Reviews in Medicine

Rheumatology

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Introduction

With the ever increasing volume of research being published in rheumatology, immunology, as well as general medical publications, it is obviously impossible to, in any way, cover every important advance in this field in a limited review such as this. We have therefore singled out specific diseases where most advances seem to have been made over the past few years. These include:

1. Rheumatoid arthritis
2. Systemic lupus erythematosus (SLE)
3. Polymyositis/dermatomyositis
4. Progressive systemic sclerosis
5. Human immunodeficiency virus (HIV)-associated rheumatic syndromes

Within these sections, we have dealt in some detail with specific areas of current interest and importance, concentrating for example on syndromes and 'subsets' of SLE, advances in genetic research in rheumatoid arthritis and new autoantibody systems and their clinical relevance in SLE as well as in polymyositis and progressive systemic sclerosis. Newer therapies have been discussed in some detail, particularly, for example, the use of methotrexate as a first- or second-line therapy in patients with aggressive rheumatoid disease. We have drawn liberally on the work of other investigators and would refer readers to the recent comprehensive survey of all the rheumatic diseases published by Current Science – 'Current Opinion in Rheumatology' which has contributed so greatly to update our information in this rapidly expanding field.

Rheumatoid arthritis

An excellent review of the disturbances in rheumatoid arthritis recently appeared in the literature, and readers should refer to this for information on both pathophysiology and molecular susceptibility.¹

Genetic

Genetic susceptibility for rheumatoid arthritis (RA) is determined by certain genes within the major histocompatibility complex (MHC). In caucasoid populations, the main HLA-DR association is with HLA-DR4 but there is also an association with HLA-DR1 particularly in Italian and Israeli populations.²

On studying and analysing the structure of the DR antigens, it is apparent that homology exists between DR1 and DR4 at the 67–76 residues of the DRB chain. T cell clones which are alloreactive can discriminate a single amino acid difference in the receptor.³ There is a common epitope with cross reactive antibodies present in large numbers of RA patients. The 'disease epitope' hypothesis⁴ postulates that specific amino acid sequences or residues can effect immune responses because of their role in determining contact with the T-cell receptor.

The B chain of the DR molecules is polymorphic. The crystallographic structure of the Class II molecule has shown that an antigen binding 'pocket' exists.

The majority of DR4-RA patients have also been shown to demonstrate a linear DNA sequence which hybridizes with the DW14 probe.⁵

Two specific DR4-associated DRB genes, DW4 and DW14, are more specific markers for genetic susceptibility than is HLA-DR4. In DW4/DW14 -ve RA patients an identical nucleotide sequence is carried by these patients in a protein of the DRB gene on codon 71.

Recently it has been clearly demonstrated⁶ that DR1 B1 chains from two patients were identical and differed from previously reported DRB1 chains from individuals without RA, by two amino acid substitutions, at positions 85 (val-ala) and 86 (gly-val) and by a silent mutation at the last nucleotide of codon 78 (C-T).

Identical DRW10 B1 chains were also found in both individuals and encoded the epitope recognized by the monoclonal antibodies 109d6 which also recognizes an epitope on the DRW 53B2 chain of the DR4 haplotype. The third diversity regions

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of the DR1B (amino acids 67–74) and the DRW10 B1 chains (amino acids 67–73) seem to be identical with those of the DR4(DW14) B1 and B2 chains. The monoclonal antibody 109d6 is therefore able to define a higher level of susceptibility to RA than is specified by DR4 or DR1 analysis.⁷

The principle of conformational equivalence of regions of different MHC molecules as the basis of susceptibility to RA will have to be proven by larger epidemiological studies. The presence or absence of a particular conformation of antigen presenting molecules suggests a unitary immune recognition event. DQW3 may also be implicated in susceptibility.⁸ It is of interest that seronegative RA patients with disease onset after the age of 60 years present with a clinical course similar to PMR, have a relatively benign course and respond to lower doses of steroids. This type of disease does not progress to joint destruction. In this group of patients, there has been no evidence for any contribution of HLA to the disease risk and clearly this may be a different disease from typical RA. The use of specific probes in other seronegative RA patients will help to resolve this question.

Studies in different ethnic groups have revealed associations with different genes – DR1 for Israeli Jews particularly, DR4 and DW15 for Japanese. However, both these genes share the same epitope described above.

The T-cell receptor (TCR) is also likely to be an important element in determining susceptibility and further studies are in progress in order to focus on TCR gene polymorphism.

A recent study has demonstrated that the DQW7 allele correlated well with the presence of high levels of IgM RF⁹ and this finding may explain the previously reported link between DQW7 and more severe forms of RA.¹⁰

Anti-perinuclear factor (APF)

These perinuclear inclusions are keratohyaline granules which are also found in vaginal epithelial cells obtained from newborn babies and in rabbit ova and oesophageal epithelium. They can only be found in cells producing soft keratin (oral mucosa/vaginal) and are present mainly in the stratum intermedium, disappearing as the cells move closer to the surface.

A high specificity for the diagnosis of RA may be obtained by the determination of the APF, one of the autoantibodies directed against a component of epithelial cells. These antibodies are directed against round or bean shaped granules of unknown chemical nature surrounding the nucleus of epithelial cells usually obtained from human buccal mucosa. The unpredictability of the buccal cells has limited its popularity – variations from donor to

donor, from one day to another and from one cell to another (same sample). The indirect immunofluorescent technique (IIF) has been improved and perfected by Sondag-Tschroots *et al.*¹¹ furthering the original observations of Nienhuis *et al.*¹² Confirmation was recently documented by Janssens *et al.*¹³ Some investigators have found some correlation with severity of disease particularly in the group with seronegative RA,^{13,14} but this has not been confirmed by others.¹⁵ This group appears to have a poor anatomical and functional course and responds poorly to classical slow-acting antirheumatoid drugs.

HaT-1 system

Another new autoantibody system in RA, documented by Abe *et al.*, was found in Japan in 1988 and is referred to as the HaT-1 system. HaT-1 is an acidic protein in human and rat liver supernatant. Its significance is unclear.¹⁶

RA and cytokines

The synovial cells secrete substantial amounts of interleukin-1 (IL-1) while the secretion of T-cell factors such as gamma interferon is decreased.^{17–21} Additionally it has been further demonstrated that interleukin-2 (IL-2) inhibitor activity is diminished in synovial fluid but elevated in sera from patients with active⁷ or inactive RA. In osteoarthritic synovial fluids there is much less IL-2 inhibition activity. It is thought that the production of IL-2 inhibitors is suppressed in RA, regardless of disease activity. Cytokine over-production, combined with deficiency of inhibitors, may result in inflammatory lesions of the joints in RA patients.²²

Decreased natural killer (NK) activity has also been reported in patients with active disease.²³ Monocytes also release inhibitors of IL-1. Although the molecular nature of this inhibitor has not been well characterized, a relationship between this substance and transforming growth factor (TGF B) has been postulated. There are multiple members of the TGF B family and it has recently been demonstrated that TGF B is a very potent inhibitor of cellular and humoral immunity.^{24,25} It inhibits lymphocyte proliferation, the generation of effector cells and the expression of class II histocompatibility antigens. It appears that rheumatoid synovial fluid contains factors that can activate latent TGF B and that some cell types may be able to release the compound. Together with IL-6, which is abundant in synovial fluids and which stimulates proliferation of CD8 cells more than CD4 cells, it probably contributes to the decreased CD4/CD8 ratio characteristic of rheu-

matoid synovial fluids, as it inhibits the proliferation of CD4 cells. TGF B also modulates upward chondrocyte proliferation function.

Clinical

Rheumatoid nodulosis

This condition was again highlighted by the publication of two further cases.²⁶ Most common in males aged 30–50 years, its clinical course is benign and it does not seem to evolve into classical RA. The authors suggest four criteria for the diagnosis:

1. Multiple subcutaneous nodules identified by biopsy.
2. Recurrent joint symptoms with minimal clinical or radiological involvement.
3. Benign clinical course.
4. None or mild systemic manifestations of RA. Subchondral cysts and positive rheumatoid factor may be accompaniments. Recurrence of nodules may occur without treatment.

Mesangial glomerulonephritis in RA

Two papers recently drew attention to isolated haematuria and with underlying mesangial glomerulonephritis in patients with RA. Renal function remained normal in all patients and this condition may be more common than previously recognized.^{27,28}

Infection and rheumatoid arthritis

Increasing reports have appeared in the literature indicating that some viruses are associated with an arthritis strongly resembling RA. This has led to speculation that perhaps 'hidden' antigens such as viruses may be aetiologically responsible for RA. Chief among these is the Epstein-Barr virus and more recently HTLV-1.

A review by Saaj and Bennett in 1987 listed all the virus diseases associated with arthritis.²⁹ Denman³⁰ in his review concluded that known virus infections produce self-limited arthritis but that there is little evidence that these viruses are involved in the pathogenesis of chronic arthritis. Direct attempts to isolate viruses from chronic arthritic joints have been almost universally fruitless. However, interactions between exogenous infections and genes controlling growth could contribute to the abnormal proliferative events characteristic of rheumatoid arthritis. Bacon and Tunn in their paper on 'Infection and Arthritis' have reviewed the current theories.³¹

Epstein-Barr virus (EBV)

It appears that EBV may be linked to the aetiology of RA by mechanisms related more to molecular

mimicry than to T-cell regulatory abnormalities. Human rheumatoid factors might actually be anti-idiotypic antibodies elicited by antibodies, and Fc-receptors present on viruses, bacteria or virus-modified autologous cells.³²

Recently Roudier *et al.*³³ reported sequence homologies between the EBV viral encoded glycoprotein gp110 and the third hypervariable region of the Beta 1 chain of HLA-DR region known to be associated with susceptibility to RA. Patients with serological evidence of previous EB virus infection have been shown to have antibodies which recognize the same peptides for both gp110 and HLA-DW4. T-cell recognition of the determinant proteins for EB virus in subjects with HLA DW4, DW14 or DR1 may distinguish those in whom RA will develop from those in whom it will not. Further studies will no doubt be able to elucidate the role of the EBV in the pathogenesis of RA and its role in defective T-cell control of B-cell proliferation as is evidenced by the rheumatoid arthritis nuclear antigen (RANA) expressed also by viral (usually EBV) activated cells.

