

## RHEUMATOLOGY 2001

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## INTRODUCTION

The first Royal College of Physicians of Edinburgh Symposium on Rheumatology in the bone and joint decade (the first decade of the 21st century has been declared the bone and joint decade<sup>1</sup>) took place on the 22 March 2001. To celebrate this decade a variety of significant topics, which will continue to have an impact on rheumatology over the next ten years, were reviewed. Many of these topics represent a development occurring over several years, such as cervical spine and joint replacement surgery. Increasingly, specialisation is essential in rheumasurgery<sup>2</sup> since the skills required are considerable and the maintenance of those skills depends upon procedures being performed regularly and frequently. It will therefore be important, with the advances in clinical governance, to limit such complicated procedures to fewer centres.<sup>3</sup> Other topics discussed in this Symposium are relatively new and their significance is only just becoming apparent. Perhaps the most exciting topic is the increased link between atherosclerosis and inflammation. This report summarises the proceedings of the Symposium.

## 1. RHEUMASURGERY – THE NECK

Cervical spine disease in rheumatoid arthritis (RA) is a management paradigm.<sup>4</sup> A large Finnish series has estimated the mortality associated with cervical spine disease in RA and has shown that it is significantly under-reported (perhaps accounting or contributing to 50% of the 38/853 deaths).<sup>5</sup> An association is reported between disease severity and survival in patients who have cervical spine RA involvement.<sup>6</sup> In a review of patients undergoing major lower limb joint replacement, 61% of patients had significant cervical spine disease at the time of surgery.<sup>7</sup> In a cohort study of 254 patients with RA who had established cervical spinal disease, followed over a mean of 10.6 years, a conservative approach resulted in deterioration of atlanto-axial subluxation in 35% (radiological deterioration) and 11% (neurological deterioration). In cases of vertical translocation deterioration occurred in 33% (radiological) and 31% (neurological): in sub-axial subluxation, 44% of patients showed radiological deterioration whilst 13% had neurological deterioration.<sup>8</sup> Over their lifetime, between 30% and 70% of patients with RA will develop cervical spine disease, of which the dominant problem is atlanto-axial subluxation; there are also significant numbers who develop sub axial subluxation and vertical translocation.<sup>9-11</sup>

This represents a potential of 62,700 candidates for cervical spine surgery in the UK *per annum*, with an equivalent figure in the US of 220,000. Compared to these figures, only 10% (i.e. 6,000) in the UK actually undergo cervical spine surgery. Of those patients with atlanto-axial subluxation, only five or six per cent actually develop myelopathy. Studies in early RA provided by the Early Rheumatoid Arthritis Study (ERAS) dataset (a series

of 600 patients with new onset RA studied over a six year period) demonstrate that between five and six per cent have developed atlanto-axial subluxation and that this incidence is increasing progressively over time.<sup>12</sup> The myelopathy of atlanto-axial subluxation is equivalent to a multiple spinal cord injury and there is no significant reversal of myelopathic changes.

Whereas previously it was thought that pannus was the most common mechanism mediating pressure on the spinal cord at the craniovertical junction, this tissue is less commonly seen perhaps with the advent of improved medication to suppress synovitis,<sup>13</sup> and most of the damage is end-stage minor cord compression. The question is whether it should be considered before damage occurs despite the significant risks of surgery.<sup>14</sup> It has been suggested that degrees of atlanto-axial subluxation should determine the urgency of surgery but in practice, if there is more than 3 mm of subluxation, it is likely that surgery will be required and centres would advocate MRI scanning at that stage with a view to surgery.

When to refer for surgery is always an issue.<sup>15</sup> Once a patient is bed-bound it is probably too late. The current philosophy is to try and avoid neural damage and a suggested assessment plan is to perform a cervical spine X-ray; in the event of instability associated with cord compression, an MRI is recommended with a view to proceeding to surgery. If there is instability but no cord compression is seen on the MRI, it is suggested that follow-up MRIs are performed. With regard to C2 nerve root pain, which is often associated with head tilt because of discomfort, the principles of management will be fixation, local injection and the use of a collar. The problem of non-reducible head tilt has been reported in around 10% of hospitalised patients with RA and is usually due to unilateral collapse of the lateral masses of the atlas and/or axis.<sup>16</sup>

Surgical techniques for neck problems have changed.<sup>17</sup> Whereas previously bone graft with wiring was recommended, along with a variety of clamps or titanium and other metal loops with occipital cervical stabilisation, newer techniques include segment saving and attempts to fix individual vertebrae together (such as C1 and C2<sup>18</sup> – although the proximity of the vertebral artery means this technique is not for the faint-hearted,<sup>19</sup> especially in view of the fact that 11% of patients have a congenitally large vertebral artery). Trans-oral decompression is no longer recommended. Posterior fixation combined with anterior decompression in the presence of spinal stenosis is a useful and safe method to treat instability and deformity caused by RA, with over 75% of patients reporting satisfactory improvement.<sup>4,20</sup> The follow-up available using the Ranawat classification (a measure of neurological disability<sup>21</sup>) shows that patients who have Ranawat IIIb (severe disability with upper motor neurone signs in all four limbs) have a 16% mortality in the immediate post-operative period with a

25% mortality at six months. Long-term follow-up of patients with Ranawat II to IIIb shows 38% mortality and, somewhat surprisingly, an average one Ranawat grade improvement in survivors.<sup>22</sup> Problems are almost certainly related to the poor quality of bony material left to operate on. Variation in clinical practice remains a significant problem that may be contributing to less than optimal outcome for these patients.<sup>3</sup> It may be that the development of a myelopathy disability index may serve as a useful measure of surgical outcome (as a variant to the health assessment questionnaire<sup>23, 24</sup>). It is important to bear in mind the significant role that trauma can play in destabilising the neck, especially after other joint surgery has occurred. Unfortunately, cervical spine disease in RA has a recurrence rate of 15% despite initial stabilisation of the neck.<sup>25</sup>

