Autoimmune diseases are the third most common disease after cardiovascular diseases and cancer. The prevalence of autoimmunity in the general population is about 5% and rising. The situation is aggravated even more by the difficulty in establishing a definite diagnosis, because of the broad range and partial overlap of the various clinical symptoms. For this reason, the role of research into the development of improved diagnostic techniques is vital. This was the subject of a recent meeting held with Professor Yehuda Shoenfeld in which current trends in the diagnostics of autoimmune diseases, such as improved screening techniques, were discussed, as well as their likely impact on diagnosis and prognosis. Head of the department of internal medicine and the Centre for Autoimmune Diseases at Tel Aviv University, Prof. Shoenfeld is the first scientific head of the German AESKU.INSTITUTE and holds the first worldwide chair of autoimmunity that was established in March 2003.

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**CLI:** Professor Shoenfeld, one of your main research focuses is the development of new strategies and approaches to the diagnosis of autoimmune diseases. Do you see any major trends in the near future?

**Prof. Shoenfeld:** At present I can see three developments which will have a major impact on the future diagnosis and treatment of autoimmune diseases. These are early prediction of the likelihood of development of autoimmunity, the development of screening techniques involving a large number of different antibody tests and finally the gain- ing of a deeper understanding of the molecular mechanisms involved in the pathogenesis of the disease.

"From diagnosis to prognosis," is how I would describe the first trend. In addition to the simple diagnosis of an existing disease, the prediction of autoimmune diseases and various specific disease characteristics will increasingly gain in significance in the coming years. These trends have been triggered by a number of retrospective epidemiological studies in the past two or three years. They have clearly shown that autoantibodies that are associated with autoimmune diseases not only play a significant role as diagnostic markers, but that their occurrence may also be used to make a well-founded prediction. So what is different now? In the past, when autoantibodies were found in a patient who apparently showed no signs of disease, this was generally assumed to be a false positive result. This used to be jokingly referred to as "laboratitis". Thanks to some excellent studies conducted with blood samples which had been stored for documentation purposes for many years, we now know that autoantibodies can occur 10 to 20 years before the outbreak of autoimmune disease, and in some cases even earlier.

The most striking example of this is with primary biliary cirrhosis, where the typical anti-mitochondrial antibodies (AMA) may be identified 30 years before the occurrence of the first symptoms. Anti-dsDNA antibodies precede the development of systemic lupus erythematosus (SLE) by 5 to 10 years. Other studies show similar results for diabetes, Crohn's disease and ulcerative colitis, where characteristic autoantibodies occur long before the onset of the initial symptoms.

**CLI:** How is it possible to differentiate truly false positive results?

**Prof. Shoenfeld:** Only a consistent follow-up can answer this question. The test result has to be checked after a reasonable period of time. For many diseases, e.g. antiphospholipid syndrome, the diagnostic criteria already require that tests be repeated after a number of weeks since the antibodies identified may have arisen as a consequence of an infection.

**CLI:** What consequences do these results have for clinicians, patients and laboratories?

**Prof. Shoenfeld:** We are entering a phase in diagnostics in which a forecast of the course of a disease will no longer be merely an educated guess. For the first time ever it will be possible to make a concrete prognosis of a disease, right down to a prediction of the individual characteristics of the disease, e.g. which organs will be affected. All currently available results illustrate the significance and importance of extensive screening at an early stage. At the same time, however, this development also requires the responsible and ethical use of the new diagnostic possibilities. Who should be tested? Unquestionably insurance companies and employers would be very interested in the results of screening tests. But should the entire population really be tested or merely groups known to be at risk, such as the relatives of patients with autoimmune diseases or those with a known genetic predisposition? Certainly it makes sense to test those patients who already have a particular autoimmune disease for other related diseases.

**CLI:** What use is an early disease prognosis for the affected patient?

**Prof. Shoenfeld:** Certainly the prediction that an apparently healthy person will eventually suffer from an autoimmune disease is not a positive piece of news. Yet in a number of clinical situations an early diagnosis allows for the possibility of effective prophylaxis. Patients who are diagnosed at an early stage as being at risk of an antiphospholipid syndrome may prevent thromboembolic events simply and with virtually no side-effects by

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Figure 1: In close cooperation with Prof. Shoenfeld’s team at Tel Aviv University, researchers from the AESKU.INSTITUTE in Wendelsheim, Germany, are now pursuing new approaches to the diagnosis of Antiphospholipid syndrome (APS). In addition to causing typical changes in the skin, this syndrome can cause venous and arterial cardiovascular problems, leading to thromboses, neurological damage and to recurring spontaneous miscarriages. With new forms of laboratory tests such as those being developed and produced by the company AESKU.DIAGNOSTICS, APS can be successfully diagnosed. However the practical, detailed consequences of such a diagnosis for the individual patient have been up till now difficult to predict. The objective of the research activities of the German-Israeli working group (see above) is to improve the testing profile so that, for example, a pre-pregnancy screen could give an early indication as to whether a young woman with APS should have to actively consider the possibility of a miscarriage. Appropriate preventive measures could then be taken.
taking anticoagulants such as aspirin. With other diseases the treating physician can offer valuable recommendations for future behaviour. If the development of a disease cannot be prevented, at least an early diagnosis offers the possibility to take therapeutic action at the earliest possible point in time.

**CLI:** What development is shaping the second trend?

**Prof. Shoenfeld:** As a rule individual autoantibodies or a small number of characteristic autoantibodies are currently selected for the diagnosis of an autoimmune disease. Yet studies clearly show that a wide range of antibodies occur with various diseases. Two examples: SLE where we have been able to identify at least 100 different autoantibodies associated with the disease, and the antiphospholipid syndrome that is accompanied by a huge number of different antibodies. In this context a patient’s individual antibody spectrum can allow predictions beyond mere diagnosis and thus enable a forecast of individual aetiopathology and even future specific characteristics of the disease. Test systems and techniques which make it possible to assay a variety of different autoantibodies in a practical and economical manner using only minute sample volumes will therefore certainly be called for in the future. Current ELISA assays already allow screening in a single sample for several autoantibodies corresponding to various clinical pathologies. Totally new so-called multiplex techniques still under development can, as far as I am aware, assay as many as 30 different antibodies. I am certain that in the not too distant future we will be able to determine, in a tiny sample volume, hundreds of antibodies in just one assay. At the same time, however, these new technical possibilities will also raise questions. If we are suddenly able to test for a plethora of autoantibodies in parallel, we will almost inevitably discover totally new antibodies in addition to the known characteristic marker for a disease. We have to make use of the coming years to carefully examine what significance and importance these newly discovered markers actually have for the diagnosis and prognosis of specific diseases.

**CLI:** And the third trend?

**Prof. Shoenfeld:** In the near future, in addition to the analysis of the diagnostic significance of autoantibodies, research into their role in the pathogenesis of autoimmune diseases will also be to the fore. Every day we learn more about the pathogenetic mechanisms with which autoantibodies induce the respective clinical pathologies. The results of this research may offer valuable clues to the prognosis, prophylaxis and development of new therapeutics. At the same time, such results also provide an indication of autoimmune mechanisms in diseases which to date have not necessarily been considered as autoimmune diseases. An example of this is the finding that the neurological diseases schizophrenia and epilepsy are associated with a variety of autoantibodies. Such discoveries may lead to new therapy forms for the diseases.

**References**


**The interviewee**

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