Relationship to retrovirus infections

HTLV-1 viruses are capable of depressing genes controlling IL-2-R.³⁴ A similar mechanism could contribute to autoimmune disease by leading to unchecked expression of receptors critical for clonal expansion of activated T-cells.³⁵

Enhanced IL-2-R activity has been reported in RA³⁶ and recent reports have provided evidence for the presence of HTLV1p19 and HTLV1p29 retroviral antigens in synovial tissue for patients with early proliferative RA.³⁷

Other investigators have reported cross-reactivities between the human MHC class BII domain and peptide gp41 derived from the human immunodeficiency virus.³⁸

Parvoviruses

Parvovirus B19 has been implicated in an arthropathy in adults which however is self limited and does not resemble RA.³⁹ Two recent patients documented, however, had evidence of a recent infection with parvovirus B19⁴⁰ and another two showed positive tests for rheumatoid factor for 6 months as well as arthritis.⁴¹

Mycobacteria

These bacteria express heat-shock proteins which are arthritogenic factors of adjuvant rat arthritis. Heat-shock proteins appear on cell surfaces in response to a variety of stress. Patients with RA have antibodies to heat-shock proteins from recombinant bacteria and in synovial fluid from RA patients are large numbers of CD4-CD8 ('double

negative') T lymphocytes which proliferative in response to bacterial antigens. A distinct CD3 associated T cell receptor comprised of alpha and beta chains appears in these cells.

Defective glycosylation of IgG

In RA, as well as in some other forms of arthritis, there are reduced glycosylation patterns of IgG,⁴² and this reduction may be related to the finding that the levels of enzymes involved in the glycosylation of proteins are diminished in RA.⁴³ It is possible that this abnormally glycosylated IgG may serve as an immunogen in the genetically susceptible host.

Magnetic resonance imaging (MRI)

The superiority of the use of MRI in the differentiation of intra- and extra-articular soft tissue structures was clearly demonstrated by Gilkeson *et al.*⁴⁴ MRI was found to be superior to standard radiographs in demonstrating synovial inflammation and in demonstrating erosions of carpal bones which were not seen on standard radiography. The expense of this procedure, however, precludes its routine use today. The technique is also superior in the demonstration of pannus and its relationship to the spinal cord and brainstem in cases where extensive bony destruction by RA makes plain film and linear tomographic assessment of the upper cervical spine difficult.⁴⁵

Neoplasia in rheumatoid arthritis

A recent editorial⁴⁶ summarized the relationship between neoplasia and rheumatoid arthritis particularly well. Patients with RA appear to develop malignancy at least at the same rate as the general population. However, there is an increased risk of developing lymphoproliferative malignancies similar to that seen in patients with other autoimmune diseases such as Sjögren's syndrome, diabetes mellitus and malignant lymphoma of the thyroid, as is seen with Hashimoto's thyroiditis. An explanation may be that clinical immune stimulation and associated lymphocyte activation predisposes to the development of lymphomas and excess numbers of lymphocytes bearing activation markers are seen in both the salivary glands and the thyroid gland in these two conditions. In RA there is evidence that lymphocyte activation occurs in the lymph nodes. The question of cytotoxic drug induced lymphomas in RA patients is still unanswered. They may well enhance the risk of neoplasias in RA.

Treatment of rheumatoid arthritis

Outcome

The question as to whether aggressive therapy affects the outcome of RA was recently discussed by Kushner.⁴⁷ 'Outcome' was defined as duration of therapy as well as a qualitative measure of efficacy. RA patients are certainly benefitted for the first few months and 'probably' for the first few years after starting second-line agents. All outcomes are relevant and these include symptoms, signs, disability, employability, joint destruction and death.

Second-line drugs are rarely taken for very long periods. After 2 years of therapy 60–70% were no longer taking gold, penicillamine or sulphasalazine and after 5 years only 20% were still taking these drugs. Functional status is mainly altered by surgery and not by any drug therapy. The outlook is indeed depressing in the absence of the availability of any specific 'targetted' therapy. It appears that despite a plethora of NSAIDs and increasing numbers of so-called 'disease modifying drugs', we are unable to influence the long term outcome of radiological progression, diminished earning capacity and increased mortality in our patients with RA in 1991.

Non-steroidal drugs (NSAIDs)

Large numbers of reports of enteropathy induced by NSAIDs have appeared over the past few years and considering that 30 million patients around the world take these compounds, this complication is of increasing importance. Clinically significant ulceration, haemorrhage or perforation occurs in 1–30% of subjects taking NSAIDs chronically. The subject was recently well reviewed in an editorial by Banerjee.⁴⁸ The complications may be summarized in Table I.

Table I   Gastrointestinal complications of NSAIDs

- Ulceration of stomach and duodenum
- Ulceration and stricture of small bowel
- Perforation of small and large intestine
- Relapse of ulcerative colitis
- (↑) Small intestinal permeability

Enteropathy affects patients of any age and either sex who have taken NSAIDs for 6 months or longer. More than two thirds of patients have subclinical intestinal inflammation and occult blood loss. Up to one fifth may have bile acid malabsorption and may develop diarrhorrea.

Iron-deficiency anaemia and hypoalbuminaemia develop if there is additional disease or dietary problems.

Occasionally obstruction or perforation of the small bowel may occur and inflammatory bowel disease is an important differential diagnosis.

The histopathological syndrome named 'diaphragm disease' is defined by the development of band-like scarring which forms diaphragms throughout the lumen of the small bowel. They may cause obstructive symptoms, but may be missed by standard radiographic techniques.⁴⁹

Individuals infected with *Campylobacter pylori* are more likely to develop dyspepsia, gastritis and erosive disease according to several studies.⁵⁰

The use of misoprostol ('cytotech'), a prostacyclin E analogue, which stimulates bicarbonate and mucus production as well as increasing mucosal blood flow as a 'cytoprotective' against NSAID-induced mucosal damage has been advocated.⁵¹ Although it appears that misoprostol heals and prevents NSAID-associated gastric ulcer, its efficacy in bowel-related effects is unproven. If the NSAID has to be continued and other factors predisposing to ulcer are addressed (e.g. smoking, alcohol abuse), misoprostol seems preferable to the use of an H₂ antagonist. Prophylaxis in the elderly and female patients may also be considered.

Nephrotoxicity may be observed at all ages, but is more of a risk in elderly patients with atherosclerotic cardiovascular disease, and several mechanisms are postulated:⁵² (1) altered renal prostaglandin synthesis; (2) inducement of interstitial nephritis; (3) inhibition of renin secretion and (4) enhancement of tubular water and sodium retention or reabsorption.

These adverse effects of NSAIDs are important in patients with severe congestive cardiac failure, cirrhosis with ascites, volume depletion due to chronic diuretic therapy, chronic renal insufficiency, diabetic nephropathy in frail elderly patients and perhaps in women with SLE. Idiosyncratic effects may result from NSAIDs. Impaired renal function, however, is usually reversible on withdrawal of the compounds. In most of these conditions listed, local synthesis of vasodilating prostaglandins is required to maintain vessel perfusion. The administration of NSAIDs to such patients places them at risk for an acute ischaemic accident because inhibition of prostaglandins allows unopposed vasoconstriction to occur. Monitoring of these effects (e.g. serum K, serum creatinine) should take place within days and not weeks, when short acting NSAIDs, such as ibuprofen, are used.

Ototoxicity is common as with salicylates. Aseptic meningitis with ibuprofen⁵³ and impaired wound healing⁵⁴ are two other uncommon side effects.

Gold compounds

Auranofin, the oral form of gold therapy, while being less toxic than the injectable sodium aurothiomalate, does not present a major advantage in the long term treatment of RA. Side effects such as diabetes, cutaneous gastrointestinal reactions, as well as lack of efficacy, lead to a high drop-out rate and animal studies indicate that although short term alteration in immune function is seen, with continuing dosage there seems to be a loss of effect on the immunological system.^{55,56} A modestly higher clinical efficacy only in children with JRA compared to placebo was recently shown.⁵⁷

Penicillamine⁵⁸

Less than 20% of patients remain on this compound in the long term, the main reason for withdrawal being side effects. Fifty per cent of withdrawals are due to penicillamine nephropathy. Most cases develop within 12 weeks of commencing the drug and nephrotic syndrome occurs in the majority. There is usually no deterioration in renal function as measured by the creatinine clearance. Resolution usually occurs within 2 years on withdrawal of the drug. This side effect may occur irrespective of dose or duration of therapy. Renal biopsy is indicated only if: (a) nephrotic range of proteinuria persists for > 1 year; (b) less severe proteinuria persists for 2 years; (c) another complication, e.g. amyloidosis, is suspected.

Sulphasalazine

This second-line agent appears to be fully effective in a dose of 3.0 g/day and most benefit is realized by the end of 15 weeks of dosing or by 2 months once a full maintenance schedule is achieved.⁵⁹ There is, however, a 28% incidence of side effects resulting in patient withdrawal. Its efficacy is comparable with injectable gold, but it may be better tolerated by patients with RA. The side effects are: (a) Minor: nausea, headache, dizziness and minor gastrointestinal complaints. The dose should be gradually increased and administered with food. (b) Idiosyncratic: e.g. agranulocytosis. Immediate withdrawal. (c) 'Allergic': Fever, rash, joint pains. Desensitization has been implemented with success in patients with inflammatory bowel disease. The overall incidence of neutropenia appears to be 1.4% and all patients recover. It most often appears within 2–10 weeks after commencing therapy.

Therapy has been discontinued in 33.5% of patients followed for up to 2 years and half of these were for adverse drug reactions.

Sulphasalazine, 2 mg, was recently compared with hydroxychloroquine 400 mg daily in 60 patients for 48 weeks by Nuwer-Zwart *et al.*⁶⁰ The

onset of response appeared earlier with sulphasalazine but there was no difference at 48 weeks.

Azathioprine (AZA)

AZA is at least as effective as gold, methotrexate, D-penicillamine or cyclophosphamide in studies reported to date.⁶¹

Three hundred and ninety-three AZA treated patients with RA were recently surveyed⁶² and these were compared with 153 similarly treated patients or retrieved from the databank of the American Rheumatism Association Medical Information System (ARAMIS) making a total of 546 patients.