## 2. RHEUMASURGERY – THE LOWER LIMB

Joint replacement surgery has an important role in the management of many arthritic conditions.<sup>26</sup> It is important that a team approach should be in place with careful evaluation of individual patients to determine the optimal timing and type of surgery. In a review of the surgical registry of patients with RA-related lower limb joint replacements, around 8,000 procedures are performed annually in Finland, with hip surgery at around five to seven operations per 100,000 population and knee replacements being similar at seven per 100,000 per annum.<sup>27</sup> There has been no significant change in these figures over the period between 1990–7. A recent estimate of knee arthroplasty requirements for the next 30 years indicates a likely increase of around one-third to meet the needs of the ageing population.<sup>28</sup> The role of synovectomy of the knee has been controversial since no good controlled studies have been carried out. A small study of multiple joint synovectomies combined with drug therapy for RA has suggested independent benefit from the synovectomy itself in helping to control disease in the long term.<sup>29</sup> Knee synovectomy has been reported to give satisfactory results in over 80% at three years' follow-up;<sup>30</sup> ten year follow-up of patients treated at a single centre in Finland show good results in 60%, and their experience suggests that cartilage preservation is an important predictor of good outcome. Hip synovectomy is a much more difficult procedure because of access. In terms of priorities in joint replacement surgery, stabilisation of the neck and/or upper limbs is advocated before lower limb surgery is considered, and then feet are operated on first if appropriate. A large series has examined the effect of multiple joint replacements compared to single knee joint replacement and found no significant difference in functional outcome or complication rates.<sup>31</sup> With regard to hip surgery, osteotomy is no longer recommended. *Protrusio acetabuli* occurs in around 40% of patients with RA, and has been successfully managed with bone grafting to pack the defect prior to joint replacement.<sup>32</sup> Patients with RA do not do as well as patients with osteoarthritis (OA) with regard to successful total hip arthroplasty.<sup>33</sup> Cemented prosthesis have been reported to loosen in OA with recommendations that bone grafts be used instead,<sup>34</sup> but cementless hip replacements in RA result in poor outcome. The average age for hip replacement in RA is between 54 and 60 years; most patients are given a Charnley hip with an 80% ten-year hip survival.<sup>35</sup> Problems arising from hip

replacements include wearing of the material; a solution to this could be to use ceramic heads, but these have very poor shock absorption. Metal-to-metal hip replacements have been tried but there is a worry about corrosion. The incidence of infection is twice as common in patients undergoing joint replacement for RA, compared to those undergoing joint replacement for OA. Figures suggest that of 181 osteoarthritic hip replacements, 0.6% become infected as compared to 1.2% of 1,053 rheumatoid hip replacements and 1.1% of 186 juvenile arthritis hip replacements.<sup>27</sup> Management of infected prostheses is primarily with early, aggressive antibiotics.

In the context of RA, when knee replacement is performed approximately 46% of the patients have a valgus deformity at the time of surgery and approximately 30% have a varus deformity at the time of surgery. Collateral ligament rupture is rare. By contrast with the hip, cementless prostheses at the knee in patients with RA are as effective as cemented prostheses. Knee replacement may have a significant impact on reducing disability in patients with severe flexion contractures.<sup>36</sup> Some centres have recommended multiple joint replacements at the same session. The complication rate is around 1.2 times greater than normal and it is suggested that two-stage procedures are preferable. Mortality following major joint replacement in RA is higher than in other disease groups, with an SMR of 1.48 for hip replacement<sup>37</sup> and between 2 and 3 for knee replacement, compared with patients with OA.<sup>38</sup> In rheumatoid foot surgery, the early 1970s showed poor results from arthroplasty and the current suggestion is that if MRI evidence of vascular damage to bone exists, arthroplasty is unlikely to be successful and therefore arthrodesis remains the best option. In a recent series of 69 patients, however, survival of ankle arthroplasties has been reported as 83% at five years and 66% at ten years.<sup>39</sup> In the forefoot, resection arthroplasty provides good functional outcome, whereas metatarsophalangeal (MTP) implants are really only useful where there is low demand on the joint, i.e. for walking only, not running.<sup>40, 41</sup> Combined MTP fusion and osteotomy of other affected MTP joints may be a better approach.<sup>42</sup>

## 3. RHEUMASURGERY – THE UPPER LIMB

New developments in upper limb surgery in orthopaedics include an improvement in outcome measures using more subjective rather than objective measures, and potential use of the arthroscope for more upper limb surgery has been suggested. The outcome from shoulder disease in RA is significantly variable. If there is significant subacromial disease there is a case for early synovectomy to prevent rotator cuff rupture. In the event of glenohumeral disease, loss of cartilage may be significant, but most of these patients do not require shoulder replacement. The timing of surgery is controversial. There is an important balance to be achieved between medical therapy and surgical intervention. On the one hand if medical therapy is failing to prevent joint damage and subsequent disability, surgical intervention offers the opportunity to minimise that disability. Synovectomy of the shoulder will result in 50% improvement (using yttrium-90) and thus can be done through the arthroscope. However, no data are available from controlled trials.

Total shoulder replacement is recommended for significant pain, loss of external rotation or the presence of a non-spherical humeral head. The state of the rotator cuff

is crucial to the likelihood of post-operative success; it is largely dependent on whether the cuff is intact before surgery, but the problem is that by the time patients reach surgery the cuff is often ruptured. Ten year results from long-term follow-up studies of total shoulder replacement show that 82% of patients are expressing significant pain relief, whereas ten per cent have moderate or severe pain.<sup>43</sup> External rotation increases on average from 5° to 38°. Around 55% of total shoulder replacements suffer the problem of proximal migration.

A variety of shoulder replacements are now available. The Liverpool shoulder, which is based on the prosthetic hip, does not have good long-term outcome. The hemiarthroplasty is technically unsuccessful although, surprisingly, patient satisfaction is reasonable.<sup>44</sup> Promising new shoulder replacements, such as the bipolar arthroplasty, are relatively untested. An anatomical arthroplasty involving reconstruction and retention of soft tissues may prove helpful. The value of cemented versus uncemented arthroplasties is undetermined at present, as is the role of subacromial synovectomy.

At the elbow, the most important determinant of disability is impairment of flexion. Other indications for elbow surgery are significant pain or poor hand function. Initial results from an open synovectomy of the elbow with radial head excision show improvement in 54% of cases.<sup>45</sup> Total elbow replacements, such as that devised by Souter,<sup>46</sup> show that all hinge joints will loosen and cannot be revised. This has led to the use of unlinked prostheses, which attempt to replicate normal biomechanics. The results of surgery relate directly to the number of operations done: in the best hands, 80% of patients should maintain improvement by ten years, but complications are increasingly common in inexperienced hands.<sup>47,48</sup> Future elbow surgery will depend on improving the design of the prosthesis,<sup>49,50</sup> a good outcome measure and consistency of surgical technique, i.e. standardising with only a few centres involved.

