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LESSONS FROM A SYMPOSIUM ON RHEUMATOID ARTHRITIS HELD IN THE COLLEGE ON 28 SEPTEMBER 1994★

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Epidemiology

In the 1950s the prevalence of rheumatoid arthritis was found to be 1% of the adult population, was three times more common in women than men and the peak age of onset was in the 30–40s which led to a peak prevalence later in life. Current evidence suggests that rheumatoid arthritis has become less common and less severe over the past 30 years.

Rheumatoid arthritis is best defined by the criteria set by the American College of Rheumatology (1990). The recent Norwich epidemiology study has shown that the incidence of rheumatoid arthritis in females increases steadily to the age of 60–70 years and then dramatically declines. The incidence in males is considerably less than that of the females but steadily increases with age and does not fall in later life. This means that over the age of 75 there are more men than women with rheumatoid arthritis. The peak age of onset in women in the USA is 40–50 years and in the Norwich study is 60 years. In the latter study the overall incidence for women is 36 per 100,000 population and 14 to 100,000 for males.

The average worldwide incidence is 1%, but is lower in rural areas in Africa, China and Hong Kong and variable in urban areas. There is some evidence from prevalence studies to suggest that the disease might have originated in North America.

Rheumatoid arthritis is associated with the DR4 haplotype in Europeans and with the DR1 haplotype in India and Asia. The possession of such an epitope may render people susceptible to developing the disease or may confer more severe disease. DR4 has been detected in over 90% of patients with Felty's syndrome, 60% of rheumatoid patients in hospital surveys and 25% in community surveys. In the future genetic screening at diagnosis may be possible, providing the opportunity to select the most aggressive therapy for patients who are likely to have the worst prognosis.

The decline in incidence and severity of rheumatoid arthritis in females over the past 30 years may be partly due to the widespread use of the oral contraceptive pill. This may protect against the onset of the disease and also its severity. Pregnancy, especially pregnancy at an early age, protects against rheumatoid arthritis but there is an increased incidence of the disease in the post-partum period. This may be partly related to breast-feeding. If a woman is primed in some way to develop rheumatoid arthritis, breast-feeding may trigger the disease. If breast-feeding does not trigger the disease in the first pregnancy, it is progressively less likely to do so in subsequent pregnancies.

Other risk factors for developing rheumatoid arthritis are nulliparity, smoking and possibly other environmental factors such as immunisation. Therefore, genetic influences (both HLA and non-HLA genes), sex and hormonal factors and environmental factors including infection, diet, immunisation and lifestyle may contribute to the development of rheumatoid arthritis.

★A list of speakers and the titles of their papers presented at this symposium is recorded in *Proceedings*, Vol. 25, p. 179.

Diagnosis of rheumatoid arthritis

The diagnosis of a polyarthritis requires a careful history and examination to determine the anatomical distribution of involved joints and the presence of extra articular features will help in the differential diagnosis of laboratory investigations and X-rays. This subject is discussed in detail on p. 380–388.

Use of disease modifying anti-rheumatic drugs (DMARDs)

Disease modifying anti-rheumatic drugs (DMARD) are considered for patients with persistent active disease in spite of treatment with non-steroidal anti-inflammatory drugs. Penicillamine, intramuscular gold, sulphasalazine and methotrexate have been shown through controlled trials to be more effective than placebos in improving early morning stiffness and in reducing the number of swollen tender joints. These drugs have also been shown to have an effect on the laboratory indicators of active disease: the erythrocyte sedimentation rate, C-reactive protein, haemoglobin level. However, functional deterioration still occurs over time despite treatment with DMARDs.

There is evidence that sulphasalazine if started in early disease before bone erosions have developed, slows down deterioration as measured radiologically (in terms of joint space narrowing and erosions) in comparison with hydroxychloroquine. This supports the early introduction of DMARDs with the aim of minimising joint damage. As yet, no DMARD has been shown to have a major impact on the remission of disease on a long term basis without causing unacceptable side effects. This lack of effectiveness of DMARDs may be due to insufficient duration of therapy, insufficient dose of the drugs or adverse reactions. It is not clear whether the reduced frequency over the past 10 years of serious extra-articular features such as scleritis is due to change in the disease itself or to better disease control with DMARDs. One advantage of these drugs is that they are both steroid and NSAID-sparing.

