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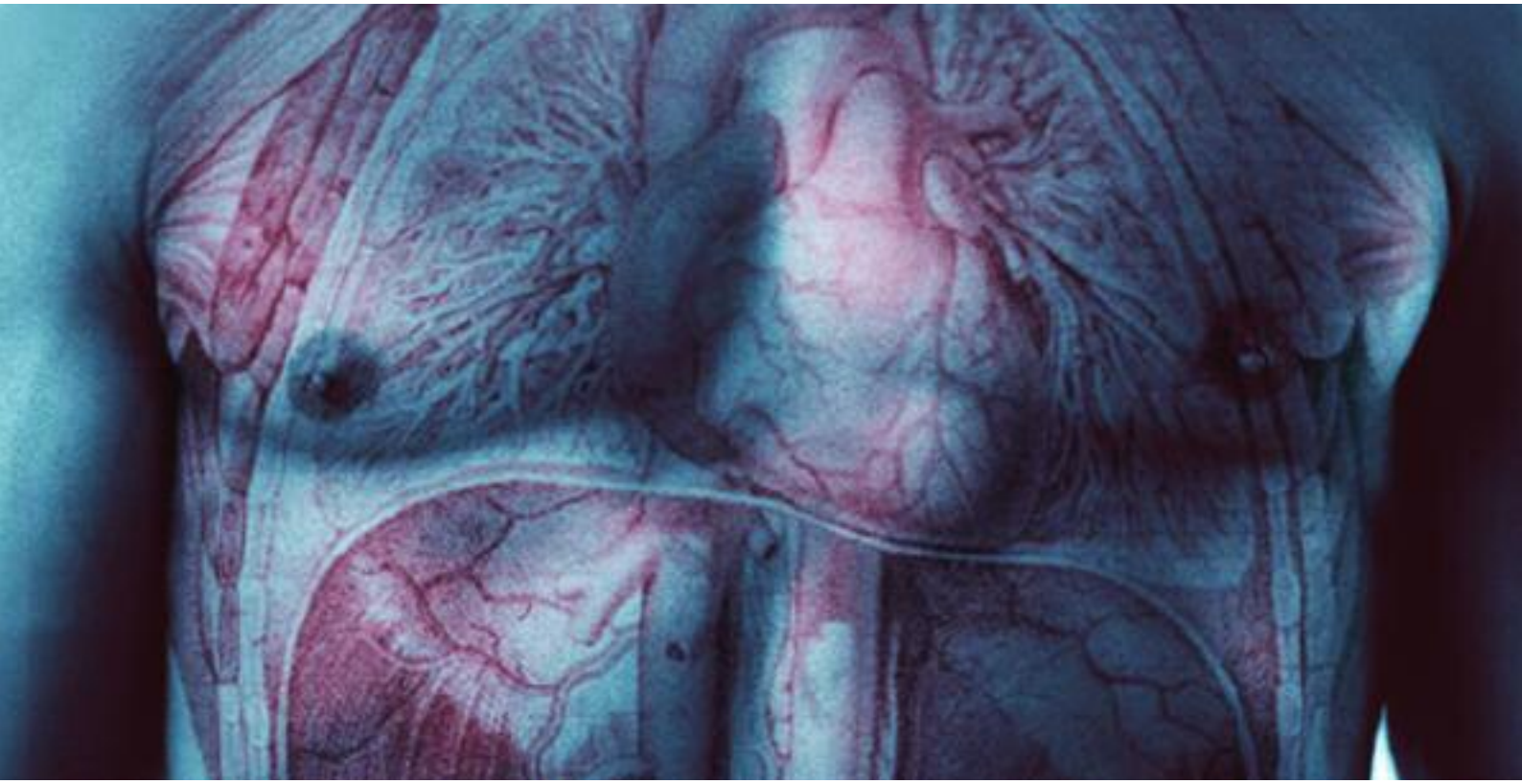

100 Years in Autoimmunity

A focus on autoimmunity and autoimmune diseases

Therapeutic antibodies for SLE

German-Israeli research activities on the anti-phospholipid syndrome

AESKU autoimmune workshop: a summary

Automation in autoimmune diagnostics

100 Years in Autoimmunity

Dr. Torsten Matthias, AESKU

Research in the field of autoimmunity looks back on a 100-year history – 100 years shaped by outstanding scientists, continuous research endeavours and major advances in knowledge, which on more than one occasion have thrown existing convictions overboard.

Nevertheless, even after 100 years the causes of and triggers for autoimmune diseases are still unknown to a great extent, while not everybody is familiar with the latest innovative possibilities in diagnosis and therapy. Which is why greater interdisciplinary exchange and intensive knowledge management are now required.