Most frequently reported side effects were nausea, vomiting and leucopenia. Gastrointestinal intolerance accounted for 60% of therapy interruptions in 95 patients. Cholestatic jaundice occurred in one patient. No lymphomas or leukaemia were encountered and only 8 patients developed neoplasms (hypernephroma, bladder, lung, ovarian, skin). Infections with herpes zoster virus occurred in 23 of the 153 ARAMIS group of patients. AZA differs very little in the short term from methotrexate. A high drop-out rate is seen in the first 6 months. However, pain, stiffness and mobility seem to improve to a greater extent in patients on methotrexate therapy.⁶³

AZA may be considered as a second line disease – modifying anti-rheumatoid arthritis drug agent in selected patients.

Methotrexate

Methotrexate (MTX), a folic acid antagonist, appears to be effective in patients who have failed with other second line antirheumatic drugs such as hydroxychloroquine, gold and D-penicillamine. Efficacy has been demonstrated as continuing for up to 53 months of treatment.

There is a high degree of overall drug tolerability. Response to MTX occurs in a dose-dependent manner, but toxicity is also more common in the higher dosage.⁶⁴

Although 7.5 mg administered weekly is appropriate initially, Fust *et al.* demonstrated that frequent, transient dosage adjustments may prevent treatment failures.⁶⁵

MTX is indicated as a first line drug in patients with severe, active disease who are unable to wait for the therapeutic effects of other second line drugs to manifest in special situations, for example being unable to work.

An anti-inflammatory rather than an immunosuppressive mode of action has been proposed for low dose MTX.⁶⁶ Single doses of MTX have recently been shown to induce rapid falls in CRP. MTX has also been shown to inhibit IL-1 activity *in vitro*⁶⁷ and IL-1 production when administered *in*

vivo.⁶⁴ Inhibition of cytokine secretion or activity is therefore one likely mode of action. There may also be an effect on the 5-lipoxygenase system.

Dosage Single doses of oral or intramuscular (i.m.) therapy are now recommended. The average oral dose is 7.5–15 mg/day but doses as high as 25 mg/day have been used without significant side effects. Absorption is affected by milk intake and oral doses should therefore be given between breakfast and lunch. If the patient requires more than 20 mg per day it is recommended that one switches to the intramuscular route at a slightly reduced dosage initially. Intramuscular therapy is also recommended for cognitively impaired patients or non-compliant patients. If no response to 20 mg of oral therapy is seen, one may switch to i.m. Gastrointestinal intolerance even with a 'cycled' regime is a further indication for i.m. dosing.

Supplemental folic acid (Citrovorum) If administered in the first 48 hours after MTX, toxicity may be offset and efficacy is not reduced. Stomatitis particularly is reduced. There is some evidence that the administration of folic acid itself results in less toxicity.

Response There may be a significant reduction in prednisolone requirements. The drop out rate because of lack of efficacy is low (80%) and the maximum effect occurs within 6–12 months. There is then a 'plateau response' and patients may require increased doses to maintain the response. NSAIDs may also be discontinued, but not usually in the first 12–24 months.

Combination therapy The concomitant use of sulphasalazine with MTX is absolutely contraindicated as both have antifolate activity. Trials with combinations have included azathioprine, oral gold preparations and hydroxychloroquine. No significant differences have been noted.

Contraindications to MTX use include morbid obesity (fatty infiltration of the liver), substantial alcohol intake, previous liver disease, and diabetes mellitus. If pregnancy is attempted it is recommended that MTX be discontinued 30 days prior to attempts in females and 90 days in males. Unrecognized HIV disease is a hazard and a full sociosexual history should be undertaken in all individuals in whom this diagnosis is suspect.

Side effects are due to polyglutamines accumulating in liver and renal cells accounting for hepatotoxic/ nephrotoxic effects. (1) *Bone marrow depression* (13%) may occur at any time during the course of MTX therapy, even as long as 72 weeks after. Neutropenia, thrombocytopenia and

anaemia occur. An anaemia due to folate deficiency may occur, usually if other unrecognized risk factors are present. These include: (a) renal disease; (b) intercurrent infections (it is recommended that MTX be discontinued during acute viral infections); (c) the use of concomitant drugs, e.g. NSAIDs (diclofenac), or trimethoprim (antifolate activity); (d) folate deficiency. This is usually because of dietary intake of folic acid-containing foods. A folate deficiency may be suspected by regular blood counts showing an elevated MCV. If more than 105, folic acid should be administered.

(2) *MTX pneumonitis* (2.5%). This may also occur with any dosage and at any time. Factors predisposing to this potentially fatal complication include: (a) excessive smoking; (b) pre-existing lung disease; (c) renal impairment; (d) non-steroidal use; (e) males are more frequently affected; (f) more common if extra-articular rheumatoid disease is present. The condition usually responds to withdrawal, steroid therapy and, if necessary, assisted ventilation. MTX therapy may be reattempted with success in some of these patients.

(3) '*Aminopterin syndrome*'. If administered during pregnancy the 'aminopterin' syndrome may result. This includes skeletal abnormalities, cleft palate, ear abnormalities, hydrocephalus, meningocele and anencephaly.

(4) *Liver disease*. Rather than doing routine liver biopsies pretreatment, it is now recommended that liver biopsy only be undertaken: (1) if there are persistently abnormal liver function tests; (2) hypoalbuminaemia; (3) after 2 years (some experts will now go as long as 4 years) on 1.50 g of MTX. Few cases of hepatic fibrosis have been reported and cirrhosis is extremely rare. Weinblatt (personal communication) now only discontinues MTX therapy if there is a three-fold elevation of liver enzymes. He also recommends that bloods for liver function tests be taken as far as possible from the day of administration of the drug. Three cases only of chronic active hepatitis with ascites have recently been reported in the USA.

(5) Although healing of erosions has been seen in sporadic cases, it seems that in most there is a worsening of the radiographic appearance with an '*osteoarthritic*' response resulting in marked loss of joint space.⁶⁹

(6) *CNS toxicity*. This consists of lightheadedness, dizziness, vertigo, headache, subtle cognitive dysfunction, mood alterations, unpleasant cranial sensations, and memory impairment. These complications usually appear within 1–2 months after starting MTX therapy and may be more common in the elderly and those with renal impairment.⁷⁰

(7) *Others*—e.g. alopecia, UV light erythema and 'malignant nodulosis'. Methotrexate and RBC folate levels should be performed at regular and frequent intervals. MTX should be undetectable 48

hours after discontinuation. Folinic acid in doses of 5–10 mg every 3 to 6 hours (where doses of 20–25 mg weekly were used) should be given intravenously. This method is indicated for haematological toxicity and renal failure.

MTX in Felty's syndrome A prompt response in a patient with Felty's syndrome treated with MTX⁷¹ with a recurrence of the neutropenia within 8 weeks of the cessation of therapy has been reported. Two other reports have shown similar results.^{72,73} Although the response occurred within 4–8 weeks in most, in one it took 7 months.

Combination chemotherapy

Much has been written in the past few years on this topic. In patients with severe and unresponsive RA, combinations of cytotoxic drugs may offer the best prospects for healing of erosions. Fear of toxicity limits this avenue of treatment. Low dose methotrexate and cyclophosphamide are superior to methotrexate alone. The combination of cyclophosphamide, azathioprine and hydroxychloroquine has also been successfully used,⁷⁴ but 4 patients developed malignancies. If a patient has responded to penicillamine therapy, but still has significant disease activity the addition of sulphasalazine or gold may produce further benefit. The addition of chloroquine or hydroxychloroquine unlikely to be helpful.⁷⁵

In a recent open study reported by Waterworth,⁷⁶ sulphasalazine, 1 g daily, plus azathioprine, 100 mg daily, was tried in 13 patients after its successful use in another patient. Haematological and hepatic side effects were not a problem. Only two patients developed leucopenia. The therapy was discontinued in one and dosages reduced in two with recovery. This combination has been suggested as an alternative for patients whose disease is only partially controlled by either azathioprine or sulphasalazine alone.

The combination of methotrexate, azathioprine and hydroxychloroquine was given to 12 patients and in 8 this was continued for 14–18 months. Four stopped after 3–4 months, one because of nausea and 3 because of lack of effect. Seven responded to this regime, one achieving complete remission and two 'near remissions'.⁷⁷

Cyclosporin A^{78,79}

This compound is an immunomodulatory agent which is relatively specific in its action in inactivating T-helper inducer lymphocytes by blocking IL-2 production. It has also been found to inhibit gamma interferon and IL-3 production. Effective clinical responses in patients studied in several open as well as randomized placebo-controlled

studies, have shown that the compound is an effective therapy for RA. A subset of 'anergic' patients with more severe immunological abnormalities and more synovial infiltration by lymphocytes appear to respond more favourably. Toxicity, chiefly nephrotoxicity, occurs in nearly all patients. A greater than 20% increase in serum creatinine levels occurred in most studies, but is usually reversible with dose reduction. Neurotoxicity is the second commonest side effect (hyperaesthesia parasthesia, tinnitus, nervousness, tremor). Hypertrichosis, hyperuricaemia, acute tophaceous gout, frequent menses and breast tenderness (?blocking effect on prolactin receptors and increase in severe prolactin levels) may also occur.

The drug possesses a very narrow therapeutic 'window'. High dosage (10 mg/kg body weight) is associated with high degree of toxicity; 1 mg/kg body weight may be ineffective and also causes toxicity. It remains to be seen whether the administration of a lower dose (2.5 mg/kg body weight) is effective and whether chronic administration of this amount also leads to toxicity.

The use of NSAIDs in combination with cyclosporin A may be associated with a lower incidence of reversible nephrotoxicity, particularly in elderly patients. Cyclosporin combined with methotrexate was used by Miescher *et al.*⁸⁰ with favourable results and this approach needs further investigation.

Fish oil

The effects of dietary supplementation with marine fish oil containing icosapentaenoic acid (EPA) on the clinical manifestations of rheumatoid arthritis have been assessed in several trials. Modest anti-inflammatory effects only have been seen although there has been an impressive 'down-regulation' of pro-inflammatory mediators, such as leukotrien B₄, interleukin-1B, interleukin-19 and TNF. Long term studies are needed to assess whether any prolonged, lasting benefit can be obtained with this laborious type of dietary supplementation.^{81,82}

Other new therapies

Recombinant human granulocyte colony stimulatory factor,⁸³ antilymphocyte immunotoxin,⁸⁴ anti-interleukin (IL-2) receptor antibody,⁸⁵ and interleukin-2 toxin⁸⁶ have been used and are still experimental. Anti-CD4 antibodies and anti-thymocyte globulin have also been tried with some success.