The probability of remaining on treatment with different DMARDs has been examined for the large number of patients who have taken part in prospective controlled trials. There were no significant differences between patients taking auranofin (oral gold), sulphasalazine, intramuscular gold or penicillamine with respect to staying on DMARD therapy. Patients with early disease and those with high ESRs are more likely to stay on treatment whatever the drug, and males were as likely to stay on treatment as females. Patients with a long duration of disease can respond to DMARDs as can those with normal or low ESRs and should be considered for treatment.

The comparative toxicity of DMARDs and prednisolone over a large number of patient years showed that auranofin had the most adverse effects followed by prednisolone. Auranofin had less effect clinically than prednisolone and the patients continued to show radiological progression. Hydroxychloroquine was less toxic than prednisolone but also had less effect in slowing radiological abnormalities. Myocrisin was less toxic than penicillamine, methotrexate, auranofin, azathioprine or prednisolone. The risk of toxicity cannot be predicted from the acetylator status, sulphoxidator status or HLA type of the patient.

The outcome of DMARD treatment in 66 studies has been assessed by meta-analysis. It was concluded that placebo is less efficacious than active drugs; auranofin is less efficacious than intramuscular gold, methotrexate, penicillamine and sulphasalazine and there is little to chose between the latter four drugs. Chloroquine is more effective than hydroxychloroquine.

The mortality in patients with rheumatoid arthritis on DMARDs whose deaths were apparently unrelated to the drug was the same in those receiving myocrisin, sulphasalazine or penicillamine.

Management of pain and psychological complications

A variety of analgesics is available for the treatment of rheumatoid arthritis to complement the non-steroidal anti-inflammatory drugs (NSAIDs) which reduce inflammation and DMARDs which may ameliorate the long-term course of chronic inflammatory polyarthritis. Paracetamol and its compound formulary preparations remain the mainstay of analgesic therapy. The cost of compound analgesic preparations is greater than the cost of the individual drugs although the commonly prescribed compounds coproxamol, cocodamol and codydramol are cheap. Interactions between analgesic or between analgesics and NSAIDs for practical purposes do not occur. Interactions between NSAIDs and DMARDs are rare but interactions between different NSAIDs are well documented. Many elderly arthritic patients are best treated with an analgesic alone since the risk of gastric toxicity with NSAIDs increases significantly in the elderly.

Psychotropic agents may be useful as adjunct analgesics in arthritis. Sleep is frequently disturbed in exacerbations of rheumatoid arthritis and ankylosing spondylitis. Tricyclic antidepressants such as amitryptiline and trazodone help restore the sleep pattern to normal, reduce anxiety and act as an adjunct analgesic. A study of two appetite suppressants demonstrated that diethylpropion which has central stimulant properties was significantly better at relieving pain in osteoarthritis than the sedative appetite suppressant fenfluramine.

Other unconventional drugs may occasionally be helpful. A controlled trial of deca-durabolin showed improvement in the normochronic normocytic anaemia of rheumatoid arthritis and relief of tiredness but no effect on bone metabolism. Selenium, in spite of advertised claims, brings no obvious pain relief in rheumatoid disease or osteoarthritis.

Many patients resort to alternative medicines and therapies such as aromatherapy, reflexology, acupuncture and spiritual healing. Controlled assessments of such alternative remedies pose tremendous problems in study design.

Role of the nurse specialist

Over the next few years with the development of a consultant-run rheumatology service the number of nurse specialists (nurse practitioners) in rheumatology is likely to increase.

Such a nurse practitioner should have a basic nursing qualification, an appropriate post-training qualification and specialised experience in rheumatology. Most nurse practitioners work in out-patient clinics. They can be involved in all parts of an holistic programme of care: assessment, planning, delivery and evaluation. It is important that the nurse practitioner has easy access to a rheumatologist and vice versa.

The role of the nurse practitioner encompasses the determination of disease

status, interpretation of clinical and laboratory data, monitoring drug therapy, assessing the psychological status of the patient, counselling and supporting the patients and their families, and referring to allied carers. As well as education of patients and their families nurse practitioners have a role in the education of other nurses, health professionals and the community. An active commitment to research is desirable, particularly in the incorporation of research tools into every day practice.

