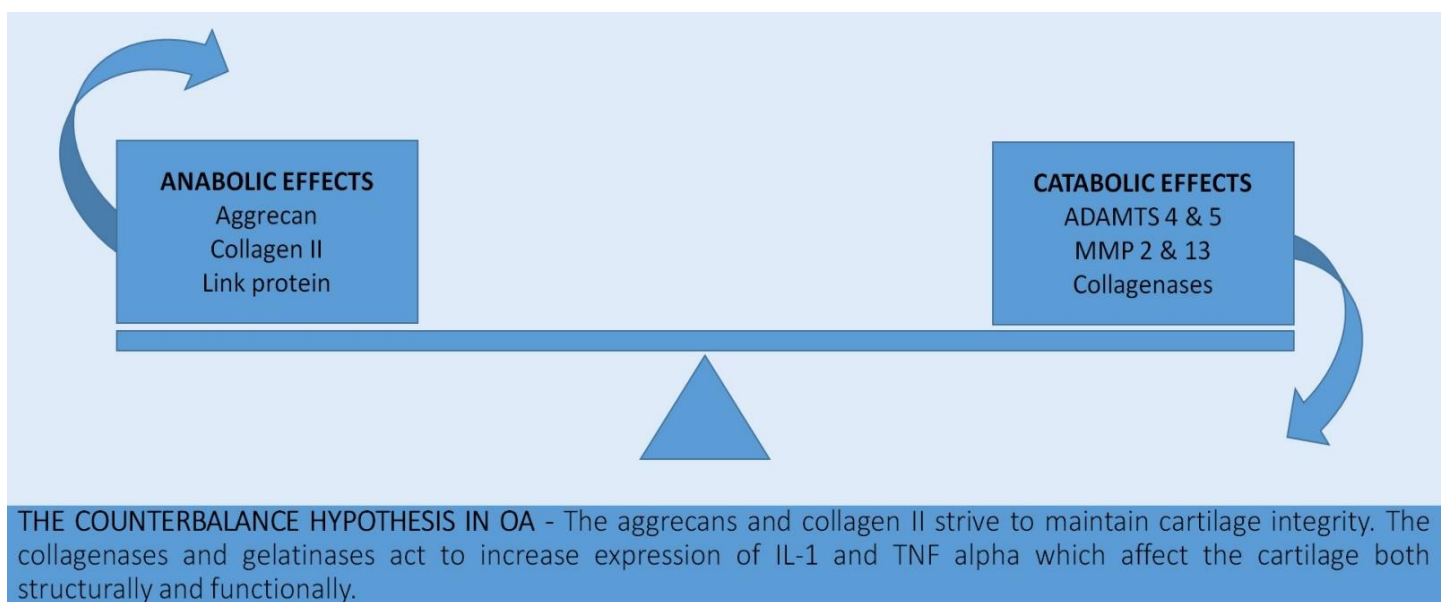
INTRODUCTION

As the obesity epidemic rages on in the Indian subcontinent, Osteoarthritis remains a cause of considerable morbidity in our country. It is the most common rheumatologic disease with some estimates suggesting a 42% prevalence in the elderly population ⁽¹⁾ The Rotterdam study found a 67 % prevalence of Hand OA in women aged over 55 years. According to another publication, OA was the principal diagnosis for inpatient hospital stays in adults 45 to 64 years of age with an increase of 151% in the rate of stays per 10,000 population. There has been a considerable increase in its incidence, with a 13% increase in OA related knee replacements in the past 20 years⁽⁶⁾. Its growing incidence and its significant impact on ambulation and mobility, is associated with a formidable personal, social and financial impact.

DEFINITION OF OSTEOARTHRTIS*	
Clinical	Pain and stiffness with limited and painful range of motion, crepitus, Heberden or Bouchard's nodes in the hand. If radiographic criteria met, then the term <i>Symptomatic OA</i> is used.
Radiological	Identification of a definite osteophyte with or without joint narrowing on plain radiograph.(<u>Kellgren</u> Lawrence grading system)
Pathological	Degeneration of the joint cartilage with various degrees of exposure of articulating bony surfaces

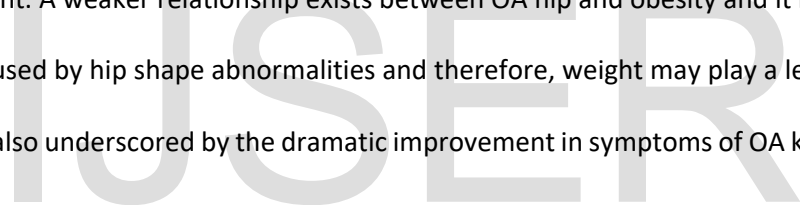
Hochberg M, Silman A, Smolen J, Weinblatt M, Weisman M. Rheumatology. 6th ed. 2015.