OM.8980⁸⁸

OM.8980 a peptidic *E. coli* extract influences the active response *in vitro* in animal models and in

man. Several trials of this new compound have been conducted (open double-blind against uranofin, placebo and combined trials). It seems that the compound is well tolerated with few side effects and may have a role to play in the management of relatively mild RA.

Thymopoetin (TP-5)⁸⁹

Seventy-six patients were treated with TP-5 (50 mg) or placebo for 7 weeks in a multicentre study. Clinical improvement with minimal toxicity was observed in the TP-5 treated group.

Podophyllum derivatives (CPH-82)⁹⁰

CPH-82 (comprised of two purified glycerides of *Podophyllum emodi*) was used in 13 patients with RA and compared with placebo. A statistically significant improvement in most clinical and immunological variables occurred. There were some patients who complained of diarrhoea and abdominal pain.

Thalidomide

Seventeen patients were treated in an open study by Gutierrez-Rodriguez *et al.*⁹¹ Seven experienced complete remission and 5 partial remission. The duration of remission appeared to be shorter in those patients who had been taking corticosteroids. Drowsiness/constipation was evident in most patients. Maculo-papular erythema developed in 8 with hard oedema of the lower limbs in a further 8. The high frequency of side effects negates the general use of this compound for refractory RA. Its administration should be restricted to males and post menopausal females because of its teratogenic effects.

Therafectin (amiprilose)

This non-metabolizable hexose sugar is an anti-inflammatory drug as well as immuno-modulator with a low toxicity profile and which showed a positive screen in animal models.⁹² Open and randomized trials are still in progress. A recent prospective, multicentre, randomized 12 week study against placebo, comprising a total of 221 patients, showed that amiprilose HCL has significant anti-inflammatory activity and a favourable safety profile when used as the sole anti-rheumatic therapy in patients with active RA. Open and randomized trials are still in progress.

An excellent and comprehensive review of new therapies for rheumatoid arthritis at all stages of the disease has recently been provided by Hams⁹³ and is also contained in the editorial by Ziff.¹

Systemic lupus erythematosus

Autoantibodies and SLE

The autoantibodies demonstrable in sera of patients with SLE may be associated with the disease itself or may identify specific subsets. The term ‘marker’ antibodies has been recently used by Venables⁹⁴ in his review of autoantibodies in the rheumatic diseases. Their use in subset definition is unquestionable, but their specific function in pathogenesis is not yet understood.

Five major antigens/antibody systems are found in SLE and these are shown in Table II.

Table II Major antigen/antibody systems in SLE	
Antigen	% Positive in active untreated patients
Natural/double stranded (ds) DNA	70–90
Sm	25
U1RNP	40–50
Ro (SS-A)	40
La (SS-B)	20
aCL	30

The anticardiolipin (aCL) antibodies are directed specifically against negatively charged phospholipids and there is a strong association with the ‘lupus anticoagulant’ phenomenon. This is dealt with separately in another section of this review. Antibodies to U1RNP, Sm, Ro and La are directed against RNA protein antigens.

Antibodies to Sm are highly specific for SLE. They appear to be more common in patients of Afro-Caribbean origin while antibodies to U1RNP are also found with overlap syndromes such as ‘mixed connective tissue disease’ (MCTD),⁹⁵ scleroderma, polymyositis and urticarial vasculitis. There may also be an increased incidence in patients with SLE and pulmonary hypertension.

More than 90% of patients with anti-La also have anti-Ro. Some patients with SLE may have anti-Ro alone. Anti-La antibodies, apart from being present in patients with SLE and primary Sjögren’s syndrome, may also be seen in patients with progressive systemic sclerosis.⁹⁶ Reichlin has recently grouped these antibodies and their relationship to the presence of renal disease as shown in Figure 1.⁹⁷

Western blotting has enabled workers to recognize the isoforms of these antigens. La is a single protein, and is a 45 kDa molecule. The heterogeneity of the Ro antigen is now established. There are four isoforms (52 kDa, 54 kDa and two distinct kinds of 60 kDa proteins). They may be found in the red cells (RBC, Ro) and in the lymphocytes

Figure 1 Relationship of autoantibody systems to renal disease (courtesy of Reichlin, M.).

(lymphocyte, Ro). The 60 kDa is totally different to the 52 kDa and 54 kDa protein. It appears that different isoforms predominate in various serological and clinical situations, for example when Ro and La are present together, the proteins are 60 kDa, 52 kDa and 45 kDa. When Ro coexists with nRNP, a 60 kDa protein and not the 54 kDa isoform is present.⁹⁸ When Ro alone is present, this is usually a 54 kDa protein.⁹⁷ There is also a relationship to the histocompatibility antigens.⁹⁹

The anti-Ro antibodies are associated with a variety of clinical subsets (Table III).⁹⁷ Additionally, specific laboratory features also appear to associate with anti-Ro (Table IV).⁹⁷

Table III Clinical subsets associated with anti-Ro (SSA)

Subacute cutaneous lupus erythematosus
ANA negative lupus
SLE associated with homozygous C2 + C4 deficiencies
Vasculitis of Sjögren’s syndrome
Neonatal lupus erythematosus

Table IV Laboratory features associated with anti-Ro (SSA) in primary Sjögren’s syndrome

a. Lymphopenia
b. Cryoglobulinaemia
c. Hypocomplementaemia
d. Hyperglobulinaemia, especially IgG
e. Antinuclear antibody

Overlap syndromes

Anti-RNP is typically found in patients with overlapping features of SLE, scleroderma and polymyositis and this combination was originally defined as a distinct clinical entity by Sharp *et al.* and termed ‘mixed connective tissue disease’ (MCTD).⁹⁵ The association also extends to a strong association between anti-RNP, Raynaud’s phenomenon, arthritis, polymyositis, fibrosing alveolitis

and tendonitis. Adult patients with MCTD may subsequently develop scleroderma, whereas children may develop SLE. Many patients with MCTD, however, remain in this category. Patients with MCTD tend to have a lower incidence of renal disease than SLE.

Idiotypes and anti-idiotypes

One way of distinguishing antibodies serologically is by analysis of the variable region of immunoglobulin, which is the antigen-binding component of the molecule. This is termed the 'idiotype' and it may reside on either the heavy or light chains of the variable region or on both. Identification of these idiotype determinants is accomplished by immunizing one species, such as a mouse, with a human monoclonal antibody thereby raising 'anti-idiotypic' antibodies which are purified by appropriate absorption techniques.

There appears to be an idiotypic connection between anti-Sm and anti-DNA antibodies.¹⁰⁰ A monoclonal antibody (28/12) shares the major cross-reactive idiotype of the anti-DNA antibodies of the MRL – lpr/lpr mice (H130), does not react with DNA but binds to Sm RNP.⁹⁵ The 16/6 idiotype and less frequently the cross-reactive 32/15 idiotype can frequently be demonstrated in the sera of lupus patients (40–54% of the 16/6 and 23–38% of the 32/15).¹⁰¹

The level of the 16/6 idiotype reflects activity of the disease¹⁰² where higher than background levels of these idiotypes may also be found in healthy first degree relatives of patients studied.^{103,104} The 16/6 and/or 32/15 idiotypes may also be found in renal tissue of lupus patients. The importance of these findings suggests modulation of the immune response by anti-idiotypic therapy and this has already been accomplished in animals.^{105,106}

Correlations with the 16/6 idiotype and disease, however, clearly depends on other immunological or genetic factors, as the same idiotype may be found in non-lupus related diseases such as macro/cryoglobulinaemia.

Assessment and prediction of lupus activity

C3 levels may predict flares of lupus activity 1–2 months prior to a clinical exacerbation particularly with CNS-LE.¹⁰⁷

Soluble interleukin 2 receptors (IL-2R), which are released by activated lymphocytes, are found in higher concentration in patients with active disease.¹⁰⁸

Decreased activity of IL-2 inhibitor in plasma of patients with severe and moderate SLE has been detected by some investigators.¹⁰⁹ Similarly, the terminal complement complex C5b-9 may correlate with disease exacerbations.¹¹⁰

Clinical SLE

A full review of the clinical manifestations and therapy of systemic lupus erythematosus was recently published in the *Reviews on the Rheumatic Diseases* and readers should refer to this for a general up-date.

Elderly patients with SLE have a higher incidence of serositis, secondary Sjögren's syndrome and antibodies to Ro. Serositis is common as the initial symptom in the elderly and serositis or musculoskeletal manifestations are the initial symptom in most patients over the age of 50 at onset of the disease.¹¹¹

Anterior uveitis is not an uncommon manifestation of SLE and physicians should be aware of this presentation.¹¹²

Pseudomotor cerebri (raised intracranial pressure in the absence of an intracranial mass or hydrocephalus) may unusually be seen in SLE and responds well to corticosteroid therapy.¹¹³

Several patients with relapsing polychondritis and nasal chondritis and SLE have been reported by Kitridou *et al.*¹¹⁴

Lupus retinopathy, which is usually a microangiopathy, has been found in approximately 8% of lupus patients. It is associated with active SLE in 88% and there appears to be a strong correlation with lupus cerebritis (73%).¹¹⁵ A similar incidence of occlusive ocular vascular disease was found in patients with antiphospholipid antibodies by Asherson *et al.*¹¹⁶

Jabs *et al.* described severe retinal vaso-occlusive disease termed 'retinal vasculitis' in 11 patients with SLE. The visual outcome was often poor and CNS involvement occurred in 73% again drawing attention to the close association of retinal and CNS disease.¹¹⁷

Seven patients with optic neuropathy were reported by the same group, the patients presenting with acute retrobulbar neuritis, ischaemic optic atrophy or showing progressive visual loss.¹¹⁸

A deforming arthropathy may occur in 5% of SLE patients, and tends to develop early on in the disease. Non-erosive carpal collapse, deformity of the thumb, non-erosive ulnar deviation and subluxation of the MCP joints, parametacarpophalangeal joint 'hook' formation, scant and asymmetric joint erosions and swan neck deformity of the fingers have also been described. These are predominantly due to ligamentous changes rather than synovitis.¹¹⁹

Lupus and thyroid disorders

The coexistence of SLE and thyrotoxicosis was reported by Rodrigue *et al.*¹²⁰ in 6 patients while a new antigen antibody system (anti-MIC-1) was found in 5 of 6 patients with SLE and hyper-

thyroidism and not present in several other groups of patients.¹²¹ A high frequency of abnormal thyroid function tests may be detected in SLE patients without diagnosed thyroid disease and elevations of TSH, low T3 as well as high anti-microsomal antibody titres indicating subclinical hypothyroidism.¹²² The association of autoimmune thyroiditis with SLE is strong.¹²³ A review of 319 patients in Malaysia revealed 9 with thyrotoxicosis, 3 with hypothyroidism and 2 with thyroiditis, a greater incidence than in the general population.¹²⁴ Viana *et al.*¹²⁵ recently found an increased incidence of antithyroglobulin antibodies in SLE patients and a positive correlation with TSH levels and antithyroid antibody dilution levels pointing to evidence of subclinical thyroid disease in SLE patients. The subset of SLE patients with thyroid antibodies tended to be older and to have a higher incidence of thyroid disease.