Wrist surgery is often recommended at too late a stage in the disease. Once the zigzag collapse of the wrist has occurred or if the distal radio-ulnar joint has subluxed, this can result in extensor tendon rupture. Urgent surgery is required to repair the tendons and remove the end of the radius. If the tendons are ruptured, then tissue balancing becomes very difficult and there is no point in attempting wrist replacement. Distal ulnar resection remains a very successful procedure in RA, with over 80% of patients reporting significant improvement in pain control.<sup>51</sup> Radio-carpal joint disease is best dealt with by arthrodesis. Combined synovectomy and arthrodesis is very successful, with 97% patient satisfaction.<sup>52</sup> Wrist replacement is a more limited option for the above-mentioned reasons. Good long-term results are reported following wrist arthrodesis.<sup>53</sup>

Thumb surgery may be appropriate in a number of cases. About 66% of patients with RA have thumb disease, resulting in disability in 60% of these cases. About one-third of these cases have carpo-metacarpal joint disease. Zigzag collapse of the thumb is common. Recommended procedures which result in improvement in functioning include excision of the carpo-metacarpal joint and fusion of the interphalangeal and metacarpophalangeal (MCP) joints<sup>54</sup> as this results in stable opposition of the thumb. Flexor synovectomy is rarely needed, apparently because of the effectiveness of immunosuppressive therapy; by

contrast, extensor tendon synovitis is still a significant problem. In the hand, the presence of ulnar drift is associated with functional impairment and poor outcome from surgery. Swan neck and boutonniere deformities are unlikely to improve as a result of current surgical techniques. Metacarpophalangeal implants may fracture between four per cent and 20% of the time, despite which the clinical outcomes may be satisfactory.<sup>55</sup> In conclusion, soft tissue surgery depends on the extent of the disease process. Arthroplasty must achieve soft tissue balance and therefore the soft tissues need to be made intact in order for a joint replacement to be successful.

#### 4. RHEUMASURGERY – CARTILAGE REPAIR AND REGENERATION

Contrary to the traditional orthopaedic approach to joint disease, newer techniques are being evaluated where articular cartilage may be amenable to repair or regeneration<sup>56</sup> and this has been shown in animal models.<sup>57, 58</sup> This phenomenon is significantly impaired by age.<sup>59</sup> The use of hyaluronan-based polymers into cartilage defects may provide scaffolding and enhance the repair process in animals.<sup>60</sup> In humans, the same techniques have been applied with some success.<sup>61</sup> Articular cartilage is isolated from blood, nerve and lymphatic supply, and simply rests on subchondral bone. Traditional treatment of OA with joint replacement surgery ignores the potential for repair or regeneration. In young patients with full thickness cartilage defects, joint injury may result in a significant risk of OA in future.<sup>62</sup> Similarly, young patients with *osteocondritis dissecans* have a 32–40% risk of subsequent development of OA.<sup>63</sup> Novel approaches to these problems in this select group of patients have recently been considered. Enhancement of intrinsic healing mechanisms might be achieved using stem cell metaplasia or the introduction of a 'super' blood clot. The use of a composite graft, which may be an allograft or an autologous graft containing cartilage and bone, along with perichondral and periosteal materials, would be another approach.<sup>64, 65</sup> Finally, a third technique would be cell regeneration using periosteal patches from cultured cells.<sup>66</sup> All these techniques are being used in some novel experiments in Oswestry, a regional orthopaedic centre in the UK with some dramatic improvements in these lesions in young, non-obese individuals with isolated cartilage damage. Femoral condyle lesions responded to treatment in up to 93% of cases in a two to nine year review of these techniques. At present there are no controlled trials. These techniques will be limited by significant cost, but the potential saving of cartilage for this group of patients may outweigh the cost of the technique in the long term. Future improvements to these strategies may include stem cell usage and modification of the genetic material before implantation.<sup>67, 68</sup>

#### 5. CARDIOVASCULAR RHEUMATOLOGY – CARDIOVASCULAR PROBLEMS IN SLE

The recognition that premature atherosclerosis occurs in systemic lupus erythematosus (SLE)<sup>69, 70</sup> has led to a closer inspection of this patient group for traditional risk factors predisposing to atheroma. The standardised mortality rate for SLE is 9.16 for patients under the age of 54.<sup>71</sup> In early SLE, i.e. within the first five years, sepsis is the most common cause of death (32%) and death is more common in patients with active, rather than inactive, SLE. In late SLE deaths,

beyond five years of onset of disease, coronary artery related events become more common (30% over five years compared to 17% under five years). The incidence of ischaemic heart disease (myocardial infarction and angina) is between 6.7% and ten per cent of large follow-up cohorts of patients with SLE.<sup>72</sup> At autopsy, around 54% of patients have moderate to severe atheroma.<sup>73</sup> In large cohort studies of patients with SLE, increased risk is documented for myocardial infarction, with an odds adjusted ratio of between 7.4 and 8.5 for pre-menopausal women, making SLE one of the strongest cardiovascular risk factors ever described. It is likely that only six to ten per cent of patients with SLE actually have clinical evidence of coronary artery disease; this suggests that the vast majority have pre-clinical disease or significant risk factors. Investigations of patients with SLE, looking for pre-clinical disease, have shown a significant incidence of abnormalities detected on single photon emission computerised tomography (SPECT) dual isotope myocardial perfusion imaging. In a study of 130 women with SLE, with an average age of 45 and 14 years' disease duration (only ten per cent of cases had known cardiovascular disease), abnormalities of perfusion were present in 35% of previously unsuspected cases and 90% of these abnormalities were reversible.<sup>74</sup> Seventy-three per cent of the abnormalities occurred in a single coronary arterial territory, implying there was a potential for treatment. The factors associated with abnormal perfusion included the presence of clinical coronary artery disease as the biggest risk factor, but post-menopausal status, current hypertension, previous steroid-related side-effects and high total cholesterol/high-density lipoprotein (HDL) ratio were all associated with an increased risk of perfusion abnormalities with an odds ratio of between 1.7 and 2.7.

Coronary artery plaques have been found in 35% of 123 women studied with SLE. Predictors of coronary artery plaques included older age at onset, high systolic blood pressure, prolonged steroid use and high C-reactive protein with odds ratios of between 1.1 and 2.7. Therefore, overall, it is likely that up to 40% of patients with SLE have sub-clinical coronary artery disease. It is likely that the mechanisms for development of coronary artery disease include the presence of vasculitis, premature atheroma (that may also be contributed to by traditional risk factors), genetic predisposition and therapy for SLE.<sup>75,76</sup> In addition, anti-phospholipid syndrome may contribute to the coronary artery events. In a risk factor study of events in patients with SLE, high cholesterol levels, older age at onset of SLE, hypertension, long duration of prednisone use, the presence of pericarditis or myocarditis, heart failure and obesity were all associated with higher risk of clinical events. Studies of the carotid circulation also suggest an increased incidence of carotid plaques in patients with SLE.<sup>77,78</sup> Although steroids clearly modify cholesterol metabolism, it has been recognised for some time that active SLE itself will raise concentrations of triglyceride and very low density lipoprotein (VLDL) and lower HDL levels.<sup>79</sup> Anti-malarial drugs are known to reduce cholesterol levels in patients with SLE.<sup>76</sup> In the Toronto risk factor study, 235 patients with SLE were studied to detect the traditional risk factors for coronary artery disease.<sup>80,81</sup> Hypertension and diabetes were found to be more prevalent in patients with SLE than in age-matched controls. Patients with SLE were more likely to have a sedentary lifestyle with a higher body

mass index, a high VLDL and triglyceride level. Insulin resistance and diabetes are probably co-associated with other abnormalities such as hypertension, lipid abnormalities and steroid use. Homocysteine levels were also found to be elevated in SLE patients compared to controls. Homocysteine is pro-oxidant and toxic to endothelial cells. It is associated with strokes and arterial events in SLE, although the role of homocysteine in coronary artery disease is still controversial. There is an association of stroke and arterial events in SLE, although its role in population studies of coronary artery disease is still controversial. Therefore, the model of coronary artery disease in SLE includes chronic vascular inflammation with activation of endothelial cells, the presence of a pro-oxidant state, and the traditional risk factors for coronary artery disease.