Osteoarthritis is a chronic degenerative disorder of varied etiology characterized by pathological changes in the articular cartilage, sub-chondral bone, and synovial membrane. Loss of joint space, subchondral bony sclerosis, subchondral cysts and deformity ensue as OA emerges as a disease of not only cartilage, but also bone, synovium, ligaments, tendons, meniscus, muscle and nerve tissues⁽⁷⁾. The ongoing joint malfunction in OA affects all structures in the joint and is essentially a failure of the total joint⁽⁸⁾. These joints typically are knees, hips, hands, spine and feet. The classification of OA may be as per distribution, as generalized or localized. However, a more commonly accepted classification is based on the supposed etiology, in the absence of which it is deemed primary OA. Secondary OA may be due to anatomic defects (SCFE or chondrodysplasias), metabolic disorders (onchrosis or hemochromatosis), trauma or previous inflammatory arthritis. This review aims at a closer look at the pathogenesis of OA, with a focus on the emerging concept of targeting the inflammatory mediators that are critical to the development of this disease. OA can be defined clinically , radiographically, or pathologically and the choice of definition can substantially affect the above mentioned prevalence estimates⁽⁸⁾. For the purposes of this review, we limit ourselves to the discussions of symptomatic OA, before we delve



THE COUNTERBALANCE HYPOTHESIS IN OA - The aggrecans and collagen II strive to maintain cartilage integrity. The collagenases and gelatinases act to increase expression of IL-1 and TNF alpha which affect the cartilage both structurally and functionally.

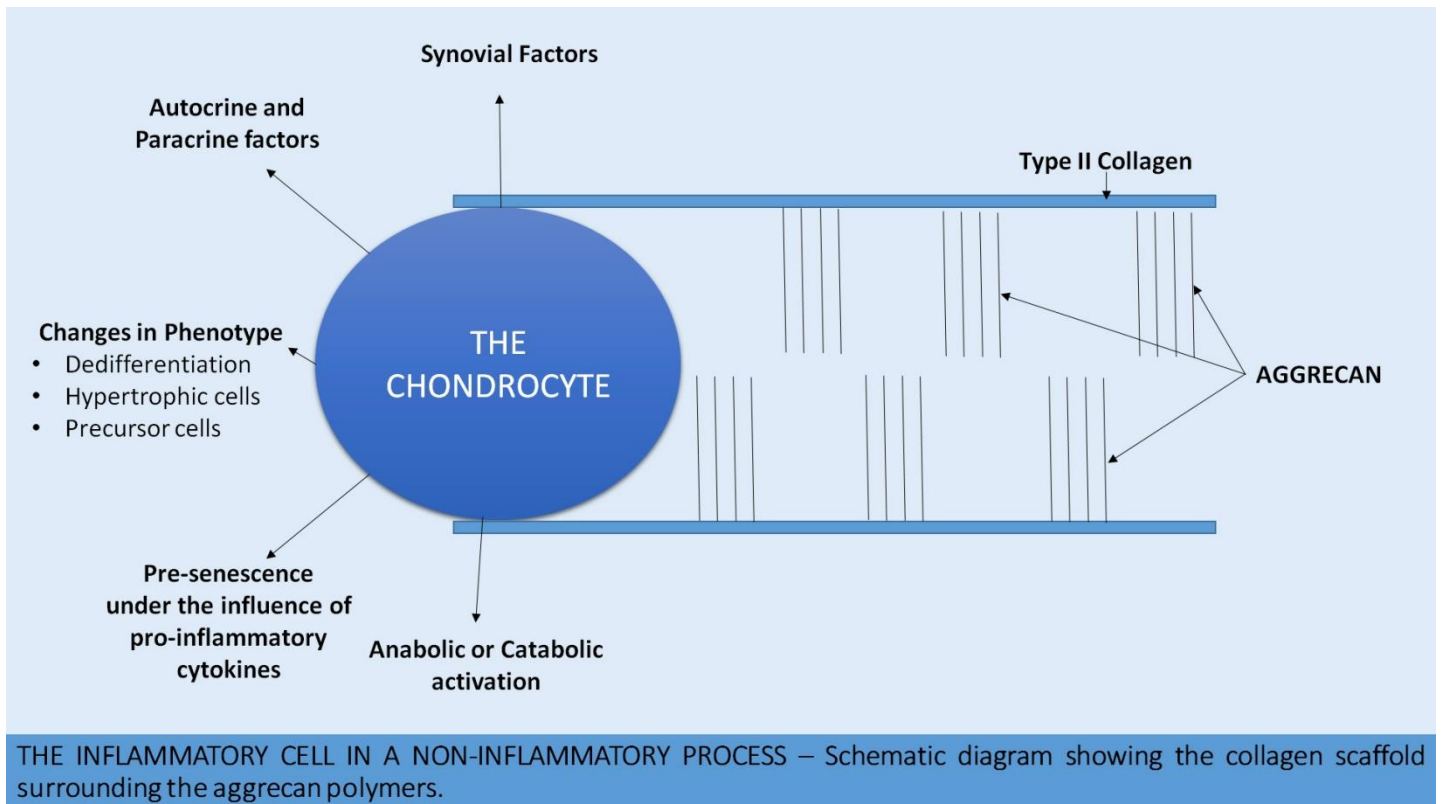
into the pathology and prospective targets of this condition. It is well known that there exists a lack of congruence between radiographic findings of the OA and clinical findings. Up to 60% of individuals with radiographic OA knee, may not complain of pain. Therefore, when viewed in unison, the presence of symptoms and radiographic evidence seems to be a logical starting point for a case definition. Analysis of the risk factors of this conditions would go a long way in the implementation of disease modifying agents, if at all, Systemic factors which affect joint vulnerability include age, female gender, race, genetic susceptibility and nutritional factors. Intrinsic joint risk factors include misalignment, proprioceptive weakness and previous damage, which includes trauma (e.g. ACL tear) or surgery (e.g. meniscectomy). The loading factors acting on the joint include obesity and injurious physical activities, such as contact sports. The presence of nutritional deficiencies need to be underlined, with Vitamin D being implicated recently in the progress and eventual outcome of OA knee. Vitamin K deficiency was suggested as the corrective measure in reducing joint space in established RA in one study. Obesity increases the risk of developing OA. There has been a demonstrable increase in the incidence of OA knee in patients who are obese or very overweight. A weaker relationship exists between OA hip and obesity and it is postulated that this is so because OA hip is often caused by hip shape abnormalities and therefore, weight may play a lesser role. The relationship between weight and OA is also underscored by the dramatic improvement in symptoms of OA knee patients who undergo bariatric surgery.