Neonatal lupus syndrome (NLE)

This is usually associated with antibodies to Ro and La,¹²⁶ but infants have been described who are positive for anti-U1RNP (nRNP) and negative for Ro and La and who demonstrated cutaneous lesions.¹²⁷

Neonatal lupus erythematosus with congenital heart block

Cardiac symptomatology, particularly atrio-ventricular block, is the predominant systemic feature of the neonatal lupus syndrome (NLE). It is now well established that the presence of anti-Ro antibodies, particularly in the mother, is associated with this complication. Mothers may suffer from frank SLE, 'primary' Sjögren's syndrome or be asymptomatic, but nevertheless still demonstrate these antibodies on testing.

It seems that congenital heart block may develop abruptly long after the completion of maturation of the fetal conducting system (16th week), usually late in the second trimester of pregnancy. It has been postulated that fetal 'myocarditis' is the initial consequence of antibody insult with subsequent degeneration of the conducting system. The majority of reported infants have been female, suggesting a hormonal influence on expression of the disease.¹²⁸⁻¹³⁰ Pacing is not usually required. A small number of children with NLE may subsequently develop features of SLE, with onset usually in their teens.

Diffuse IgG staining of the myocardium was detected by Litsey *et al.*¹³¹ and Taylor *et al.*¹³² on postmortem studies on infants with congenital heart block while Lee *et al.*¹³³ recently found IgG and complement deposition in a particulate pattern around the conduction system.

The projected frequency of a mother with one

affected child having a further infant with CHB is estimated at 1 in 5.

Non-congenital high grade atrio-ventricular block (HGAVB)

A case of this problem in SLE was documented and the literature of 7 previously reported cases briefly reviewed.¹³⁴ The HGAVB resolved spontaneously in 12 hours in only 1 patient. Three received corticosteroids resulting in resolution in all three, but in one there was a recurrence 4 weeks after while on steroids. Sudden death occurred in 3 patients. Permanent pacemakers may need to be inserted.

The antiphospholipid antibodies and antiphospholipid syndromes

The antiphospholipid antibodies (aPL) (the 'lupus anticoagulant', antibodies to cardiolipin, false positive test for syphilis (VDRL)) are a family of cross-reacting antibodies which, when present, predominantly in patients with SLE and 'lupus-like' disease, are strongly associated with thrombotic events, both venous and arterial.¹³⁵⁻¹³⁷ These are often recurrent and associated with a moderate thrombocytopenia. Recurrent fetal loss is also frequently encountered in this group of patients¹³⁸ and the combination of thrombosis/recurrent fetal loss and thrombocytopenia has been termed the 'antiphospholipid syndrome' (APS).¹³⁹ It is now clear that another group of patients with the identical features but without any of the clinical or serological features of SLE exists and this has been called the 'primary' antiphospholipid syndrome ('Primary' APS). Several reviews of this new 'subset' of patients have recently been published.¹⁴⁰⁻¹⁴³ These patients may be complement deficient and are often DR7, rather than DR2/DR3, as is seen with classical lupus.¹⁴⁴ They may have relatives with SLE or a familial clotting tendency.¹⁴⁵ It is now clear that aCL antibodies may occur in a wide variety of conditions other than SLE/SLE-related diseases such as with other autoimmune diseases, e.g. primary Sjögren's syndrome,¹⁴⁶ systemic sclerosis,¹⁴⁷ rheumatoid arthritis,¹⁴⁸ malignancies (e.g. carcinoma prostate/bronchus),¹⁴⁹ 'primary' pulmonary hypertension,¹⁵⁰ and haematological disorders (particularly idiopathic thrombocytopenic purpura).¹⁵¹ They may be induced by infections (viral, infective endocarditis)¹⁵²⁻¹⁵⁵ or drugs (chlorpromazine, procainamide), and in most, the response is of a low level and the isotype is IgM. High levels of IgG aCL antibodies and on occasion high levels of IgM seem to be linked to thrombotic events.¹⁵⁶ Thrombotic events do not usually occur with the other conditions listed above.

The aPL antibodies may be linked to the development of idiopathic deep venous thrombosis, strokes¹⁵⁷ and less often myocardial infarction¹⁵⁸ particularly in younger people (<45 years) as well as to idiopathic recurrent abortions in the absence of any definable connective tissue disease.

Other associations are chorea^{159,160}, positive Coomb's test (occasionally accompanied by haemolytic anaemia), multi-infarct dementia,^{161,162} idiopathic Addison's disease,^{163,164} and pseudo multiple sclerosis.¹⁶⁵

Recent studies have, however, not borne out the associations of the aPL antibodies with high levels alone. Clearly other factors are operating in those patients demonstrating features APS. A high incidence of aCL antibodies has been found in relatives of patients with systemic lupus erythematosus; 7.9% of sera were strongly positive but there was no evidence of any features of the 'syndrome'.¹⁶⁶ It is also clear from several recent reports that patients with identical features of the syndrome but with negative aPL antibodies are being encountered, although infrequently.

Therapy of the APS and aPL-associated complications is empiric. The use of systemic steroids when not indicated for the underlying lupus illness is not recommended. Cytotoxic drugs/plasmapheresis, although resulting in a fall of antibody levels, results in a rapid rise to pretreatment figures. The use of long term anticoagulant therapy, low dose aspirin or antiplatelet compounds (e.g. dipyridamole) is justified and may control the clotting tendency in these patients. Pregnancy is a different situation and the use of low dose heparin (5000 U twice daily subcutaneously) combined with low dose aspirin from the commencement of the pregnancy is the regimen recommended by most authorities.^{167,168} The use of high-dose steroids is associated with complications in the mother such as pre-eclamptic toxemia, diabetes or opportunistic infections and also appears not to be justified. Fifteen to 20 mg oral prednisolone daily is an option which can be reserved for problem cases. The use of intravenous globulins (e.g. Sando-globulin) has been associated with live births in several reported cases,¹⁶⁹ but has not been necessarily associated with a fall in aCL levels or disappearance of the 'lupus anticoagulant'.¹⁷⁰ Multicentre controlled trials are presently being conducted in order to determine the efficiency of a variety of differing regimens.

The B2-glycoprotein I (apolipoprotein H) co-factor

Recently, two separate groups have described a co-factor^{171,172} which appears to be necessary for the binding of anticardiolipin antibodies. This 'co-factor', present in human serum, human plasma and bovine serum, influences the binding of antibodies in a dose-dependent manner. It has been

identified by N-terminal region sequence analysis as a plasma protein (aB2-Glycoprotein I – B2GP1) known to bind anionic phospholipids. This B2GP1 exerts multiple inhibiting effects on the intrinsic coagulation pathway and platelet aggregation. The protein has been shown to bind to lipoproteins, platelets, heparin as well as to mitochondria, DNA, and anionic phospholipids; 40% is associated with lipoproteins of various classes.

Interference with its function by aPL antibodies may explain the thrombotic diathesis seen in association with these antibodies as one of its functions may be to bind and neutralize negatively charged macromolecules which might enter the blood stream and thus diminish unwanted activation of blood coagulation.

Newer therapies in SLE

High dose intravenous immunoglobulin (IVIG)

The use of IVIG therapy in three patients with SLE was documented by Covetta *et al.*¹⁷³ Striking improvement in neurological function was observed in a patient with central nervous system disease and coma. There was a significant transient increase of C1q binding activity after the infusion and the authors postulated that circulating immune complexes interacting with the immunoglobulins may favour their clearance.

In their second patient with thrombocytopenia, the platelet count normalized after a 5 day course of IVIG. Renal function deteriorated in one patient with elevation of blood pressure and pulmonary oedema in another.

Monthly intravenous cyclophosphamide

Nine patients with SLE were treated with monthly pulses of cyclophosphamide and an improvement in creatinine clearance, 24-hour urinary protein level, complement and ESR was observed.¹⁷⁴ Pulse cyclophosphamide is usually reserved for lupus patients with acute cerebral, renal or respiratory complications and is clearly more effective than azathioprine.

Selective thromboxane antagonists

The use of selective thromboxane receptor antagonist (BM 13: 177) given by intravenous infusion to patients with renal disease and SLE may be beneficial. Impairment of renal function may be haemodynamically mediated and be reversible with a thromboxane antagonist.¹⁷⁵

Danazol

Danazol (200 mg four times a day) may be very useful in treating refractory thrombocytopenia in

SLE, and platelet counts may return to normal within 6 weeks of starting therapy.¹⁷⁶

Polymyositis/dermatomyositis (PM/DM)

This inflammatory disease of striated muscle is characterized by the presence of widespread degeneration of muscle fibres with hyalinization, swelling, vacuolation and disruption of muscle cells. Regeneration of other muscle cells may be seen simultaneously. A chronic inflammatory cell infiltrate, comprised mainly of lymphocytes, is seen between the muscle fibres. Eventually, muscle atrophy and fibrosis supervene. A central role for the CD8 cytotoxic T-cells has been postulated. When accompanied by typical skin changes, the condition is termed dermatomyositis. Polydermatomyositis has to be distinguished primarily from the metabolic myopathies, the mitochondrial myopathies, which have in common abnormalities of muscle energy metabolism, resulting in skeletal muscle dysfunction, the muscular dystrophies, and the fibromyalgia syndrome. Polymyositis/dermatomyositis (PM/DM) is characterized by inflammatory changes in muscles associated with muscle weakness and usually very little in the way of pain which may be absent altogether. The proximal muscles are predominantly involved and in the early stages there may be considerable oedema overlying the affected muscles.