The endothelial cell activation status has been studied with the finding that E-selectin is up-regulated on active endothelium in patients with SLE. It has been suggested that low dose aspirin is an important long-term treatment for SLE because of the cardiovascular risks.<sup>82</sup> The absolute contribution of inflammatory, metabolic and genetic factors to the overall risk of atherosclerosis has not been completely determined, but there is enough evidence for patients with SLE to have traditional risk factors identified and managed.<sup>79,83</sup>

#### 6. CARDIOVASCULAR RHEUMATOLOGY – THE PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Traditional risk factors for atherosclerosis have been identified as partly modifiable and partly non-modifiable. The pattern of involvement of atherosclerosis is often at vessel branches or where there is complex dynamics flow.<sup>84,85</sup> Low-density lipoprotein normally does not have access to vessel tissues unless the endothelial layer has been injured.<sup>86</sup> This may result in the trapping of low-density lipoprotein (LDL) on intimal proteoglycan, resulting in oxidative pressure.<sup>87</sup> Experimental evidence shows that leucocytes will bind endothelial cells of pigs fed on a high fat diet, implicating a role for inflammatory cells in atherosclerosis.<sup>88</sup> The mechanisms for adherence of the leucocyte to endothelium are now well established: a variety of adhesion molecules regulating the rolling process onto endothelium (using E and P selectin). Activation of the leucocyte with IL8 and MCP1, and finally the arrest of the leucocyte using ICAM-1 and VCAM-1, both of which can be up-regulated by the endothelial cells via interleukin-1, TNF Alpha and LDL, follows.<sup>89</sup> Eventually a monocyte cap will form over the fatty thrombogenic material.<sup>90,91</sup>

Atherosclerosis tends to occur as a series of acute events, and evidence for this is obvious on studies showing laminated appearances of atherosclerotic plaques. The fate of a plaque is determined by any inflammation occurring at the shoulder region of the plaque.<sup>92</sup> In mice, models for atherosclerosis have been developed using LDL receptor knockout mice and apolipoprotein knockout mice.<sup>93,94</sup> By contrast, mice that lack monocytes, P selectin, E selectin, MCP1, the ability to make adhesion molecules like ICAM-1 or VCAM-1 and who lack macrophage scavenger receptors, are incapable of developing atherosclerosis.

In animal models, and in human observations, it has been shown that there is an important role for infection in aggravating atherosclerosis.<sup>94-6</sup> In humans it has been shown that approximately four per cent of patients with a bacteremia will develop acute myocardial infarction and

that, in patients undergoing abdominal surgery where a bacteremia occurs, this also increases the risk of an acute myocardial infarction.<sup>96</sup> Human studies also show that postmenopausal women have an increased risk of atherosclerosis which is around 4.4-fold on those women with a high C-reactive protein. High ratio of total to HDL cholesterol further raises their risk of atherosclerotic events, with a relative risk of 6.<sup>97</sup> The role of B-cells is considered to be important; with the production of antibodies to oxidised LDL innate antibodies are usually IgM and IgG 3 subclass, but acquired antibodies to oxidised LDL are usually IgG 2a and IgG1 subclass.<sup>98</sup> These antibodies cross-react with bacterial cell walls and may affect macrophage uptake of native oxidised LDL. T-cells are likely to be involved, especially the CD4 Th1 subclass which produce interferon gamma; these cells react with oxidised LDL. There is evidence for oligoclonality and they are undoubtedly involved in plaque stability.

The finding of CD4<sup>+</sup> and CD28<sup>-</sup> T-cells in patients with unstable angina and active RA suggests they play an active role in mediating coronary events.<sup>99-101</sup> These cells are responsible for making high levels of interferon gamma, granzymes and other mediators capable of inducing inflammation at the plaque. Patients with rheumatic disease also have traditional risk factors for atherosclerosis such as hypertension and abnormal lipid profiles. Despite these factors, markers of systemic inflammation remain independent risk factors for cardiovascular disease progression.<sup>102</sup> These patients have an inflammatory disease and some of the drugs they take, such as methotrexate, can raise homocysteine levels.<sup>103</sup>

The role of steroids is also significant. Immunologically, these patients often have a variety of antibodies, including antiphospholipid antibody, antibodies to HDL and antiendothelial cell antibodies. Some patients have increased circulating immune complexes. The cell-mediated immune system is activated.<sup>104</sup> The findings would beg the question as to whether anti-rheumatic drugs used for RA would be of any value in protecting against atherosclerosis. Current mouse models of atherosclerosis show that the use of intravenous gammaglobulin, anti CD40 ligand and IL1 receptor antagonist, IL10 and anti TNF or soluble TNF receptor antibodies are all effective in the mouse model of atherosclerosis. As a corollary, one could ask whether the drugs used in cardiology have any effect on the immune system. Most of the statin drugs tested show an influence on reducing macrophage cytokine release, macrophage DR exposure, endothelial cell expression of nitric oxide and possibly influence the interaction between macrophages and endothelial cells. It will be intriguing to discover exactly how these mechanisms can be influenced in both patients with rheumatic disease and those with no rheumatic disease, all of whom may be at risk of atherosclerosis in the future.<sup>105</sup>

#### 7. HEALTH CARE FUNDING AND RATIONING IN RHEUMATOLOGY

A debate was held on the rational use of available finances; at one extreme, management of mechanical problems, such as back pain, and at the other extreme the management of complex inflammatory diseases, such as RA. Back pain is very common<sup>106, 107</sup> and costs the UK £1.6 billion per annum;<sup>108</sup> simple strategies for managing back pain have been shown to be effective<sup>109</sup> although only modest benefit has been demonstrated in controlled trials.<sup>110-13</sup>

Nevertheless, extrapolating that across large numbers of patients, a modest benefit in a few will result in a major benefit to the population as a whole. Investment in physiotherapists as educators for managing back pain, patient education and also physician education to appropriately manage the conditions were recommended.<sup>114</sup> There are potential crossover benefits to other conditions since improving fitness may result in lower levels of heart disease and obesity in the community, although it is controversial as to how effective these measures can be since lifestyle advice is often poorly taken up. Nevertheless, there is a good case for using money wisely and influencing the high societal cost of back pain with the more modest cost of physiotherapy regimens. This is in stark contrast to the strategies currently available for managing RA, where specific individuals may receive expensive compounds (currently the TNF blockade strategies will cost around £7,000 per patient per annum) with major therapeutic benefits.<sup>115-19</sup> This may seem a very poor return for society considering how few patients could be treated with the available budget. However, this has to be balanced against the cost to society as a whole of RA, which is estimated to be about £1.3 billion per year, as well as the long-term implication of rheumatoid disease on the individual and family. A vote on this debate resulted in a surprising draw, with exactly the same number of participants voting for each strategy. The implications to health care providers are clear: both of these strategies are considered to be of equal merit in the management of rheumatic diseases.