The effect of physical activity on the development of OA has been a matter of controversy. In the simplest terms, this association varies with specific activity and stage of disease. For instance, marathon runners are at a high risk of developing early onset osteoarthritis, usually between ages 30 and 40. People with jobs which require use of specific muscle and joint groups, such as laborers, are at risk of developing OA in these areas, thereby illustrating the effect of overuse in the genesis of OA. Furthermore, players with injuries, who continue to play are also at a additional risk, thereby highlighting the dual role of previous damage and overloading. Although the exact mechanism remains unknown, high bone mineral density increases the risk of OA.

PATHOGENESIS

Many hypotheses about the underlying pathology in OA have been proposed. Genetic defects and structural genes give rise to severe and premature OA in families Animal models represent an important adjunct to study the disease process in OA^(9, 10). A variety of mechanisms have been used to induce OA including but not limited to chemical, mechanic and genetic. There has been only little progress in defining an all-encompassing 'universal model' for the condition. Therefore, it is more prudent to consider a multi-factorial and multi-model scheme to define the pathological process.



MANAGEMENT OF PATIENTS WITH HIP OR KNEE OSTEOARTHRITIS	
Non-pharmacologic interventions	Pharmacologic interventions
• Patient education	• Acetaminophen
• Aerobic and Strengthening exercises	• NSAIDS
• Weight loss	• Topical capsaicin
• Insoles and braces	• Opioid analgesics
• Acupuncture	• Diacerein
• Yoga	• Glucosamine sulphate
• Low energy lasers	• Chondroitin sulphate
• Patellar taping	• Intra-articular steroids and hyaluronic acid
• Transcutaneous electrical nerve stimulation	• Oral steroids

CONVENTIONAL THERAPEUTIC OPTIONS IN OA

The articular cartilage is a highly specialized and uniquely designed biomaterial. ⁽⁸⁾ The scarce resident cells - the chondrocytes – are part of an essentially avascular, aneural structure. The basic micro-structure consists of a collagen scaffold, which forms the relatively inflexible part of the articular cartilage. The shock absorbing capabilities come from the aggrecan layer, which are bound by the collagen and prevent the former’s excursion beyond physiological and functional limits. Under compression, the water molecules move out of the matrix. When the deforming forces are withdrawn, the water rushes back, like into a sponge, resuming the structure and tenacity of the micro-environment.