Distinct clinical differences between PM and DM have been emphasized by Dalakas.¹⁷⁷ These may be summarized as follows:

1. PM is characterized by restricted Class I – immune effector mechanisms in which the cytotoxic CD8 lymphocytes play a major part.
2. The lymphocyte infiltrate of DM consists of lymphocytes with a higher CD4 to DC8 ratio, a higher percentage of B cells and by relative absence of invasion of non-necrotic muscle fibres by lymphocytes, suggesting a predominantly luminal mechanism. A variety of extra muscular manifestation may also be seen.
3. Childhood DM appears to be a distinct clinical entity characterized by a membranolitic complement attack complex deposited in arteries and capillaries indicating a complement-mediated intramuscular microangiopathy. This is not seen with advent PM. A major role for cellular immune attack has also been postulated in inclusion body myositis (IBM).

The inflammatory muscle diseases have been classified by several authors into essentially the same subcategories.

Autoantibodies in PM/DM

Much interest has been shown in recent years in the wide variety of autoantibodies directed against both nuclear and cytoplasmic intracellular components which are exclusively found in patients with myositis and which serve to identify particular subsets of patients (Table V).

Table V Specific autoantibodies in PM/DM¹⁷⁸

	Clinical associations
I. With identified clinical associations	
Antisynthetases	
Anti Jo-1 (histidyl ± RNA synthetase)	PM/ILD
Anti PL-7 (threonyl ± RNA synthetase)	PM/ILD
Anti PL-12 (alanyl ± RNA synthetase)	PM/ILD
Anticytoplasmic antibodies	
Anti SRP	PM
Anti KJ	PM/ILD
Myositis-associated antinuclear antibodies	
Anti PM-Scl	PM/PSS
Anti Mi-2	DM
Others	
Anticytoskeletal antibodies	PM
Anti 56 kd	PM
II. Unidentified associations	
Antisynthetases	
Anti-OJ (isoleucyl ± RNA synthetase)	
Anticytoplasmic antibodies	
Anti-Fer	
Anti-Mas	
Others	
Anti-nuclear pore	

PM = polymyositis; DM = dermatomyositis; ILD = interstitial lung disease.

Viruses and myositis

This topic has also been much discussed. A variety of viruses may be associated with myositis (Table VI).

Table VI Viral associations of polymyositis

Picornavirus infection	
Coxsackie	: Juvenile DM ^{179–181}
Echovirus	: DM (with agammaglobulinaemia) ¹⁸²
Encephalomyocarditis virus	: Experimental (Micc) ¹⁸³
Influenza virus	:
Retrovirus infection	
HIV ^{184,185}	
HTLV-1 ¹⁸⁶	

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The production of myositis-associated antibodies as a result of viral infection has a number of explanations.¹⁸⁷ Certain picornaviruses have transfer RNA-like structures as part of their genome and host synthetases could bind to these, as they would to transfer RNA, rendering such complexes immunogenic. Other mechanisms such as complementary viral and host structures could lead to autoantibodies by anti-idiotypic mechanisms. Molecular mimicry by which antibodies against infectious agents cross-react with homologous areas of host proteins might be another explanation.

Interstitial lung disease and polymyositis

Interstitial lung disease (ILD) as a complication of myositis has been recognized in recent years and has been associated particularly with antibodies to RNA synthetases especially Anti-Jo-1.¹⁸⁸ ILD occurs in approximately 9% of PM/DM patients. An association of this autoantibody with HLA-DR3 and DR6 has been described particularly in white patients.¹⁸⁹

HLA-DR1 associated with ILD, with increased DR5, has been found in patients with antibodies to the signal recognition particle.¹⁹⁰

Vasculitis and PM/DM

The presence of vasculitis in PM/DM has only recently been emphasized. Most patients with this complication have had the typical rash of PM/DM. Feldman¹⁹¹ described 7 out of 76 patients seen over an 11-year period with cutaneous vasculitis. Twenty-four per cent of patients in the series reported by Ramirez *et al.*¹⁹² had cutaneous vasculitis; one of their patients additionally developed a severe intestinal vasculitis which led to perforation and death.

Treatment¹⁹³

Immunotherapy for PM/DM still remains empirical with no prospective studies documented to date. In summary, therapy comprises:

1. Corticosteroids
2. Immunosuppressive drugs
3. Other therapeutic modalities
4. Drugs to prevent therapeutic-induced complications
5. Physical therapy
6. General nursing care and pulmonary toilette
7. Adequate nutritional management
8. Psychosocial encouragement
9. Aggressive control of infections

1. Corticosteroids

The use of steroids in this condition has been extensively reviewed by Dalakas.¹⁹⁴ An aggressive high dose approach is recommended either orally (80–100 mg a day) or by pulse intravenous route (methylprednisolone 1 g daily for 3 consecutive days).¹⁹⁵ Oral therapy should be maintained in high dose for 3 to 4 weeks switching to alternate day therapy of 80–100 mg daily, reducing by 5–10 mg increments every 3 to 4 weeks. A maintenance dose of 20–25 mg on alternate days should be continued when all signs of the disease have abated.

2. Immunosuppressives

The use of immunosuppressives such as azathioprine/cyclophosphamide early on in the disease has many advocates, some investigators preferring to use them simultaneously with corticosteroid administration in order to achieve (a) a 'steroid sparing' effect; (b) prevent relapses consequent on steroid reduction. These agents should certainly be used together with steroids in patients with rapidly progressive disease with severe weakness and respiratory failure.

Pulse intravenous cyclophosphamide may be administered at the same time as high dose steroids in these patients and continued at 1–3 weekly intervals. 'Burnt out' cases of course will not respond favourably and therefore many authors think that this therapy should not be delayed in serious cases. Patients with ILD are more difficult to treat and have a less favourable prognosis.

3. Other therapeutic options

When steroids and immunosuppressives have both appeared to fail, a variety of other options may be considered. These include:

- (a) *Methotrexate*. Several reports have described the efficacy of this compound in the treatment of PM/DM.^{196,197}
- (b) *Cyclosporine*. Isolated cases have responded favourably to this drug particularly in patients with juvenile dermatomyositis.^{198–200}
- (c) *Plasmapheresis*. This may be effective and three patients recently treated in an open study by Clarke *et al.*²⁰¹ improved.
- (d) *Total body irradiation*.²⁰²
- (e) *Intravenous gammaglobulin*.

These forms of treatment may be useful in resistant cases or in relapses but controlled studies on larger series of patients are required.²⁰³

4. Drugs

Drugs to prevent therapeutic-induced complaints. These include antacids, cimetidine or ranitidine,

for gastric complications of steroid therapy and calcium supplements to prevent osteoporosis.

5. Physical therapy

The avoidance of disuse atrophy therapy directed towards the preservation of existing muscle function, and the prevention of contractures should be vigorously pursued by suitably trained physiotherapists. Stretching exercises, a passive range of motion exercises, massage and moist heat packs are recommended. Vertebral compression fractures (corsets), crutches and ultrasound for aseptic necrosis may be indicated.

6. Adequate local nursing care

Treatment for skin ulceration (e.g. bed sores, ulcerated calcinotic deposits) as well as padded supports for the elbows, knees and heels may be necessary. Respiratory complaints should be prevented by regular physiotherapy and postural drainage.

7. Diet

A high protein, low carbohydrate, low salt diet is recommended.

8. Psychosocial

Clearly psychosocial encouragement is an essential part of therapy and the early and vigorous treatment of any infections, particularly respiratory, is essential if a low morbidity and mortality is to be expected.

Scleroderma (systemic sclerosis)

In the past few years, the use of more sophisticated diagnostic procedures has increased our knowledge of the clinical and serological disturbances in the different types of scleroderma and related syndromes. However, their aetiology, as in all autoimmune diseases, is unknown and we are still left with the problem of what induces the connective tissue abnormalities present in these disorders. In addition, our better understanding has not led to more satisfactory treatment or a better prognosis.

Aetiology and pathogenesis

The aetiology of scleroderma is almost certainly multifactorial, and includes both genetic and environmental factors.

The application of molecular biological techniques, especially those relating to the major histocompatibility complex and T-cell receptors, has

helped in the understanding of the role of genetic factors. The most classic association of the major histocompatibility complex is with the HLA-B8, DR3 haplotype. In addition, associations with DR1 and DR5 have been observed. Recent data acquired by the newly developed technique of restriction fragment length polymorphic (RFLP) analysis appear to confirm the previous serotypic findings. Studies by Dunckley *et al.*²⁰⁴ have shown that DRw11 (the common form of DR5) is increased in frequency in both progressive systemic sclerosis and its 'CREST' variant. Myers *et al.*²⁰⁵ have shown that the DR3a-DRw52a haplotype (which cosegregates with HLA-B8 and C4AQ0) appears to be a marker for the development of pulmonary fibrosis in these patients. Using this new technique, Kratz *et al.*²⁰⁶ found an association with gamma-chain polymorphism. However, no association has been found with alpha or beta-gene T-cell receptor polymorphism. Lymphocytes bearing the gamma-delta T-cell receptor predominate in epidermal tissues, which implies that these cells may contribute to the dermal nature of the disease.