#### CONCLUSION

Rheumatology in the bone and joint decade is a thriving specialty with multi-dimensional aspects. There are significant improvements being made in rheumasurgery resulting in more appropriate referrals and improved techniques, but this needs to be guided by more evidence-based research with properly controlled trials and appropriate outcome measures which are being developed. The controversial new evidence for the increasing involvement of the immune system in mediating atherosclerosis may herald a significant change in cardiological, as well as rheumatological, practice. Rheumatology is a subject of breadth and depth and, whilst newer techniques are being developed, and newer expensive treatment modalities become available to interfere more specifically with the abnormalities in the immune system, we must not neglect the important role that rheumatology can and should play in the management of more common musculo-skeletal problems which are amenable to simpler intervention.

#### REFERENCES

- 1 Woolf AD, Acession K. Understanding the burden of muscular skeletal conditions. *BMJ* 2001; **322**:1079-80.
- 2 Rudd E. Rheumato-orthopaedics. Many orthopaedists in Europe and Japan work almost exclusively with RA patients. *Orthop Rev* 1980; **9(11)**:25-7.
- 3 Christensson D, Saveland H, Rydholm U. Cervical spine surgery in rheumatoid arthritis: A Swedish nation-wide registration of 83 patients. *Scand J Rheumatol* 2000; **29(5)**:314-9.
- 4 Crockard HA, Calder I, Ransford AO. One-stage transoral decompression and posterior fixation in rheumatoid atlanto-axial subluxation. *J Bone Joint Surg Br* 1990; **2(4)**:682-5.
- 5 Neva MH, Myllykangas-Luosujarvi R, Kautiainen H *et al*. Mortality associated with cervical spine disorders: A