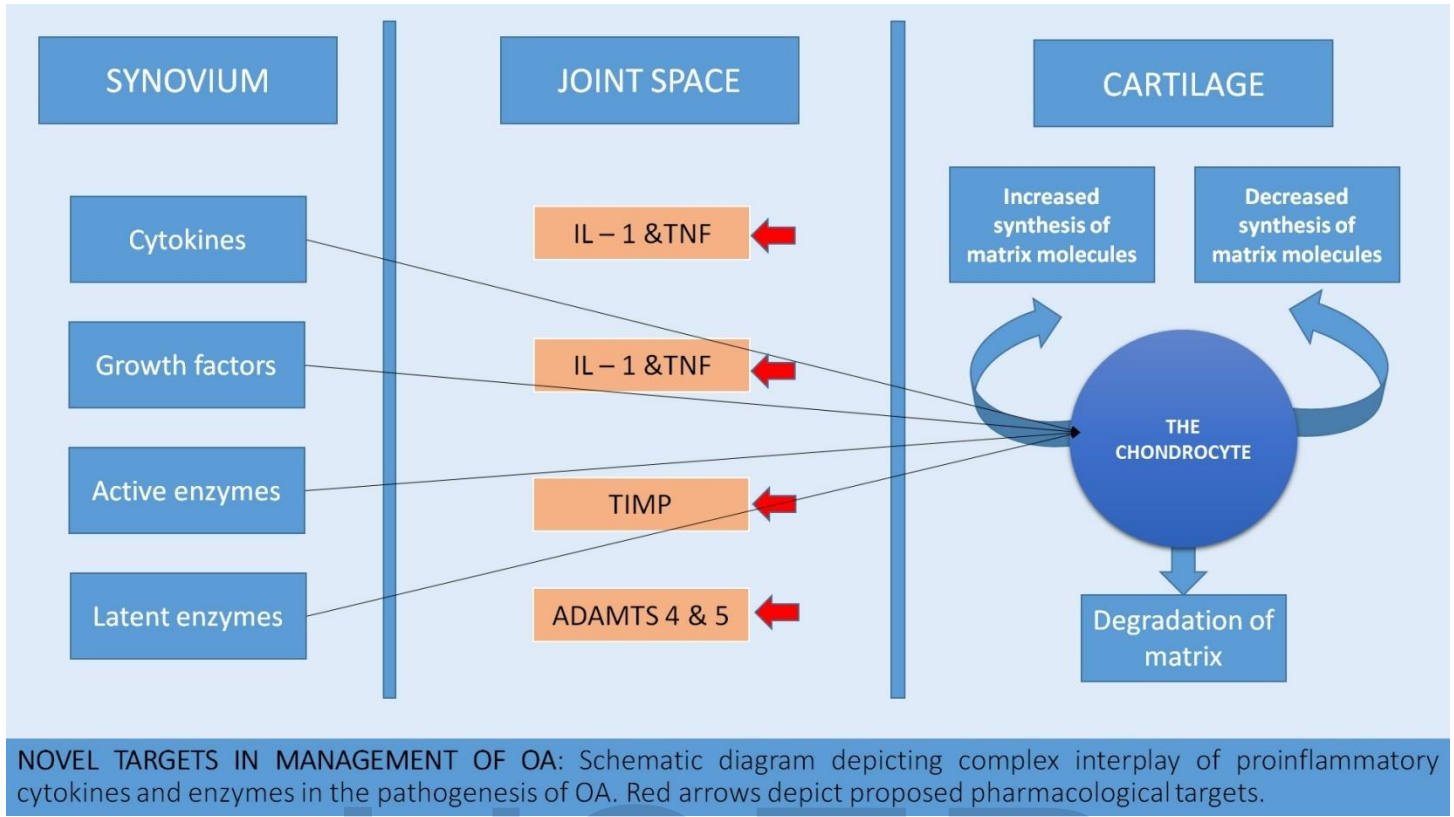
With this basic collagen bound aggrecan model, the joint essentially must function for a lifetime. While the collagen only undergoes minor changes, the aggrecans and the proteoglycans are variably modified through a series of processes.

Matrix degrading enzymes that destroy the collagen network and proteoglycans constitute the biggest threat to the cartilage. These enzymes constitute the ADAMTS (a disintergrin and metalloproteinase with thrombospondin motifs) family. ADAMTS-4 and ADAMTS-5 are among the favored molecules attributed in this process. MMP-13 and MMP-2 are also good candidates⁽¹¹⁻¹³⁾. The balance between the anabolic factors (aggrecan, collagen II and link proteins) and catabolic factors (MMP, ADAMTS 4 & 5) form the basis for the counterbalance hypothesis, which simply alludes to the loss of this

balance, which is central to the pathogenesis of Osteoarthritis. The effect of enzymes and other variables start at the most superficial area of the articular cartilage (the progression zone) and proceed sequentially inward.