A study in Leeds assessed the impact of a nurse practitioner clinic on outcome for patients with rheumatoid arthritis. Seventy patients consecutively attending the clinic were subdivided into 2 groups, one group of 35 patients who continued to see the consultant rheumatologist (CR) and the other 35 patients attended the nurse practitioner (NP). The patients were matched for age, sex and educational status. Monitoring of disease activity was done by recording the duration of early morning stiffness, pain score and analgesic intakes in addition to a full blood count and C-reactive protein. Patient knowledge questionnaires, patient satisfaction questionnaires and AIMS tests to assess physical function, psychological status and pain scores in addition to anxiety and depression scores were completed. Each patient attended 6 times over a 12 month period. Early morning stiffness and pain scores at 6 and 12 months were less for those attending the NP clinics than the CR clinics. Patient knowledge and satisfaction were greater at 6 and 12 months in the NP than in the CR clinic and the NP made more referrals to other allied healthcare workers such as occupational therapist and physiotherapist than the CR. There was a higher non-attendance rate at the CR clinic (20%) than in the NP clinic (<2%). Overall the results were in favour of the NP rather than the CR clinics. This probably reflects the amount of time spent with the patients. The CR saw over twice the number of patients as the NP per clinic. Since this survey was completed the consultant rheumatologist is referring more patients for physiotherapy and occupational therapy.

Disease related and corticosteroid induced osteoporosis

Both periarticular and generalised bone loss occur in rheumatoid arthritis. Periarticular loss, which almost certainly relates to local cytokine production and other inflammatory mediators such as nitric oxide, does not seem to be increased by corticosteroids. Generalised bone loss appears to be related in the spine to the activity of the disease and at the hip perhaps to reduced mobility in patients with active disease. Corticosteroid effects are most marked at the sites where there is a higher content of trabecular bone, especially the spine and possibly the hip. The increased incidence of hip fractures associated with corticosteroid therapy is not as marked as for vertebral fractures.

Not all patients on corticosteroids lose bone. The reasons for this variation are not clear but may relate to genetic differences and possibly to variation between individuals in the pharmacokinetics of steroids. Corticosteroid-induced bone loss occurs most rapidly in the first 6–12 months of treatment. Some studies in rheumatoid arthritis have shown that doses of prednisolone of 7·5 mg/day (equivalent to physiological replacement) are relatively safe while others have not. The threshold for steroid-induced bone loss probably lies between 5 and 10 mg of prednisolone per day but will vary from individual to individual.

Generalised and periarticular bone loss is minimised by controlling disease activity. Corticosteroid-induced bone loss may be preventable and to a certain

extent reversible. More studies are necessary to determine whether reversibility in bone loss translates to reduction in fracture rates. The problem is that vast numbers of patients would need to be recruited to demonstrate a meaningful reduction in fracture rate.

Treatment may be primary prevention in patients starting corticosteroids or treatment of established loss in patients on chronic therapy. Hormone replacement therapy (HRT) improves lumbar spine bone mass but has no effect on disease activity. Cyclical etidronate therapy (a bisphosphonate) increases bone mineral density in the lumbar spine but not in the femoral neck in both steroid-induced osteoporosis and postmenopausal osteoporosis. Pamidronate, a bisphosphonate, and calcitonin may be beneficial in treating established corticosteroid osteoporosis. Calcium and vitamin D supplements prevent bone loss at the lumbar spine but not at the femoral neck. Calcitriol, a vitamin D analogue, is beneficial in preventing lumbar spine loss in patients initiating corticosteroid treatment. Deflazacort, a corticosteroid with less apparent effect on bone than prednisolone, needs further evaluation.

In patients beginning long term high dose treatment with corticosteroids it is appropriate to consider prophylaxis either with bisphosphonates, such as etidronate, or calcitriol or calcium and vitamin D and HRT in postmenopausal women. It is unknown whether there is any advantage of vitamin D analogues over bisphosphonates or if there is a benefit in using both treatments concurrently.

Lower limb surgery in rheumatoid arthritis: indications and contra-indications

Pain relief is the main indication for lower limb surgery in rheumatoid arthritis; such surgery is most appropriate where pain causes disturbance of sleep. The other indication for surgery is to correct deformity with the aim of improving function. A patient, wheelchair-bound because of pain despite adequate doses of NSAIDs and analgesia, is in need of an operation. If in contrast, a patient has an established painless life in a wheelchair then surgical caution must be exercised. Deformities which merit surgical intervention are bilateral 45° flexion deformities of the knees and combined hip and knee fixed flexion deformities.

Good results require a surgeon with a special interest in rheumatoid arthritis, a rheumatologist to provide medical support and a combined orthopaedic/rheumatology clinic to ensure accurate assessment and good communication between the specialists.

