Publication of the Month 2004

Issue 12/2004	SmD peptide as target in SLE
Issue 11/2004	Decrease of anti-CCP and RF following anti-TNFalpha therapy
Issue 10/2004	Comparison of different anti-citrullinated filaggrin antibodies
Issue 9/2004	Mass screening for celiac disease
Issue 8/2004	Oats in gluten-free diet for celiac disease?
Issue 7/2004	Alpha-Actinin as Target for dsDNA Antibodies
Issue 6/2004	Anti-tTG antibodies in Sjögren's Syndrome
Issue 5/2004	Relation of anti-tTG reactivity to age and gender
Issue 4/2004	Treatment of ANCA-Associated Vasculitis
Issue 3/2004	How Do Antiphospholipid Antibodies Bind ß2-Glycoprotein I ?
Issue 2/2004	Antinuclear antibody testing
Issue 1/2004	Epidemiology of autoimmune diseases

December 12/04:

SmD peptide as target in SLE

Anti-Sm is considered a serological hallmark of SLE and is included in the ACR criteria for SLE. On average, anti-Sm reactivity is found in 5-30% of patients with SLE, depending on the detection system used and the racial and genetic makeup of the SLE population.

The Sm complex is comprised of at least nine different core polypeptides: B, B', N, D1, D2, D3, E, F, and G. All of these core proteins can be targets of the anti-Sm immune response, but the most prevalent response is to the B and D polypeptides. However, SmBB' share cross-reactive epitopes with U1-specific snRNPs, which are more frequently targeted by antibodies that are present in patients with mixed connective tissue disease (MCTD). Thus, SmD is regarded as the Sm autoantigen that is most specific to SLE. Unfortunately, purified SmD is always at risk of being contaminated with SmBB', and thus may be not specific enough. Until now, all trials to produce an antigenic recombinant SmD protein with a good reactivity failed because of its very special structure.

In the following study, Mahler et al. developed a peptide-based ELISA and analyzed the anti-Sm immune response directed towards the Sm antigens D1 and D3:

Mahler M, Fritzler MJ, Blüthner M (2004)
Identification of a SmD3 epitope with a single symmetrical dimethylation of an arginine residue as a specific target of a subpopulation of anti-Sm antibodies
Available online http://arthritis-research.com/content/7/1/R19

The authors showed that one particular SmD3 peptide represents a highly specific substrate for detecting a subclass of SLE-specific anti-Sm antibodies by ELISA. At a defined cutoff value of 13 U/ml, the sensitivity was 15.9% and the specificity was 99.8%, yielding an exceptionally high positive predictive value for SLE of 96.6 %.

Because no international "gold standard" is available for detection of anti-Sm antibodies, the results were compared with the results of the Varelisa Sm Antibodies (using purified Sm). The sensitivities were comparable but the specificity of Varelisa was significantly lower than the specificity of the new peptide-based assay (88% compared to 99.8%,). The authors concluded that the peptide-based anti-Sm ELISA offers a new serological reagent that will improve our ability to diagnose SLE and to discriminate SLE from other autoimmune and infectious diseases.

Pharmacia Diagnostics was clearly convinced by these findings and subsequently reworked the Varelisa Sm Antibodies assay. The new Varelisa Sm antibodies (No. 18296), launched in October 2004, already uses this synthetic Sm peptide. The next step will be the inclusion of the SmD peptide antigen in the three updated ANA Profile assays, which will be launched soon.

November 11/04:

Decrease of anti-CCP and RF following anti-TNFalpha therapy

Rheumatoid arthritis is a polyarticular chronic inflammatory disease. TNFalpha (tumour necrosis factor) has many proinflammatory activities and is widely expressed in the rheumatoid joint. Two substances interfering with TNFalpha have been recently approved for therapeutic use in RA: etanercept, a soluble TNFalpha receptor, and infliximab, a chimeric anti-TNFalpha antibody. Treatment with infliximab often results in high clinical efficacy, delay in radiological progression, decrease in serum C reactive protein, and downregulation of inflammatory cytokines stimulated by TNFalpha. However, despite an impressive overall clinical impact, more than 25% of patients still have a poor response to these biological agents. So far, no reliable indices have been identified as possible predictive factors for the clinical response in patients undergoing treatment with infliximab.