On the other hand, environmental factors, such as exposure to chemical substances (vinyl chloride, silica dust, epoxy resins, paraffin or silicone, toxic oils, trichlorethylene, perchlorethylene, benzene, solvents, metaphenylenediamine) or various drugs (bleomycin, L-5-hydroxytryptophan, carbidopa, pentazocine, cocaine, appetite suppressants), are now recognized as a cause of scleroderma in certain patients.^{207,208}

Immunological abnormalities, including both cellular and humoral systems, play a predominant role in the pathogenesis of the disease. The link between these disturbances and the development of the vascular and fibrotic lesions seen in this condition have been the subject of many studies over the past few years. Mark *et al.*²⁰⁹ detected induction of antibody-dependent cytotoxicity by scleroderma sera. Kahaleh and LeRoy²¹⁰ found circulating interleukin-2 in the sera of most scleroderma patients and a correlation of serum levels with the extent of skin involvement and the disease duration. Finally, Kahari *et al.*²¹¹ have shown that interferon-alpha and gamma reduce excessive collagen synthesis and procollagen mRNA levels of scleroderma fibroblasts in culture. It is reasonable to speculate that immune cell activation leads to cytokine release and stimulation of fibroblast proliferation with collagen synthesis on the one hand and vascular injury on the other.²¹²

Classification

Based on clinical involvement and serological markers, there have been several attempts to classify the broad spectrum of the sclerosing

disorders. An international group lead by LeRoy²¹³ recently agreed to subdivide them into (a) localized scleroderma (including limited, generalized and other types of morphea, and linear scleroderma) and (b) systemic sclerosis differentiating those patients with limited cutaneous involvement from those with diffuse involvement of the skin (Table VII). Nevertheless, the relationship of the different types of well defined scleroderma to related syndromes ('CREST' syndrome, 'mixed' and 'undifferentiated' connective tissue disease, 'overlap' syndromes, environmentally induced scleroderma, Raynaud's phenomenon, 'localized fibroses') is being continuously re-examined. In addition, there is a desire for developing indices of severity, activity, and progression. The aim of this classificatory work is obviously to develop a more rational approach to subsequent drug therapy.

Table VII Proposed classification of scleroderma

Localized
Morphea
Limited
Plaque
Guttate
Generalized
Others (deep)
Nodular
Subcutaneous
Profunda
Linear scleroderma
Linear
En coup de sabre
Systemic
Limited cutaneous
Diffuse cutaneous
CREST syndrome

Clinical and serological aspects

The main progress achieved recently has been in the clinical and serological approach to the disease. From the clinical point of view, two aspects must be focused. Firstly, there is a challenge for the physician to identify patients who will develop the disease in the future from the far larger numbers of patients with Raynaud's phenomenon and other sentinel manifestations of systemic sclerosis. Subsequently, in those patients destined to develop systemic sclerosis, he should quantify the degree of involvement of the six major target organs affected, i.e. skin, lungs, heart, gastrointestinal tract, musculoskeletal system, and kidneys.

Two non-invasive procedures have recently been developed which may detect virtually all future systemic sclerosis patients arising from within the Raynaud's group: (1) nailfold capillary micro-

scopy²¹⁴ and (2) autoimmune serology using a human, rapidly dividing cell substrate – the human laryngeal carcinoma cell line (HEp-2).

A large series of autoantibodies has been observed in patients with scleroderma and some of them appear to be useful as specific disease markers^{215–217} (Table VIII). Three patterns of staining may be found in scleroderma sera: (a) homogeneous staining of the nucleus; (b) speckled nuclear staining; (c) nucleolar staining which may be clumpy, speckled or homogeneous. These patterns appear to be more specific for sclerodermatous disease rather than for other autoimmune disorders.

A speckled pattern on indirect immunofluorescence is indicative of antibodies directed against ribonucleoprotein and to topoisomerase I (previously referred to as Scl-70). Topoisomerase I is both nucleolar and nucleocytoplasmic, but varies in concentration from one cell to another. Anticentromere antibodies react with centromeric antigens localized in the nucleolus of cells during division. Anti-Ro antibodies are found predominantly in patients with a secondary Sjögren's syndrome.

Once a patient has been identified as having systemic sclerosis, the one manifestation that has proved most useful in predicting outcome with remarkable precision is the extent of skin involvement, as has been found in clinical studies by Barnett *et al.*,²¹⁸ Lally *et al.*,²¹⁹ LeRoy *et al.*,²¹³ and Masi,²²⁰ among others. Patients with limited cutaneous systemic sclerosis usually have a favourable long-term prognosis, whilst those with diffuse cutaneous involvement are at major risk for multisystem organ failure (Table IX).

Disease severity can also be correlated with autoantibodies. Scleroderma is less severe in those patients with anticentromere antibodies, which are strongly associated with the limited cutaneous form of the disease including the CREST type patients.^{221,222} Antibodies to topoisomerase I occur predominantly with diffuse disease and may be

Table VIII Autoantibodies detected in patients with scleroderma

Anti-topoisomerase I (Scl-70)
Anticentromere antibodies
kinetochore proteins-A, B, and C
Antinucleolar antibodies
RNA polymerase I
Fibrillarin (U3 RNA protein complex)
PM-Scl
To
Nor-90
Anti-ribonucleoprotein
Anti-Ro
Anti-type IV collagen
Anti-laminin

associated with a higher frequency of pulmonary fibrosis.²¹⁷ Antibodies to type IV collagen have been found to be associated with lung disease by certain investigators.²²³

Table IX Manifestations of limited and diffuse cutaneous systemic sclerosis

<i>Limited cutaneous systemic sclerosis</i>
Raynaud's phenomenon for years (occasionally decades).
Skin disease limited to hands, face, feet, and forearms (acral) or absent.
A significant late incidence of pulmonary hypertension with or without interstitial lung disease, trigeminal neuralgia, skin calcification, telangiectasia.
A high incidence of anticentromere antibodies (70–80%).
Dilated nailfold capillary loops, usually without capillary dropout.
<i>Diffuse cutaneous systemic sclerosis</i>
Onset of Raynaud's phenomenon within one year of onset of skin changes (puffy or hidebound).
Truncal and acral skin involvement.
Presence of tendon friction rubs.
Early and significant incidence of interstitial lung disease, oliguric renal failure, diffuse gastrointestinal disease, and myocardial disease.
Absence of anticentromere antibodies, but presence of antitopoisomerase antibodies (30%).
Nailfold capillary dilatation and capillary destruction.

Treatment

Evaluation of the efficacy of therapy is difficult because the disease is so highly variable in its severity and rate of progression. Therefore, baseline measurements of disease activity are mandatory. Tests proposed which may assist in the evaluation of this activity are summarized in Table X.^{214,224–227} However, no single test has proved to be completely satisfactory for this purpose.

On the other hand, the therapy of systemic sclerosis continues to be nonspecific. During the past few years a considerable number of well-designed clinical trials of adequate duration have been published. A 3-year, parallel, randomized, double-blind trial of 65 patients with chlorambucil has not demonstrated any effect on the natural history of the disease.²²⁸ Cyclophosphamide, 5-fluorouracil, 6-thioguanine, methotrexate, azathioprine, cyclosporine A, interferons alfa and gamma, plasma exchange, lymphoplasmaapheresis, total lymphoid irradiation, antithymocyte-globulin, and the antifibrotic agents colchicine, D-penicillamine and potassium para-aminobenzoate are some of the other agents that have been used.^{229–237} Although encouraging, the results have thus far been very poor. Therefore, a greater effort in the future is needed in order to study newer agents

which might have disease-modifying activity based on the results of laboratory investigations.

Table X Proposed tests to evaluate scleroderma activity

- Nailfold capillary microscopy
- Factor VIII complex levels
- Serum-soluble interleukin-2-receptor levels
- Proto-oncogens
- Serum aminoterminal type III procollagen peptide
- Serum type IV collagen
- Laminin fragments

Relationship of Raynaud's phenomenon to scleroderma

Raynaud's phenomenon is reported as being the presenting sign in 80–90% of patients with scleroderma and may precede the development of the disease by many years. A subject which has concerned rheumatologists has been the search for markers, both clinical and serological, which might characterize those patients with 'primary' Raynaud's phenomenon who are more likely to develop full blown scleroderma at a later stage. These include: (a) clinical markers – patients who have some other clinical symptoms or signs of a connective tissue disorder ('broad' Raynaud's phenomenon), but without fulfilling any definite criteria. These patients may have previously been classified as 'secondary' Raynaud's. (b) Serological markers – the presence of antinuclear antibodies, highest in the 'broad' Raynaud's phenomenon category. These include antibodies directed against the centromere. When this antibody is accompanied by digital oedema, digital telangiectasia, greater impairment of blood flow and an increased number of dilated capillary loops on nailfold microscopy, these patients could be described as having definite limited cutaneous scleroderma.

Antibodies to topoisomerase I may be seen in 3–10% of patients with 'primary' Raynaud's phenomenon. Although patients with negative antinuclear antibodies might also develop signs of a connective tissue disorder, from a number of studies it seems that patients with antibodies to both the centromere and topoisomerase I are at the greatest risk for the development of scleroderma. Long term studies are still needed in a sufficient number of patients before any definitive conclusions can be achieved regarding the predictive value of these autoantibodies.²³³

Cancer and scleroderma

Reports of patients having scleroderma temporally associated with carcinoma of the ovary, oesopha-

oesophagus, stomach, bladder, colon, rectum, cervix, multiple myeloma and lymphoma have been published.²³⁴ However, the mechanisms involved in these associations are unknown.

Rheumatological manifestations of HIV infection

Arthritis has been described at all stages of HIV infection (Table XI). It may be the presenting feature in an otherwise asymptomatic patient, occurring with the 'ARC' phase of the infection (AIDS related complex) or presenting in the full blown AIDS syndrome.

The pattern of the arthritis may vary from oligoarticular (1–5 joints) in the majority or polyarticular (> 5 joints). The knee is usually the most frequently affected joint and may be bilaterally affected. Spinal pain suggestive of axial joint involvement may also occur and may be either thoraco-lumbar or cervical and may often be seen in association with peripheral arthritis. Sacroiliitis may be evident.

Psoriatic arthritis developing simultaneously with the onset of dermatopsoriasis is not uncommon and the psoriatic lesions are characteristically found affecting the trunk, limbs, and head. Keratoderma blenorrhagica may occur. The arthritic symptoms are generally severe and may be persistent, recurrent or migratory. A sudden flare-up of pre-existing psoriasis should also raise the suspicion of underlying HIV infection.

Seborrhoeic dermatitis may also accompany arthritic symptoms and should also give rise to suspicion.