Deficiencies in nursing, physiotherapy, occupational therapy, social care can have a detrimental effect on outcome. Good liaison with the general practitioner is also desirable. Medical problems such as pathology of the veins and limb ischaemia should be considered when joint reconstruction is advocated. The risk of venous thrombosis is increased in obesity, those with varicose veins, a history of a previous venous thrombosis or pulmonary embolus, those taking the contraceptive pill and possibly those on hormone replacement therapy. The age of the patient is important as there is a significantly higher medical morbidity and mortality after total knee replacement in patients over 75 years, although the mechanical results of these operations are as good as those in patients under this age.

Surgery should not be undertaken without a general medical assessment of the patient. There is a need to assess overall medical fitness, modify drug therapy,

exclude significant cervical instability, exclude the presence of septic foci, examine the limb in relation to other joints, assess the skin and circulation of the limb and explore the patient's expectations from the operation and ability to co-operate with the rehabilitation programme. Medical contraindications to surgery are a myocardial infarction in the previous 6 months, uncontrolled arrhythmia, poorly-controlled diabetes, anaemia (haemoglobin <10 g) and poor renal or respiratory function. Modifications to drug therapy include discontinuation of methotrexate perioperatively, reducing corticosteroids to the lowest possible dose to aid wound healing and consideration of deep venous thrombosis prophylaxis.

It is important to consider upper limb functions, especially the possible need for crutches; before lower limb surgery upper limb surgery may be necessary to allow rehabilitation. Careful planning is essential to establish the optimum sequence of operative procedures if multiple surgical interventions are required. In general the feet should be done first followed by hips, knees and ankles. Walking aids after surgery are useful for a few weeks as a reminder to patients that they have had a joint replacement.

Hospital and day care in rheumatoid arthritis

There is increasing pressure for providers in all medical disciplines to produce a 'value for money' service. Critical analysis of the costs and benefits of treatment allows the quantification in terms of economic efficiency of different medical interventions to be assessed. This allows a rational basis for decisions on health care expenditure.

It may not be possible to modify the natural history of rheumatoid arthritis but it is important to provide cost-effective treatment which improves quality of life and optimises physical function. A high proportion of the expenditure on patients with active rheumatoid arthritis is attributable to the direct medical costs of in-patient care. Most of these are fixed costs e.g. heating, maintenance and capital charges over which the clinician has little control. Day-patient care where the fixed costs may be less may provide an equally efficacious but cheaper alternative. A small pilot study comparing in-patient and day-patient therapy in Edinburgh demonstrated that day care is acceptable to patients, the short term clinical outcome is not compromised and it is less expensive.

New drugs and their biological mechanisms

Cytokines are peptide mediators of inflammation, haematopoeis and immunity. They are involved in homeostatic regulation but have also been implicated in the pathogenesis of acute inflammatory diseases such as septic shock, infectious diseases and chronic inflammatory diseases such as rheumatoid arthritis. Cytokines have intercellular signalling properties that are mediated through specific ligand receptors on target cells. The cytokine-receptor interaction leads to a series of biochemical events resulting in an alteration in the control of the target cell genes. Interleukin-1(IL-1), Interleukin-6, Interleukin-8 and tumour necrosis factor α (TNFα) are the key cytokines involved in the inflammatory response in rheumatoid arthritis. IL-1 and TNF are present in high concentrations within affected joints and are produced within the inflamed synovium. IL-1 and TNF have several functions including the stimulation of collagenase which degrades collagen and the stimulation of proteoglycanases which deplete proteoglycan in the extracellular matrix.

The aim of cytokine inhibition therapy in rheumatoid arthritis is to minimise the tissue damaging effects of the inflammatory response on the articular cartilage and periarticular structures. Opportunities to inhibit cytokines include; blocking cytokine production; inhibiting cytokine-receptor interaction either by blocking the receptor itself, inhibiting receptor synthesis or by removing the receptor completely: inhibiting the intracellular phosphorylation pathways that lead to changes in regulation of the target gene.

Blocking of cytokines or their receptors may be achieved by humanised mouse monoclonal antibodies which have been synthesised to IL-1 and IL-1 receptors, IL-8 and IL-8 receptors and TNF and TNF receptors. Natural inhibitory molecules exist; a natural IL-1 receptor antagonist binds to IL-1 receptors but fails to transduce any signal and therefore acts as a competitive receptor inhibitor; soluble cytokine receptors (e.g for IL-1 and TNF) may be shed from the surface of cells, bind soluble cytokines and prevent interaction with cellular receptors. On the bais of this, recombinant forms of the IL-1 receptor antagonist are being used in therapy. In addition, a challenge for genetic engineering would be to either create receptors or use natural receptors for pro-inflammatory cytokines that have the property of binding to their natural cytokine but prevent interaction with target cells. A possible further avenue for intervention is inhibition of the IL-1 converting enzyme (ICE) which cleaves IL-1 to its active form.