In the following study, Alessandri et al. measured antibodies to cyclic citrullinated peptides (anti-CCP) and rheumatoid factor (RF) at baseline and after six months in patients undergoing infliximab treatment.

Alessandri C, Bombardieri M, Papa N, Cinquini M, Magrini L, Tincani A, Valesini G (2004)
Decrease of anti-cyclic citrullinated peptide antibodies and rheumatic factor following anti-TNFalpha therapy (infliximab) in rheumatoid arthritis is associated with clinical improvement
Ann Rheum Dis 63, 1218-1221

43 patients with rheumatoid arthritis were enrolled in the study. All patients had a history of failed treatment with at least one disease modifying antirheumatic drug (DMARD). At baseline, 38 of the 43 patients were positive for anti-CCP antibodies, and 41 were positive for RF. Although no patients who were positive for anti-CCP or RF at baseline became negative following the anti-TNFalpha treatment, the serum titre of anti-CCP antibodies and RF decreased significantly after 6 months of treatment. A significant decrease was observed only in those who were clinically improved according to ACR criteria. Variation in anti-CCP levels after treatment was positively correlated with variation of the tender joint count. Thus, modification of serum anti-CCP seems to parallel the improvement in clinical and laboratory variables observed during treatment with infliximab.

Furthermore, the importance of a quantitative evaluation of anti-CCP is suggested by the observation that lower levels of anti-CCP antibodies at baseline seemed to predict a better clinical response after six months of treatment with infliximab.

October 10/04:

Comparison of different anti-citrullinated filaggrin antibodies

In the last 50 years, different markers for rheumatoid arthritis (RA) have been described and include anti-perinuclear factor (APF), anti-keratin antibodies (AKA) and antibodies to the Sa antigen (which is identical to post-translationally-modified vimentin). Since 1998 it has become evident that all of the above antibodies target citrullinated proteins. Citrulline is a non-standard amino acid that is not incorporated into proteins during protein synthesis but created by deimination of arginine residues. RA patients recognise different linear citrullinated peptides. The citrulline-flanking residues influence the reactivity with the antibodies. In the first attempts to design an ELISA for detecting anti-citrullinated protein antibodies, several linear filaggrin epitopes were used. The sensitivity of this initial ELISA could be improved by making cyclic variants of peptides in which the citrulline residue is optimally exposed for antibody binding. This led to the first generation anti-CCP (cyclic citrullinated peptide) test (CCP1 test).

However, the idea that filaggrin is -most likely- not the triggering agent in the anti-CCP antibody response, since it is not present in the joint, sparked investigations to obtain novel peptides from dedicated libraries of citrullinated peptides using RA sera for selecting the most reactive species. After selection, such peptides were made cyclic to ensure exposure of the antigenic citrulline moiety. These investigations have resulted in the second generation anti-CCP assay, which is now available as the CCP2 test. The diagnostic use of the CCP2 test is the topic of this publication of the month.

Dubucquoi S, Solau-Gervais E, Lefranc D et al. (2004)
Evaluation of anti-citrullinated filaggrin antibodies as hallmarks for the diagnosis of rheumatic diseases
Ann Rheum Dis 63, 415-419

The aim of the study by Dubucquoi et al. was to establish the relative performance of several anti-citrullinated peptide antibody detection methods in order to optimize the diagnosis of RA.

They evaluated 271 sera to compare both the sensitivity and specificity of AKA, anti-citrullinated linear filaggrin, and anti-CCP2 antibodies.

Anti-CCP2 kits showed the best sensitivity and specificity (65% and 96%, respectively). In the group of RA patients with very recent disease, the sensitivity of anti-CCP2 kits decreased to about 50%. Nevertheless this assay remained the most accurate when compared with AKA or homemade EIA using linear filaggrin peptides. The combination of anti-CCP2 and RF only slightly increased the sensitivity of the diagnosis of very early rheumatoid disease.