- population-based study of 1,666 patients with rheumatoid arthritis who died in Finland in 1989. *Rheumatology* (Oxford) 2001; **40**(2):123-7.
- 6 Saway PA, Blackburn WD, Halla JT *et al.* Clinical characteristics affecting survival in patients with rheumatoid arthritis undergoing cervical spine surgery: A controlled study. *J Rheumatol* 1989; **16**(7):890-6.
  - 7 Collins DN, Barnes CL, FitzRandolph RL. Cervical spine instability in rheumatoid patients having total hip or knee arthroplasty. *Clin Orthop* 1991; **272**:127-35.
  - 8 Hiraizumi Y, Namiki O, Fujimaki E. Time course changes of the cervical spine in conservatively treated rheumatoid arthritis. *Journal of Orthopaedic Surgery* 1997; **5**(2):41-7.
  - 9 Pellicci PM, Ranawat CS, Tsairis P *et al.* A prospective study of the progression of rheumatoid arthritis of the cervical spine. *J Bone Joint Surg Am* 1991; **63**(3):342-50.
  - 10 Fujiwara K, Yonenobu K, Ochi T. Natural history of upper cervical lesions in rheumatoid arthritis. *J Spinal Disord* 1997; **10**(4):275-81.
  - 11 Paimela L, Laasonen L, Kankaanpaa E *et al.* Progression of cervical spine changes in patients with early rheumatoid arthritis. *J Rheumatol* 1997; **24**(7):1280-4.
  - 12 Young A, Dixey J, Cox N *et al.* How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). *Rheumatology* (Oxford) 2000; **39**(6):603-11.
  - 13 Neva MH, Kauppi MJ, Kautiainen H *et al.* Combination drug therapy retards the development of rheumatoid atlantoaxial subluxations. *Arthritis Rheum* 2000; **43**(11):2397-401.
  - 14 Casey ATH, Crockard HA, Bland JM *et al.* Predictors of outcome in the quadriparetic nonambulatory myelopathic patient with rheumatoid arthritis: A prospective study of 55 surgically treated Ranawat class IIIB patients. *J Neurosurg* 1996; **85**(4):574-81.
  - 15 Marks JS, Sharp J. Rheumatoid cervical myelopathy. *Q J Med* 1981; **50**(199):307-19.
  - 16 Halla JT, Fallahi S, Hardin JG. Nonreducible rotational head tilt and lateral mass collapse. A prospective study of frequency, radiographic findings, and clinical features in patients with rheumatoid arthritis. *Arthritis Rheum* 1982; **25**(11):316-1324.
  - 17 Crockard HA, Pozo JL, Ransford AO *et al.* Transoral decompression and posterior fusion for rheumatoid atlantoaxial subluxation. *J Bone Joint Surg Br* 1986; **68**(3):350-6.
  - 18 Madawi AA, Casey ATH, Solanki G *et al.* Radiological and anatomical evaluation of the atlantoaxial transarticular screw fixation technique. *J Neurosurg* 1997; **86**(6):961-8.
  - 19 Abou Madawi A, Solanki G, Casey ATH *et al.* Variation of the groove in the axis vertebra for the vertebral artery. *J Bone Joint Surg Br* 1997; **79**(5):820-3.
  - 20 Grob D, Schutz U, Plotz G. Occipitocervical fusion in patients with rheumatoid arthritis. *Clin Orthop* 1999; **366**:46-53.
  - 21 Ranawat CS, O'Leary P, Pellicci P *et al.* Cervical spine fusion in rheumatoid arthritis. *J Bone Joint Surg Am* 1979; **61**(7):1003-10.
  - 22 Matsunaga S, Ijiri K, Koga H. Results of a longer than 10-year follow-up of patients with Rheumatoid arthritis treated by occipitocervical fusion. *Spine* 2000; **25**(14):1749-53.
  - 23 Casey ATH, Bland JM, Crockard HA. Development of a functional scoring system for rheumatoid arthritis patients with cervical myelopathy. *Ann Rheum Dis* 1996; **55**(12):901-6.
  - 24 Casey ATH, Crockard HA, Bland JM *et al.* Surgery on the rheumatoid cervical spine for the non-ambulant myelopathic patient - Too much, too late? *Lancet* 1996; **347**(9007):1004-7.
  - 25 Agarwal AK, Peppelman WC, Kraus DR *et al.* Recurrence of cervical spine instability in rheumatoid arthritis following previous fusion: Can disease progression be prevented by early surgery? *J Rheumatol* 1992; **19**(9):1364-70.
  - 26 Bernard AA, Zrinzo LU. Joint replacement: The final solution? *Adv Exp Med Biol* 1999; **455**:451-61.
  - 27 Paavolainen P, Hamalainen M, Mustonen H *et al.* Registration of arthroplasties in Finland. A nationwide prospective project. *Acta Orthop Scand* (Supplement) 1991; **62**(241):27-30.
  - 28 Robertsson O, Dunbar MJ, Knutson K *et al.* Past incidence and future demand for Knee Arthroplasty in Sweden: A report from the Swedish Knee Arthroplasty Register regarding the effect of past and future population changes on the number of arthroplasties performed. *Acta Orthop Scand* 2000; **71**(4):376-80.
  - 29 Nakamura H, Nagashima M, Ishigami S *et al.* The anti-rheumatic effect of multiple synovectomy in patients with refractory rheumatoid arthritis. *Int Orthop* 2000; **24**(5):242-5.
  - 30 Klug S, Wittmann G, Weseloh G. Arthroscopic synovectomy of the knee joint in early cases of rheumatoid arthritis: Follow-up results of a multicenter study. *Arthroscopy* 2000; **16**(3):262-7.
  - 31 Papanikolaou A, Droulias K, Nikolaidis A *et al.* Results of a single total knee prosthesis compared with multiple joint replacement in the lower limb. *Int Orthop* 2000; **24**(2):80-2.
  - 32 Rosenberg WWJ, Scherer's BW, De Wail Makefast MC *et al.* Impacted morsellized bone grafting and cemented primary total hip arthroplasty for acetabular protrusion in patients with rheumatoid arthritis: An 8- to 18-year follow-up study of 36 hips. *Acta Orthop Scand* 2000; **71**(2):143-6.
  - 33 Tang WM, Chiu KY. Primary total hip arthroplasty in patients with rheumatoid arthritis. *Int Orthop* 2001; **25**(1):13-6.
  - 34 Kinzinger PJM, Karthaus RP, Slooff TJJH. Bone grafting for acetabular protrusion in hip arthroplasty. 27 cases of rheumatoid arthritis followed for 2-8 years. *Acta Orthop Scand* 1991; **62**(2):110-12.
  - 35 Lehtimäki MY, Kautiainen H, Lehtoand MUK *et al.* Charnley low-friction arthroplasty in rheumatoid patients: A survival study up to 20 years. *J Arthroplasty* 1999; **14**(6):657-61.
  - 36 Lu H-S, Mow CS, Lin J-H. Total knee arthroplasty in the presence of severe flexion contracture: A report of 37 cases. *J Arthroplasty* 1999; **14**(7):775-80.
  - 37 Lie SA, Engesaeter LB, Havelin LI *et al.* Mortality after total hip replacement: 0-10-Year follow-up of 39,543 patients in the Norwegian Arthroplasty Register. *Acta Orthop Scand* 2000; **71**(1):19-27.
  - 38 Bohm P, Holy T, Pietsch-Breitfeld B *et al.* Mortality after total knee arthroplasty in patients with osteoarthritis and rheumatoid arthritis. *Arch Orthop Trauma Surg* 2000; **120**(12):75-8.
  - 39 Carlsson AS, Henricson A, Linder L *et al.* A 10-year survival analysis of 69 Bath and Wessex ankle replacements. *J Foot Ankle Surg* 2001; **7**(1):39-44.
  - 40 Hamalainen M, Raunio P. Long term follow up of rheumatoid forefoot surgery. *Clin Orthop* 1997; **340**:34-8.
  - 41 Hanyu T, Yamazaki H, Ishikawa H *et al.* Flexible hinge toe implant arthroplasty for rheumatoid arthritis of the first metatarsophalangeal joint: Long-term results. *J Orthop Sci* 2001; **6**(2):141-7.
  - 42 Rosenberg WWJ, De Waal Malefijt MC, Laan RFJM *et al.* Forefoot reconstruction with combined first metatarsus osteotomy, metatarsophalangeal fusion and resection of the lesser metatarsal heads in rheumatoid patients. *J Foot Ankle Surg* 2000; **6**(2):99-104.
  - 43 Sojbjerg JO, Frich LH, Johannsen HV *et al.* Late results of total shoulder replacement in patients with rheumatoid arthritis. *Clin Orthop* 1999; **366**:39-45.
  - 44 Alund M, Hoe-Hansen C, Tillander B *et al.* Outcome after cup hemiarthroplasty in the rheumatoid shoulder: A retrospective evaluation of 39 patients followed for 2-6 years. *Acta Orthop Scand* 2000; **71**(2):180-4.
  - 45 Herold N, Schroder HA. Synovectomy and radial head excision in rheumatoid arthritis. *Acta Orthop Scand* 1995; **66**(3):252-4.
  - 46 Souter WA, Nicol AC, Berme N *et al.* A new approach to