Inhibition of pro-inflammatory cytokines in rheumatoid arthritis can induce a clinical remission. A recent trial of 20 patients injected with monoclonal antibodies to TNFα and followed up for 8 weeks demonstrated a remission with an impressive fall in mean joint score and a sustained reduction in acute phase response proteins. Subsequent placebo-controlled trials support this finding. This treatment is therefore effective and appears safe in the short-term but there are theoretical problems of antigenicity in the long-term by regularly injecting partly foreign proteins in the form of humanised mouse monoclonal antibodies.

In the future it may be possible to select appropriate patients for responses to particular types of therapy on the basis of clinical criteria, biochemical and genetic markers.

Toxicity of anti-rheumatic drugs

Long term outcomes in patients with rheumatic diseases has been monitored for 20 years by ARAMIS (Arthritis, Rheumatism and Aging, Medical Information System). Outcomes are defined in terms of death, disability, discomfort, drug toxicity and dollar cost. The incidence of NSAID-induced gastropathy, the frequency with which it causes hospital admission or death and the risk factors which influence the likelihood of adverse events have been measured. The rate of admission for gastrointestinal disorders associated with NSAIDs in the USA is approximately 1.3%/year. Aspirin is relatively non-toxic. There are 3–4 fold differences in toxicity between NSAIDs with the highest incidence of adverse reactions (indomethacin, tolmetin and ketoprofen) and the lowest (ibuprofen and aspirin) with piroxicam and fenoprofen intermediate. When the toxicity of different DMARDs and NSAIDs are compared, interestingly, the latter are more toxic than expected and DMARDs which have the potential to improve long term outcome are less so.

For analgesia low doses of NSAIDs are as effective as high doses and simple analgesics are as effective as NSAIDs.

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MEDICAL EDUCATION IN HONG KONG*

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In John Richmond's tribute to Sir Stanley Davidson, he said 'when the history of 20th century British medicine comes to be written, Stanley Davidson will figure as one of the truly great professors of medicine'.[1] None would disagree. Sir Stanley was external examiner in medicine at the University of Hong Kong in 1959. Then as a young lecturer I was awestruck, for he was most impressive, both as a physician and as a man. His textbook of medicine remains a standard text at the University of Hong Kong. It is a great honour to have been invited to deliver the Sir Stanley Davidson Lecture, particularly this year, which is the 100th from his birth. I thank you, Mr President and Members of your Council for this privilege.

During the inauguration of the Hong Kong Academy of Medicine in December 1993, the Hong Kong College of Physicians organized a symposium on 'Medical Training: Internists' Perspective'. The first lecture, 'A History of Medical Education in Hong Kong', was given by Professor Gerald H. Choa, Vice-President of the College. This fascinating lecture, now published,[2] gives a comprehensive account, beginning with the arrival of Protestant missionaries in China in the early 19th century, and ending in 1974, the year when Professor A. J. C. McFadzean retired. McFadzean was the first post-Pacific war professor of medicine in Hong Kong and profoundly influenced medical education here.

Medical education in Hong Kong can be divided into four periods:

1887–1915	Years of the Hong Kong College of Medicine for the Chinese
1915–1941	Pre-war years of the Faculty of Medicine, University of Hong Kong
1942–1945	War years
1946-Present	Post-war years

Here, the pre-war and war years are considered the past and from 1946 to now the present.

THE PAST

Hong Kong was ceded to the British in 1842. Medical education can be said to have had its beginnings in 1843 when Dr Benjamin Hobson, a graduate of University College Hospital, London working with the London Missionary Society, took on students from a neighbouring school as pupil-assistants in the Medical Missionary Hospital of Hong Kong. However, formal medical education was only established in 1887, after forty-four years of British rule, with the opening of the Hong Kong College of Medicine for the Chinese. The intention was to educate doctors not only for Hong Kong, but for China and East Asia as

*A Stanley Davidson lecture delivered at the Joint Meeting with the Hong Kong College of Physicians and the Hong Kong College of Paediatricians held in Hong Kong on 22–23 October 1994.

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