September 09/04:

Mass screening for celiac disease

Celiac disease is a gluten dependent enteropathy associated with increased risk of autoimmune disease that is underdiagnosed. The prevalence has been reported to be 1:150 to 1:250. Since only few patients have the classical gastroenterological symptoms, most cases remain unnoticed, with a 1:7 ratio of diagnosed to undiagnosed cases. At the same time, long-term effects of the disease are immense, leading to increased morbidity and mortality. Therefore, the introduction of mass screening for celiac disease has been under discussion for some time. Doubts have focused on compliance to gluten-free diets in asymptomatic subjects, on the choice of the screening test and on cost efficiency.

In the following study, a mass screening for celiac disease of a large population of Italian schoolchildren was performed using a home-made IgG anti-human transglutaminase (htTG) assay:

Tommasini A, Not T, Kiren V, Baldas V, Santon D, Trevisiol C, Berti I et al. (2004)
Mass screening for coeliac disease using antihuman transglutaminase antibody assay
Arch Dis Child 89, 512 - 515

A commentary on this study is found in the following publication:

Young EH, Wareham NJ (2004)
Screening for celiac disease: what evidence is required before population programmes could be considered?
Arch Dis Child 89, 499 - 501

3188 Italian school children were screened using the htTG assay and 48 of them (1.5 %) were identified as positive. 31 out of this group tested also positive for anti-endomysial antibodies (EMA). 41/48 children agreed to be rescreened, and in all cases, the results were confirmed. 28/31 children with positive EMA test underwent intestinal biopsy, and all biopsy specimens showed the lesions that are typical for celiac disease. The ratio of symptomatic to asymptomatic patients was 1:2. The prevalence of celiac disease that results from this study is 1:96 or 1:91 (if two subjects already known as celiacs before the study were included). At follow up, all 30 patients with celiac disease reported compliance with gluten-free diet, and 20 of them were negative for anti-htTG antibodies after a period of 12 to 24 months.
The overall costs of the screening program, including materials, equipment, time spent by health professionals, and further more, were € 46,000, equivalent to € 1,400 per case diagnosed compared to € 8700 in case of delayed or complicated diagnosis in Italy.

August 08/04:

Oats in gluten-free diet for celiac disease?

Celiac disease, also known as gluten intolerance, is caused by the intake of gluten (storage proteins, like gliadin) that is present in cereals like wheat, barley, rye and spelt. Celiac disease affects North Americans and Europeans in a prevalence of about 1:133. Symptoms can range from classic features, such as diarrhea, weight loss, and malnutrition to atypical or latent forms. Treatment of celiac disease consists of a gluten-free diet, usually life-long. The question, if this diet may contain oats is discussed controversially. Whereas in the past, oats was considered toxic for patients with celiac disease, there are more recent studies indicating that this cereal is tolerated without any harm.

The following recent publication addresses this issue by a comparative evaluation of an oats-containing and an oats-free diet in patients with celiac disease:

Peräho M, Kaukinen K, Mustalahti N, Vuolteenaho N, Mäki M,Laippala P,Collin P (2004)
Effect of Oats-containung Gluten-free Diet on Symptoms and Quality of Life in Coeliac Disease. A Randomized Study
J Gastroenterol 39, 27 - 31

23 Celiac disease patients received an oats-containing gluten-free diet and 16 patients with celiac disease were under an oats- and gluten-free diet for one year. After this period there were no differences between the two groups in small-bowel mucosal morphology. Evaluation of general well-being by the PGWB score (Psychological General Well-Being Index) was not significantly different between both groups, and the GSRS (Gastrointestinal Symptoms Rating Scale) was somewhat higher in the patients receiving the oats-containing diet. The symptoms of diarrhea were statistically significant more severe in this group at the end of the study.

As oats had no effect on the quality of life as measured by the PWBS questionnaire, the authors conclude that this cereal may be included in the gluten-free diet for celiac disease patients. Recent in-vitro studies have indicated that oat prolamine avenin does not stimulate endomysial antibody or cytokine production. Nevertheless the adoption of oats products in a gluten-free diet is often discouraged. This is mainly due to the possibility that commercially produced oats may be contaminated with traces of other cereals, like wheat.