- elbow arthroplasty. *J Bone Joint Surg Br* 1981; **63**:293-4.
- <sup>47</sup> Gschwend N, Scheier NH, Baehler AR. Long-term results of the GSB III elbow arthroplasty. *J Bone Joint Surg Br* 1999; **81(6)**:1005-12.
- <sup>48</sup> Shah BM, Trail IA, Nuttall D *et al*. The effect of epidemiologic and intraoperative factors on survival of the standard Souter-Strathclyde total elbow arthroplasty. *J Arthroplasty* 2000; **15(8)**:994-8.
- <sup>49</sup> Kudo H, Iwano K, Nishino J. Total elbow arthroplasty with use of a nonconstrained humeral component inserted without cement in patients who have rheumatoid arthritis. *J Bone Joint Surg Am* 1999; **81(9)**:1268-80.
- <sup>50</sup> Radmer S, Andresen R, Sparmann M. Wrist arthroplasty with a new generation of prostheses in patients with rheumatoid arthritis. *J Hand Surg [Am]* 1999; **24(5)**:935-43.
- <sup>51</sup> Fraser KE, Diao E, Peimer CA *et al*. Comparative results of resection of the distal ulna in rheumatoid arthritis and post-traumatic conditions. *J Hand Surg [Br]* 1999; **24B(6)**:667-70.
- <sup>52</sup> Chantelot C, Fontaine C, Flipo RM *et al*. Synovectomy combined with the Sauve-Kapandji procedure for the rheumatoid wrist. *J Hand Surg [Br]* 1999; **24B(4)**:405-09.
- <sup>53</sup> Rehak DC, Kasper P, Baratz ME *et al*. A comparison of plate and pin fixation for arthrodesis of the rheumatoid wrist. *Orthopedics* 2000; **23(1)**:43-8.
- <sup>54</sup> McGovern RM, Shin AY, Beckenbaugh RD *et al*. Long-term results of cemented Steffee arthroplasty of the thumb metacarpophalangeal joint. *J Hand Surg [Am]* 2001; **26(1)**:115-22.
- <sup>55</sup> Schmidt K, Willburger RE, Miehle RK *et al*. Ten-year follow-up of silicone arthroplasty of the metacarpophalangeal joints in rheumatoid hands. *Scand J Plast Reconstr Surg Hand Surg* 1999; **33(4)**:433-8.
- <sup>56</sup> Caplan AI, Elyaderani M, Mochizuki Y *et al*. Principles of cartilage repair and regeneration. *Clin Orthop* 1997; **342**:254-69.
- <sup>57</sup> Lee CR, Grodzinsky AJ, Hsu H-P *et al*. Effects of harvest and selected cartilage repair procedures on the physical and biochemical properties of articular cartilage in the canine knee. *J Orthop Res* 2000; **18(5)**:790-9.
- <sup>58</sup> Salminen H, Vuorio E, Saamanen A-M. Expression of Sox9 and type IIA procollagen during attempted repair of articular cartilage damage in a transgenic mouse model of osteoarthritis. *Arthritis Rheum* 2001; **44(4)**:947-55.
- <sup>59</sup> O'Driscoll SWM, Saris DBF, Ito Y *et al*. The chondrogenic potential of periosteum decreases with age. *J Orthop Res* 2001; **19(1)**:95-103.
- <sup>60</sup> Solchaga LA, Yoo JU, Lundberg M *et al*. Hyaluronan-based polymers in the treatment of osteochondral defects. *J Orthop Res* 2000; **18(5)**:773-80.
- <sup>61</sup> Richardson JB, Caterson B, Evans EH *et al*. Repair of human articular cartilage after implantation of autologous chondrocytes. *J Bone Joint Surg Br* 1999; **81(6)**:1064-8.
- <sup>62</sup> Bentley G, Minas T. Science, medicine, and the future. Treating joint damage in young people. *BMJ* 2000; **320(7249)**:1585-8.
- <sup>63</sup> Twyman RS, Desai K, Aichroth PM. Osteochondritis dissecans of the knee. A long-term study. *J Bone Joint Surg Br* 1991; **73(3)**:461-4.
- <sup>64</sup> Bugbee WD, Convery FR. Osteochondral allograft transplantation. *Clin Sports Med* 1999; **18(1)**:67-75.
- <sup>65</sup> Wakitani S. Repair of articular cartilage defect by cell transplantation. *Journal of Artificial Organs* 2000; **3(2)**:98-101.
- <sup>66</sup> Minas T. Autologous cultured chondrocyte implantation in the repair of focal chondral lesions of the knee: Clinical indications and operative technique. *Journal of Sports Traumatology & Related Research* 1998; **20(2)**:90-102.
- <sup>67</sup> Evans CH, Ghivizzani SC, Smith P *et al*. Using gene therapy to protect and restore cartilage. *Clin Orthop* 2000; **379(Suppl)**:214-19.
- <sup>68</sup> Sellers RS, Zhang R, Glasson SS *et al*. Repair of articular cartilage defects one year after treatment with recombinant human bone morphogenetic protein-2 (rhBMP-2). *J Bone Joint Surg Am* 2000; **82(2)**:151-60.
- <sup>69</sup> Haider YS, Roberts WC. Coronary arterial disease in systemic lupus erythematosus. Quantification of degrees of narrowing in 22 necropsy patients [21 women] aged 16 to 37 years. *Am J Med* 1981; **70(4)**:775-81.
- <sup>70</sup> Bruce IN, Burns RJ, Gladman DD *et al*. Single photon emission computed tomography dual isotope myocardial perfusion imaging in women with systemic lupus erythematosus. I. Prevalence and distribution of abnormalities. *J Rheumatol* 2000; **27(10)**:2372-7.
- <sup>71</sup> Esdaile JM. Prognosis in systemic lupus erythematosus. *Springer Semin Immunopathol* 1994; **16(2-3)**:337-55.
- <sup>72</sup> Manzi S, Meilahn EN, Rairie JE *et al*. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: Comparison with the Framingham study. *Am J Epidemiol* 1997; **145(5)**:408-15.
- <sup>73</sup> Abu-Shakra M, Urowitz MB, Gladman DD *et al*. Mortality studies in systemic lupus erythematosus. Results from a single center. I. Causes of death. *J Rheumatol* 1995; **22(7)**:1259-64.
- <sup>74</sup> Bruce IN, Gladman DD, Urowitz MB. Premature atherosclerosis in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000; **26(2)**:257-78.
- <sup>75</sup> Bruce IN, Urowitz MB, Gladman DD *et al*. Natural history of hypercholesterolemia in systemic lupus erythematosus. *J Rheumatol* 1999; **26(10)**:2137-43.
- <sup>76</sup> Rahman P, Urowitz MB, Gladman DD *et al*. Contribution of traditional risk factors to coronary artery disease in patients with systemic lupus erythematosus. *J Rheumatol* 1999; **26(11)**:2363-8.
- <sup>77</sup> Manzi S, Selzer F, Sutton-Tyrrell K *et al*. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum* 1999; **42(1)**:51-60.
- <sup>78</sup> Roman MJ, Salmon JE, Sobel R *et al*. Prevalence and relation to risk factors of carotid atherosclerosis and left ventricular hypertrophy in systemic lupus erythematosus and antiphospholipid antibody syndrome. *Am J Cardiol* 2001; **87(5)**:663-6.
- <sup>79</sup> Bruce IN, Gladman DD, Urowitz MB. Detection and modification of risk factors for coronary artery disease in patients with systemic lupus erythematosus: A quality improvement study. *Clin Exp Rheumatol* 1998; **16(4)**:435-40.
- <sup>80</sup> Rahman P, Gladman DD, Urowitz MB *et al*. The cholesterol lowering effect of antimalarial drugs is enhanced in patients with lupus taking corticosteroid drugs. *J Rheumatol* 1999; **26(2)**:325-30.
- <sup>81</sup> Bruce IN, Gladman DD, Urowitz MB. Premature atherosclerosis in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000; **26(2)**:257-78.
- <sup>82</sup> Malaviya AN, Mourou M. Should low-dose aspirin also be a background therapy for all patients with systemic lupus erythematosus (SLE)? *Lupus* 2000; **9(7)**:561-2.
- <sup>83</sup> Wierzbicki AS. Lipid-lowering drugs in lupus: An unexplored therapeutic intervention. *Lupus* 2001; **10(3)**:233-6.
- <sup>84</sup> DeBakey ME, Lawrie GM, Glaeser DH. Patterns of atherosclerosis and their surgical significance. *Ann Surg* 1985; **201(2)**:115-31.
- <sup>85</sup> Iiyama K, Hajra L, Iiyama M *et al*. Patterns of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 expression in rabbit and mouse atherosclerotic lesions and at sites predisposed to lesion formation. *Circ Res* 1999; **85(2)**:199-207.
- <sup>86</sup> Lusis AJ. Atherosclerosis. *Nature* 2000; **407(6801)**:233-41.
- <sup>87</sup> Napoli C, D'Armiento FP, Mancini FP *et al*. Fatty streak formation occurs in human fetal aortas and is greatly enhanced maternal, hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. *J Clin Invest* 1997; **100(11)**:2680-90.