Table XI Rheumatological manifestations of HIV infection

AIDS, arthralgias and polyarthritis
Seronegative arthritis e.g. psoriatic arthritis
Reiter's syndrome
Sjögren's syndrome
Necrotizing vasculitis
SLE-like syndromes
Polymyositis
Opportunistic joint infections due to unusual organisms

Reiter's syndrome

Increasing numbers of patients with Reiter's syndrome (RS) and AIDs are being seen in both the USA and the UK. Several theories have been proposed as to the co-concurrence of the two diseases. (a) Increased propensity for infection in AIDS patients. Arthritogenic bowel pathogens may be present in an increased frequency. (b) Immunodeficiency and the elevation of suppressor cytotoxic T cells may increase the likelihood of an

untoward immune response which results in RS. (c) Activation of the immune response associated with RS may contribute to conversion of a latent HIV infection to an active infection and AIDS, such as occurs with herpes zoster infections. (d) There are common epidemiological features responsible for the two diseases. (e) There may be a genetic susceptibility of certain patients with AIDS to develop RS.

Great care should be taken in administering methotrexate to patients with HIV infections. Fulminant Kaposi sarcoma and *Pneumocystis carinii* infections followed by death in two such patients have been reported by Winchester *et al.*²³⁵

Erosive arthropathy is common in these patients and there may be florid joint inflammation which is protracted, with the joints of the lower limbs predominating. Enthesopathy of the Achilles tendons and dactylitis producing 'sausage' digits are also common.

The majority of patients who develop RS are HLA B27 positive.²³⁶ No clear arthrogenic infection has been found in most RS patients, but infections with shigella, campylobacter, yersinia or unidentified diarrhoeal illness have been possible precipitants in HIV patients. Eleven of the patients in the Winchester series had a diarrhoeal illness preceding the arthritis.

Patients with RS are usually refractory to conventional therapy.

AIDS arthritis^{239–241}

Apart from Reiter's syndrome and psoriatic arthritis, several other patterns of arthritis can be identified: (a) subacute oligo-articular arthritis. Severe pain and disability lasting for one week to several months affecting the joints and the lower limbs particularly. Response to NSAIDs is generally ineffective, but intra-articular steroids may be dramatically effective. (b) An acute painful articular syndrome lasting for 2 to 24 hours often requiring narcotics. Emergency medical care and hospitalization may be required for these patients. No synovitis is evident.

Septic arthritis

Infection with organisms such as *Sporotrichon scheskiei*, *Cryptococcus neoformans* and *Histoplasma capsulatum* has been reported, but generally septic arthritis is not as common in HIV infection as might be expected.

Polymyositis

Proximal muscle pain, stiffness and weakness are suggestive of myositis. The myositis may be undistinguishable from polymyositis and may be

accompanied by a rash typical of dermatopoly-myositis.^{237,238}

A number of patients however demonstrate evidence of inflammation on muscle biopsy. There may be an inflammatory myopathy with lymphocytic infiltrates and individual muscle cell necrosis and regeneration, indistinguishable from classical polymyositis. Abundant nemaline rods have been noted by others, generally without inflammation. These rods may occasionally be seen in patients with polymyositis or myopathy. It is, however, noted that should they be seen in muscle biopsy specimens, HIV infection should strongly be considered.

Sjögren's syndrome

A syndrome closely resembling Sjögren's syndrome may be seen in patients with HIV infections. The differences between HIV-associated disease and the idiopathic variety may be summarized in Table XII.²³⁶ DR52 seems to be common in the HIV patients as well as DR-5 positivity, as opposed to the A1, B8 DR3, DR2 and DQ1/DQ2 antigens in the idiopathic variety. CD8 positivity is predominant as compared with CD4 positivity, which is the major infiltratory lymphocyte in salivary glands in patients with the idiopathic variety.

'Lupus-like' syndromes

The clinical and serological features which may mimic SLE are outlined in Table XIII.²³⁶ HIV-associated disease in the presence of T-helper cell depletion should always be suspected.

No cases with antibodies to DNA or to Sm have been encountered. There are two case reports where SLE and HIV actually co-existed.

Additionally, false positive HIV tests may occur in SLE. The presence of a multisystem disease with

Table XII Comparison of HIV-associated and idiopathic or classic Sjögren's syndrome

	HIV	Idiopathic
Sex		
Male	+++	+
Female	+	+++
Sicca symptoms	+++	+++
Lymphadenopathy	+++	+
Hypergammaglobulinaemia	+++	+++
Anti-Ro/SS-A	○	++
Anti-LA/SS-B	○	++
HIV antibody	+++	○

Relative weight of individual findings represented on a scale of ○ to + + + +.

Table XIII Clinical and laboratory features of HIV infection that may mimic SLE²³⁶

Constitutional
Fever, malaise, weight loss
Dermatological
Butterfly rash due to seborrhea
Alopecia
Cutaneous vasculitis
Oral aphthosis
Musculoskeletal
Arthralgia/arthritis
Myalgia/myositis
Neurological
Psychosis
Seizures
Peripheral neuropathy
Renal
Azotaemia
Proteinuria/haematuria
Lymphadenopathy
Haematological
Immune thrombocytopenia
Leukopenia, lymphopenia
Coomb's-positive haemolytic anaemia
Immunological
Antinuclear antibodies
Hypergammaglobulinaemia
Circulating immune complexes

a malar rash of seborrhoeic dermatitis, resembling the butterfly rash of LE, neurological abnormalities, renal involvement and the typical serological features of hyperglobulinaemia, leucopenia, anaemia, thrombocytopenia, positive antinuclear and anticardiolipin antibodies as well as circulating immune complexes clearly might give rise to diagnostic difficulties between the two conditions.²⁴² The varieties of autoimmune phenomena occurring with HIV infection are shown in Table XIV.²³⁶

Table XIV Autoimmune laboratory phenomena associated with HIV infection

Polyclonal hypergammaglobulinaemia
Circulating immune complexes
Autoantibodies
Antinuclear factor
Rheumatoid factor
Anticardiolipin
Anticellular antibodies
Antiplatelet
Anti-red blood cell
Anti-lymphocyte
Anti-brain
Anti-parietal cell
Miscellaneous
β ₂ -microglobulin
Acid-labile interferon alpha
Serum lysozyme
Urinary neopterin
Interleukin II receptors (serum)

HIV-associated vasculitis

More than 14 cases of necrotizing vasculitis have been reported in association with HIV infection. A polyarteritis nodosa (PAN) like illness with vasculitis of medium-sized vessels involving the skin, nerve and muscle has been documented. Several cases of vasculitis limited to the central nervous system have also been reported and these may resemble primary angiitis of the central nervous system. Leucocytoclastic vasculitis, necrotizing vasculitis of the temporal arteries and a variety of other vasculitic syndromes have been reported.

Seronegative spondyloarthropathies

Ankylosing spondylitis and reactive arthritis are associated with the HLA B27 histocompatibility antigen. One of the most interesting concepts in the pathogenesis of these diseases is the hypothesis that certain bacteria carry components that are cross-reactive with HLA B27 antigens. Organisms such as shigella, salmonella, yersinia, campylobacter, clostridia and chlamydia species are associated with the development of reactive arthritis and there is some evidence, albeit controversial, to suggest that *Klebsiella pneumoniae* may be involved in ankylosing spondylitis.

There are three hypotheses to explain the involvement of HLA B27 – a class I molecule, in the development of reactive arthritis. Firstly, HLA B27 may behave as an antigen presenting molecule which T lymphocytes recognize. However, it has not been proved conclusively that the arthritis is mediated entirely by T lymphocytes. Secondly, HLA B27 may behave as a receptor for factors released by arthritogenic organisms. These factors are encoded by bacterial plasmids which may then become encoded in the genome of the patient's synovial cells. Finally, the hypothesis of molecular mimicry has attracted a great deal of attention.

In a review article, Yu *et al.*²⁴³ discuss the evidence for cross reactivity between bacterial and HLA B27 antigens. Specifically, they found that a monoclonal antibody to *Yersinia pseudotuberculosis* Ye-2 reacted with a 19 kDa outer membrane protein of the organism and also reacted specifically with HLA B27. Similar experiments by Raybourne showed that the monoclonal antibodies B27M1 and B27M2 to HLA B27 also reacted with 23 kDa and 36 kDa envelope proteins of *Shigella*

flexneri, *Shigella sonnei*, *Salmonella typhimurium*, *Klebsiella pneumoniae* and *Escherichia coli*.

In the same review, Schaak then describes the basis for molecular mimicry. Certain amino acid sequences are responsible for binding antibodies and/or T cells. Thus if a patient's cell surface and a bacterial envelope carry similar amino acid sequences, T cells or antibodies may cross react with both epitopes. It has been demonstrated that the HLA B27 molecule has a six amino acid sequence that is identical to a sequence on the surface of *Klebsiella pneumoniae*. A single antibody preparation raised in rabbits against the HLA B27 derived sequence reacted with the peptide sequence derived from *K. pneumoniae*, the entire *K. pneumoniae* protein as well as a synthetic peptide with this sequence. There is thus good evidence for cross reactivity between HLA B27 and certain bacterial antigens although whether this is the exact mechanism by which these diseases arise remains to be seen.

One other phenomenon seen in patients with the spondyloarthropathies is interesting and not fully explained. This is the persistence of high levels of IgA antibodies directed against *Yersinia enterocolitica* in patients with reactive arthritis secondary to infection with the organism. The antibody may develop following oral ingestion of the organism and may persist in response to the continued presence of either the bacteria or certain bacterial components in the synovium. Similar IgA antibodies directed against *Klebsiella pneumoniae* have been found in ankylosing spondylitis patients^{244,245} and *Klebsiella nitroreductase* epitopes that cross react with HLA B27 have been demonstrated in the inflamed synovial tissue of HLA B27 +ve patients.²⁴⁶ This subject is reviewed in an excellent editorial by Mielants and Veys.²⁴⁷

In the field of seronegative reactive arthritis the organism *Borrelia burgdorferi* is becoming increasingly important. As well as being the recognized cause of Lyme disease, there is some evidence to suggest that it may be implicated in reactive arthritis.²⁴⁸ Thus patients who are HLA B27 positive may be at risk of developing a reactive arthritis rather than Lyme disease following infection with the spirochaete. *B. burgdorferi* must therefore be added to the list of infectious agents including HIV which may be associated with the development of Reiter's syndrome. The therapeutic implications of this are reviewed in a leading article by Arnett.²⁴⁹

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