Notwithstanding these doubts, according to the authors, the presented study reveals that oats can be included in the gluten-free diet for celiac disease patients. However, patients and physicians should be aware that gastrointestinal complaints might be aggravated by this kind of diet

July 07/04:

Alpha-Actinin as Target for dsDNA Antibodies

dsDNA antibodies are a hallmark of systemic lupus erythematosus (SLE). They are highly specific for the disease, their titer parallels disease activity and they have been implicated in the pathogenesis of renal disease. However, the mechanism of pathogenic action remains unresolved. It is not known, why some dsDNA antibodies deposit preferentially in the kidney and the nature of the target antigen(s) and the binding interaction is a matter of discussion.

It has been suggested that some dsDNA antibodies do not bind directly to dsDNA deposited in the kidney but are cross-reactive and bind directly to kidney antigens. One of the recently proposed candidate antigens is a-actinin, a component of glomerular epithelial cells. a-Actinin is an integral part of the contractile system within the podocyte foot processes. The topic of crossreactivity of dsDNA antibodies with a-actinin was already addressed in the Publication of the Month in July 2001 ("dsDNA Antibodies (possible pathogenic mechanisms)"). In that article, evidence was presented for the binding of mouse pathogenic (but not nonpathogenic) monoclonal dsDNA antibodies to a-actinin. This year a new study dealing with human antibodies has been published on this important and fascinating issue:

Mason LJ, Ravirajan CT, Rahman A, Putterman C, Isenberg DA (2004)
Is alpha-Actinin a Target for Pathogenic Anti-DNA Antibodies in Lupus Nephritis?

Arthritis Rheum 50, 866 - 870

Two human monoclonal dsDNA antibodies that have been shown to be pathogenic in SCID mice bound strongly to a-actinin in ELISA. The binding of one of these antibodies could be partially inhibited by preincubation with purified calf thymus DNA . Another monoclonal antibody, however, that had not been pathogenic in SCID mice, bound only very weakly. Furthermore, all 7 human dsDNA IgM antibodies tested bound to a-actinin. This finding supports previous suggestions that human dsDNA antibodies exhibit cross-reactive binding to a-actinin.

Additionally it was shown that sera from patients with SLE bound a-actinin to a significantly higher extent than sera from healthy controls. However, no difference between sera from patients with lupus nephritis was observed compared to patients without renal involvement. This result on the one hand reveals reactivity of human SLE sera with a-actinin (44 % of the patients), on the other hand it only partially supports the hypothesis of involvement in renal pathogenicity. This question needs further exploration. An additional support for the "crossreaction hypothesis" is the preliminary finding that dsDNA antibodies that were eluted from the kidneys of SLE patients bound to both DNA and a-actinin.

June 06/04:

Anti-tTG antibodies in Sjögren's Syndrome

Sjögren's syndrome is an autoimmune exocrinopathy characterized by dry eyes, dry mouth and circulating autoantibodies directed against intracellular antigens, such as 52 kD SSA/Ro, 60 kD SSA/Ro, SSB/La and a-fodrin. Sjögren's syndrome has been reported in up to 15 % of patients with biopsy proven celiac disease. The diagnosis of celiac disease in the setting of Sjögren's syndrome or other systemic rheumatic diseases may be difficult because they are often associated with gastrointestinal symptoms. In case of Sjögren's syndrome, these may comprise dysphagia due to decreased saliva production, impaired pancreatic function, gastric inflammation and atrophy, and autoimmune liver disease.

Although the diagnosis of celiac disease is often confirmed by a small bowel biopsy, marker autoantibodies directed against the endomysium (EMA) and tissue transglutaminase (tTG) are highly correlated with biopsy-proven disease and serve as a valuable screening test.

In the following recent study, the authors have evaluated the performance of an anti-tTG ELISA as screening test in patients with Sjögren's syndrome and other autoimmune diseases:

Luft LM, Barr SG, Martin LO, Chan EKL, Fritzler MJ (2003)
Autoantibodies to Tissue Transglutaminase in Sjögren's Syndrome and Related Rheumatic Diseases

J Rheumatol 30, 2613 - 2619

Sera were obtained from 50 patients with primary Sjögren's syndrome. For comparison, 50 sera from SLE patients, 50 sera from patients with rheumatoid arthritis, 30 sera from patients with systemic sclerosis as well as 50 healthy volunteers and 40 sera from patients with biopsy-confirmed celiac disease were studied. The frequency of anti-tTG antibodies in the Sjögren's syndrome group was 12 %, as compared to 4 % in the combined control group (including SLE, rheumatoid arthritis, systemic sclerosis and healthy volunteers). Retrospective analysis revealed that 5/6 Sjögren's syndrome patients with anti-tTG antibodies had a concurrently positive EMA and biopsy-proven celiac disease with typical gastrointestinal symptoms.