- <sup>88</sup> Gerrity RG, Naito HK. Lipid clearance from fatty streak lesions by foam cell migration. *Artery* 1981; **8**:215-19.
- <sup>89</sup> Ross R. Atherosclerosis – An inflammatory disease. *N Engl J Med* 1999; **340**(2):115-26.
- <sup>90</sup> Gerrity RG. The role of the monocyte in atherogenesis. I. Transition of blood-borne monocytes into foam cells in fatty lesions. *Am J Pathol* 1981; **103**(2):181-90.
- <sup>91</sup> Gerrity RG. The role of the monocyte in atherogenesis. II. Migration of foam cells from atherosclerotic lesions. *Am J Pathol* 1981; **103**(2):191-200.
- <sup>92</sup> Davies MJ. Stability and instability: Two faces of coronary atherosclerosis: The Paul Dudley White lecture 1995. *Circulation* 1996; **94**(8):2013-20.
- <sup>93</sup> Wright SD, Burton C, Hernandez M *et al*. Infectious agents are not necessary for murine atherogenesis. *J Exp Med* 2000; **191**(8):1437-41.
- <sup>94</sup> Burnett MS, Gaydos CA, Madico GE *et al*. Atherosclerosis in apoE knockout mice infected with multiple pathogens. *J Infect Dis* 2001; **183**(2):226-31.
- <sup>95</sup> Zhu J, Quyyumi AA, Norman JE *et al*. Effects of total pathogen burden on coronary artery disease risk and C-reactive protein levels. *Am J Cardiol* 2000; **85**(2):140-6.
- <sup>96</sup> Valtonen V, Kuikka A, Syrjanen J. Thrombo-embolic complications in bacteraemic infections. *Eur Heart J* 1993; **14**(Suppl K):20-3.
- <sup>97</sup> Ridker PM, Hennekens CH, Buring JE *et al*. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; **342**(12):836-43.
- <sup>98</sup> Shoji T, Nishizawa Y, Fukumoto M *et al*. Inverse relationship between circulating oxidized low density lipoprotein (oxLDL) and anti-oxLDL antibody levels in healthy subjects. *Atherosclerosis* 2000; **148**(1):171-7.
- <sup>99</sup> Schmidt D, Goronzy JJ, Weyand CM. CD4+ CD7- CD28- T cells are expanded in rheumatoid arthritis and are characterized by autoreactivity. *J Clin Invest* 1996; **97**(9):2027-37.
- <sup>100</sup> Liuzzo G, Kopecky SL, Frye RL *et al*. Perturbation of the T-cell repertoire in patients with unstable angina. *Circulation* 1999; **100**(21):2135-9.
- <sup>101</sup> Liuzzo G, Goronzy JJ, Yang H *et al*. Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes. *Circulation* 2000; **101**(25):2883-8.
- <sup>102</sup> Wallberg-Jonsson S, Cederfelt M, Dahlqvist SR. Hemostatic factors and cardiovascular disease in active rheumatoid arthritis: An 8 year follow up study. *J Rheumatol* 2000; **27**(1):71-5.
- <sup>103</sup> Landewe RBM, Van den Borne BEEM, Breedveld FC *et al*. Methotrexate effects in patients with rheumatoid arthritis with cardiovascular comorbidity. *Lancet* 2000; **355**(9215):1616-17.
- <sup>104</sup> Kanda T, Hirao Y, Oshima S *et al*. Interleukin-8 as a sensitive marker of unstable coronary artery disease. *Am J Cardiol* 1996; **77**(4):304-7.
- <sup>105</sup> Ledford DK. Immunologic aspects of vasculitis and cardiovascular disease. *JAMA* 1997; **278**(22):1962-71.
- <sup>106</sup> Schonstein E, Kenny DT. Diagnoses and treatment recommendations on workers compensation medical certificates. *Med J Aust* 2000; **173**(8):419-22.
- <sup>107</sup> de Bono JP, Hudsmith LE, de Bono AM. Back pain in pre-registration house officers. *Occup Med [Lond]* 2001; **51**(1):62-5.
- <sup>108</sup> Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain* 2000; **84**(1):95-103.
- <sup>109</sup> Haas M. Evaluation of physiotherapy using cost-utility analysis. *Aust J Physio* 1993; **39**(3):211-16.
- <sup>110</sup> Koes BW, Bouter LM, Van Mameren H *et al*. Randomised clinical trial of manipulative therapy and physiotherapy for persistent back and neck complaints: Results of one year follow up. *BMJ* 1992; **304**(6827):601-5.
- <sup>111</sup> Malmros B, Mortensen L, Jensen MB *et al*. Positive effects of physiotherapy on chronic pain and performance in osteoporosis. *Osteoporos Int* 1998; **8**(3):215-21.
- <sup>112</sup> Meszaros TF, Olson R, Kulig K *et al*. Effect of 10%, 30%, and 60% body weight traction on the straight leg raise test of symptomatic patients with low back pain. *J Orthop Sports Phys Ther* 2000; **30**(10):595-601.
- <sup>113</sup> Hurley DA, Minder PM, McDonough SM *et al*. Interferential therapy electrode placement technique in acute low back pain: A preliminary investigation. *Arch Phys Med Rehabil* 2001; **82**(4):485-93.
- <sup>114</sup> Stucki G, Kroeling P. Physical therapy and rehabilitation in the management of rheumatic disorders. *Baillieres Best Pract Res Clin Rheumatol* 2000; **14**(4):751-71.
- <sup>115</sup> Elliott MJ, Maini RN, Feldmann M *et al*. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994; **344**(8930):1105-10.
- <sup>116</sup> Moreland LW, Baumgartner SW, Schiff MH *et al*. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *New Engl J Med* 1997; **337**:141-7.
- <sup>117</sup> Maini R, St Clair EW, Breedveld F *et al*. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A randomised phase III trial. *Lancet* 1999; **354**(9194):1932-9.
- <sup>118</sup> Lipsky PE, Van der Heijde DMFM, St Clair EW *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *New Engl J Med* 2000; **343**(22):1594-602.
- <sup>119</sup> Fox DA. Cytokine blockade as a new strategy to treat rheumatoid arthritis: Inhibition of tumor necrosis factor. *Arch Intern Med* 2000; **160**(4):437-44.