The matrix and its functional ability changes with age⁽¹⁴⁾. The cartilage is prone to micro fracture and undergoes molecular disintegration. Accumulation of glycosylation end products also contribute to this process, which makes age, the most prominent risk factor in the development of OA. The senescence theory of OA which postulates that chondrocytes become senescent through a diffuse aging process which is essentially due to cumulative DNA damage. This process is termed cellular senescence, as opposed to replicative senescence which occurs in cells with mitotic capacity, due to telomere damage. Apoptosis rarely seemed to occur in chondrocytes, rather, they seemed to suspended in pre-apoptotic or para-apoptotic state which change with age or other risk factors⁽¹⁵⁾.

The deposition of calcium pyrophosphate dehydrate crystals are strongly associated with development of RA. These can be detected radiographically or by polarizing microscopy. This deposition has the propensity to cause damage to the articular micro-cosmos. However, it remains unclear as to which comes first, the damage or the crystal deposition. Furthermore, transthyretin deposition is also being implicated in pathogenesis of OA.⁽¹⁶⁾



THE INFLAMMATORY CELL IN A NON-INFLAMMATORY PROCESS

The normal adult chondrocyte is a stable, post mitotic, differentiated cell which maintains joint homeostasis, thereby preserving integrity and functionality. As mentioned before, the articular cartilage is an avascular tissue. The chondrocyte is in a relatively hypoxic environment and oxygen tension within deep layers of the tissue are approximately 1%⁽⁸⁾. Chondrocyte adaption is dependent on Hypoxia inducible factor alpha, which affects energy generation and matrix function. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are formed as normal by products. Depletion of anti-oxidants, combined with supra-physiological stress creates persistence of ROS and RNS, resulting in damage which is apparent both at a cellular level and tissue level. Furthermore, when faced with physiological or pathological adversity, the chondrocyte activates pro-inflammatory signaling cascades and pathways (e.g. MAP kinase and NFKB) and the classical inflammatory cytokines (IL-6, IL-1, IL-17, IL-23) are activated ^(17, 18). Therefore, while tissue responses and clinical manifestations do not suggest an inflammatory onslaught, the processes at a molecular and cellular suggest a classical inflammatory sequence, which should form the basis for our future interventions.

The obvious mechanical stress caused on knees of obese individuals fails to explain the higher incidence of OA Hand in obese individuals. This is believed to be in part, due to induction of adipokines. These are proteins which are secreted predominantly by the white fat and are the major biological factors linking obesity to OA, as opposed to the more commonly held mechanical stress hypothesis. Leptins, the prototype adipokine, is found to be active in the chondrocyte and acts as a pro-inflammatory cytokine via induction through MMPs.

The role of synovial inflammation remains largely limited. It is believed to be secondary to the cartilage debris released in the bathing fluid. This contrasts with Rheumatoid arthritis, where the disease begins in the synovial membrane and spreads to the articular cartilage.

The influence of mechanical load on cartilage is a double-edged sword. Through activation of JAK/STAT and MAP kinase pathways, gene expression is altered, which may improve the structure of the joint matrix. On the other hand, overloading activates the catabolic pathway, which causes damage to the matrix and increases the risk of OA.

CONCLUSION

The inflammatory component of OA has long been targeted with NSAIDS, both topical and systemic. Surgical options, like total joint arthroplasty, have been considered the gold standard as they are quite effective in relieving pain and improving functional status. The number of patients opting for surgery in OA knee is also increasing exponentially⁽¹⁹⁾. However, the final implementation of a surgical intervention is affected by co-morbid illness, extremes of age and patient willingness to undergo major surgery. When financial constraints are thrown into the mix, the need for further targeted pharmacological, non-surgical options and interventions are highlighted. The existing treatment options are summarized in the chart above. Additionally, the aggrecan family has received much attention recently with a view to target the structural alternations that are the hallmark of this disease. The need of the hour is to conceptualize and find new targets within the inflammatory subset of the entire framework. These could be the IL-1, IL-6, TNF alpha or the ADAMTS family. Clinical trials targeting the IL-1 subfamily are already underway. Similarly the role of Protamdin and 6-Gingerol is also being explored⁽²⁰⁾. Monoclonal antibodies against aggrecans are on the verge of being inducted into clinical practice⁽²¹⁾. The objective will be to relieve

pain, reduce functional limitation and improving overall quality of life from a disease about which only little is known, despite significant advancements in the clinical medicine.

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