One of two anti-tTG positive healthy controls was found to be EMA positive and to have clinical as well as small bowel biopsy features typical of celiac disease. The rate of false positive reactions was surprisingly low in this cohort of systemic autoimmune diseases (up to 2.6 % overall). 4 of the 7 false positives had anti-tTG levels < 30 units. These data represent maximum numbers as some patients were lost during followup. These findings show that anti-tTG ELISA may be used as a screening test also in patients with Sjögren's syndrome to identify a risk of celiac disease.

May 05/04:

Relation of anti-tTG reactivity to age and gender

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten and characterised by villous atrophy and inflammatory cell infiltration within the intestine. Additionally, there is a serological response, evident as autoantibodies towards tissue transglutaminase (tTG) or endomysium and gliadin, respectively. Celiac disease, like most other autoimmune conditions, is more common in females, with a female-to-male ratio of at least 2:1. So far, little is known about the epitopes bound by tTG autoantibodies and nothing at all about a distinct tTG autoantibody recognition in association with age and/or sex of the celiac subjects, as previously demonstrated in other autoimmune disorders.

It was the aim of the following recent study to characterise in a large cohort of new-onset celiac patients the autoimmune response against three tTG constructs with respect to differences in age and gender:

Tiberti C, Bao F, Bonamico M et al. (2003)
Celiac disease-associated transglutaminase autoantibodies target domains at diagnosis are age and sex dependent

Clin Immunol 109, 318 - 32

Sera from 175 CD patients at diagnosis were studied. 113 of them (64.6 %) presented classic CD, 23 (13.1 %) presented atypical CD and 39 (22.3 %) had silent CD. The patients were subdivided according age in five groups: group I (0 - < 4 years), group II (4 - < 8 years), group III (8 - < 12 years), group IV (12 - < 16 years) and group V (> 16 years). Three constructs of tTG [one full-length: tTG(1 – 687) and two deletion mutants: tTG(227 – 687) and tTG(473 – 687)] were tested for anti-tTG reactivity in a serum ^{35}S-radioimmunoassay.

All CD patients had antibodies directed against full-length tTG with no significant differences related to age and sex. Anti-tTG(227 – 687) reactivity was detected in only 50.9 % of the patients, whereas 83.4 % of all sera reacted with tTG(473 – 687). This result is surprising, as the latter comprises only a part of the aminoacid sequence of the former and it may be due to different folding, steric hindrance and epitope exposition. For construct tTG(227 – 687), a particularly strong reactivity (with respect to frequency and titer) was found in group I female patients with significant differences to all other female groups. This result was partially confirmed with the second construct. With respect to gender, reactivity towards tTG(473 – 687) was always significantly higher in titers for females compared to males, and for tTG(227 – 687), group I females had a higher frequency and titer than the corresponding males. Evidently, there are sex and age related differences in the reactivity towards tTG that warrant further analysis.

April 04/04:

Treatment of ANCA-Associated Vasculitis

Vasculitis is defined by inflammation of the bloodvessel wall and is present in a group of various disease entities. Among the primary systemic vasculitides, Wegener's granulomatosis and microscopic polyangiitis share several common features, including pauci-immune focal crescentic necrotizing glomerulonephritis and circulating antineutrophilic cytoplasmic antibodies (ANCA). Before treatment became available, patients with generalized Wegener's granulomatosis had a median survival of five months. In the early 1970s, a regimen combining daily cyclophosphamide with prednisone given on an alternate-day schedule was introduced. This treatment has reproducibly been found to induce remission in 80 to 100 % of patients and can result in long-term survival. However, when therapy is tapered and discontinued, relapses are common. In one study, in which patients with Wegener's granulomatosis were followed for a mean of eight years, relapse occurred in 50 % of patients.

Although cyclophosphamide is effective in managing these relapses, repeated courses of cyclophosphamide treatment are associated with a number of serious side effects, such as bone marrow suppression, infection, infertility, cystitis and cancer of the bladder. Due to these problems, recently safer treatment options for ANCA-associated vasculitis have been developed.

For example, azathioprine, methotrexate or mycophenolate mofetil may be used instead of cyclophosphamide for the maintenance of remission.

One of these approaches using azathioprine is presented in the following publications:

Langford C (2003)
Treatment of ANCA-Associated Vasculitis
N Engl J Med 349, 3 - 4

Jayne D, Rasmussen N, Andrassy K et al. (2003)
A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Antibodies
N Engl J Med 349, 36 - 44

155 patients with a new diagnosis of Wegener's granulomatosis were studied. All patients received at least 3 (or 6) months of therapy with cyclophosphamide and prednisolone. 144 (93 %) of them achieved remission and were randomly assigned to azathioprine (71 patients) or continued cyclophosphamide (73 patients) as maintenance therapy. The frequency of relapses was not different between both groups: 11 relapses in the azathioprine group (15.5%), and 10 in the cyclophosphamide group (13.7 %). Thus, the duration of exposure to cyclophosphamide may be safely reduced by substitution with azathioprine during maintenance therapy.

March 03/04:

How Do Antiphospholipid Antibodies Bind ß2-Glycoprotein I ?

Antiphospholipd antibody syndrome (APS) is now the most common cause of acquired hypercoagulability and a major cause of morbidity in pregnancy. It is characterized by clinical features such as vascular thromboses, recurrent fetal loss and thrombocytopenia in association with the presence of antiphospholipid antibodies (aPL) in the blood.

The only treatment proven to reduce the risk of thrombosis in APS is long-term anticoagulation, which may have severe side effects. It is therefore important to develop new treatments that are both more effective and more accurately targeted to the disease process in APS. In particular, it may be advantageous to block and manipulate interactions between aPL and their major epitopes.

For their binding to negatively charged phospholipids, aPL require serum cofactors, such as ß2-glycoprotein I (ß2GPI), protein C, protein S and prothrombin. ß2GPI is the most extensively studied and appears to be one of the most relevant clinically. The following recent review focuses on the nature of the interaction between aPL and ß2GPI:

Giles IP, Isenberg DA, Latchman DS, Rahman A (2003)
How Do Antiphospholipid Antibodies Bind ß2-Glycoprotein I?
Arthritis & Rheumatism 48, 2111 - 2121

ß2GPI is a 50 kd single-chain polypeptide with 5 oligosaccharide attachment points. It is composed of 5 common, structurally related repeats, each of which is ~ 60 amino acid residues in length, in addition to domain V, which contains 82 amino acids and a long carboxyl-terminal tail. Although ß2GPI is a major target antigen in the pathogenesis of APS, the exact nature of the aPL-ß2GPI interaction remains a matter of some debate. Opinion is divided as to whether pathogenic aPL are directed against the ß2GPI-phospholipid complex or against a cryptic epitope revealed on ß2GPI by binding to phospholipids (or certain synthetic surfaces), or whether they bind directly to an increased density of ß2GPI immobilized on phospholipids or ?-irradiated plates. Arguments in favour of and against these possibilities are presented.

The debate as to the nature and sites of the major epitopes on ß2GPI is likely to continue. Since aPL are heterogeneous, it is not surprising that different results have been obtained by different groups. The balance of the most persuasive evidence from crystallography, clinical studies, and studies of domain-deletion mutants of ß2GPI points to the existence of a major noncryptic epitope on domain I

February 02/04:

Antinuclear antibody testing

Antinuclear antibodies (ANA) play a significant role in the diagnosis of a number of systemic autoimmune diseases. In fact, their theoretical value is well known but it is equally interesting to come to know the results of practical approaches. For example, in the context of cost calculations it appears very useful to be informed about the percentage values of positivity found for ANA screening.

The following recent publication presents this kind of information. It describes the authors' 6 years experience in detecting and characterizing ANA in a regional Australian laboratory:

Roberts-Thomson PJ, Nikoloutsopoulos T, Cox S, Walker JG, Gordon TP (2003)
Antinuclear antibody testing in a regional immunopathology laboratory
Immunology and Cell Biology 81, 409 - 412

The authors describe their 6 years experience in detecting and characterizing ANA in a regional diagnostic immunopathology servicing a population of 400,000 and located near Adelaide. ANA testing was performed by indirect immunofluorescence on HEp-2000 cells. This cell line is transfected with a Ro containing plasmid and is considered to be particularly sensitive for Ro. In total, 20205 ANA determinations were performed. 28.3 % of these were positive (with titre >/= 1:80). The frequency of the various patterns obtained is shown in Table 1. 39.1 % of all positive results represented the homogenous pattern, 20.1 % were speckled/atypical speckled, 8.4 % were nucleolar, 7.1 % represented Ro and 4.3 % were of centromere pattern.

10929 samples were tested for extractable nuclear antibodies (ENA). Among these, 12.9 % (1409) were positive. The analyses were performed by counter immunoelectrophoresis precipitation. The frequency of the specific ENA detected is indicated in Table 3 (p. 410). 30.2 % of positive results were characterized as Ro, in 25.66 % being associated with La. 12.5 % of positive results represented RNP and 17.8 % were unidentified precipitin lines (UPL).

DNA testing was performed employing the Farr RIA on 12068 samples. 10.96 % (1323) of them gave a positive result. These included multiple sera from 347 patients, many with a definitive diagnosis of SLE. 83 of these patients, however, had a negative ANA and their DNA was only slightly elevated. Their clinical diagnosis varied and many of them were of aboriginal origin (characterized by high background immunoglobulins) so that the authors suggested an adjustment of the cut-off for this ethnic group.

January 01/04:

Epidemiology of autoimmune diseases

Autoimmune diseases comprise a clinically quite heterogeneous group of disorders that are characterized by the common fact that the immune system in these patients attacks their own tissues and organs. The majority of autoimmune disease patients is female. Although some autoimmune diseases are comparably rare, this group of disorders has significant impact on mortality and morbidity. Autoimmune diseases are among the leading causes of death among young and middle-aged women (age below 65 years) in the United States.

For this reason, recent epidemiological data are of interest. The following publication contains an overview over incidence, prevalence and sex distribution of autoimmune diseases:

Cooper GS, Stroehla BC (2003)
The Epidemiology of autoimmune diseases
Autoimmunity Reviews 2, 119 - 125

Table 1 (page 121) summarizes available epidemiological data on 24 selected autoimmune diseases. The estimated incidence (number of newly diagnosed cases per year) ranged from less than 1/100,000 per year for chronic active hepatitis, scleroderma, myasthenia gravis or primary biliary cirrhosis to more than 20/100,000 per year for adult-onset rheumatoid arthritis and thyroiditis.
The prevalence (number of patients with the disease at a certain time) ranged from less than 5/100,000 (chronic active hepatitis, Wegener's granulomatosis, uveitis) to more than 500/100,000 (Graves' disease, rheumatoid arthritis, thyroiditis). These values are only average estimates. The incidence/prevalence rates for single countries may differ significantly, as specific ethnic groups may be at higher risk for some diseases. Type 1 diabetes, for example, is more common in Northern European countries compared with Southern European countries. A similar pattern is suggested for multiple sclerosis. In some diseases (e.g. thyroiditis, scleroderma, SLE, Sjögren disease) 85 % or more of patients are female. The estimated total incidence (90/100,000 per year) and prevalence (~ 3%) may be viewed as conservative rates since the list does not contain all disorders and for some diseases no data are available.

There are notable differences in the age distribution among autoimmune diseases (Table 2, p. 122). The mean age of juvenile rheumatoid arthritis and type 1 diabetes is approximately 8 – 10 years, whereas other diseases (Graves' disease, multiple sclerosis, myasthenia gravis) generally occur between ages 30 and 50 years. An older age at diagnosis (40 – 70 years) is seen in Sjögren disease, rheumatoid arthritis, Wegener's granulomatosis, myositis and thyroiditis.