AESKU is actively committed to interdisciplinary communication and knowledge transfer in the field of autoimmune diseases. AESKU cooperates closely with renowned scientific institutions and scientists on the one hand, and, on the other hand, it has a lively exchange of information with industry to create new opportunities that improve therapy of autoimmune diseases substantially. Its unique corporate structure unites research on development, therapy and diagnosis of autoimmune diseases under one roof.

AESKU.SCIENCE is an expression of this commitment. Our new magazine, the first issue of which you now have in front of you, intends to be the basis for interdisciplinary exchange between the various specialist areas, and between treating physicians and laboratories. AESKU.SCIENCE quite consciously looks at current knowledge from a practical stance, so as to bring research and daily practice closer together.

Given the long and sometimes turbulent history of autoimmune diseases, in the first issue of AESKU.SCIENCE Prof. Dr. K. Helmke begins with an overview of the history of autoimmune diseases, and at the same time looks at the current trends and visions in therapy and diagnostics. In the coming issues the focus will be on various different autoimmune diseases.

We wish you lots of reading pleasure!

100 years of autoimmune diseases also prompted us, together with renowned scientists, to create the new "AESKU.AWARD for life contribution to autoimmunity". The AESKU.AWARD for life contribution to autoimmunity does not only want to show the importance of research on autoimmune diseases, it also aims to establish the significant field of autoimmunity as an independent research area and to foster interdisciplinary cooperation.

Editorial

Focus

Reports and Essentials

Profile

Autoimmunity and Autoimmune Diseases

Prof. Dr. Klaus Helmke, Städt. Krankenhaus München-Bogenhausen, Germany

11. März 1901. BERLINER KLINISCHE WOCHENSCHRIFT. 255

Es scheint demnach die Vereinigung von Immunkörper und Complement durch die Gegenwart des Complementoids nicht gehindert zu werden. Wir haben hierüber noch besondere Versuche angestellt und abwechselnd Inactivirung und Complementzusatz mehrmals hintereinander ausgeführt, ohne dass durch die immer stärkere Anhäufung von Complementoiden eine Beeinträchtigung der Complementwirkung stattfand. Es ist diese Erscheinung nur so zu erklären, dass die haptophore Gruppe des Complements bei der Umwandlung in Complementoid in ihrer Affinität zu der complementophilen Gruppe des Immunkörpers eine Verminderung erfährt.

andere Gruppe ausüben kann.

III. Ueber Auto-Anticomplemente.

In der 3. Mittheilung über Isolysine haben wir darauf hingewiesen, dass der Organismus über Einrichtungen verfügt, die verhindern, dass in ihm die Immunitätsreaction, die so leicht durch die allerverschiedensten Zellarten ausgelöst wird, sich gegen die eigenen Elemente richtet und dass Autotoxine entstehen. Unsere weiter fortgesetzten Untersuchungen haben diese Anschauung bestätigt, so dass man gewissermassen berechtigt wäre, von einem Horror autotoxicus des Organismus zu sprechen. Es sind diese Einrichtungen natürlich für die Existenz des Individuums von der allergrössten Bedeutung, da im Laufe des Lebens schon unter physiologischen, besonders aber unter pathologischen Bedingungen häufig genug Resorption des eigenen Zellmaterials eintreten kann und muss, so dass die Bildung von Gewebsautotoxinen eine Schädlichkeit wäre, die den Organismus häufiger und in viel stärkerem Masse bedrohen würde, als alle exogenen Gefahren. Nach unserer Ansicht ist das Studium dieser Regulationseinrichtungen, von denen nach unseren vorläufigen Untersuchungen in erster Linie Receptorenschwund oder Auto-Antitoxine in Betracht kommen, von grösster Bedeutung. Es wird sich daher darum handeln, alle Momente, die in dieser Beziehung von Wichtigkeit sind, einer eingehenden Analyse zu unterwerfen [1].

An dieser Stelle wollen wir einige Beobachtungen mittheilen, die sich auf die Complemente beziehen und die auf einen artigen und noch nicht beschriebenen Regulationsvorgang hinweisen scheinen.

Das normale Serum der Kaninchen besitzt eine Reihe Eigenschaften, die auf die Anwesenheit von Complement zurückzuführen sind. In erster Linie erwähnen wir hier, dass normales Kaninchenserum Meerschweinchenblutkörperchen [illegible] Es geschieht dies durch das Zusammenwirken eines Co[illegible] mit einem, im Serum in verhältnissmässig geringer Menge vorhandenen Immunkörper. Ferner ist das Kaninchen[illegible] gestellt worden.

Eine analoge [illegible] schilderten identisch [illegible] Kaninchen, das mit [illegible] Zweck der Gewinnung [illegible] war. Zehn Tage [illegible] Serum überhaupt keine [illegible] Gegensatz zu zahlreichen [illegible] darauf, dass sich im Verlaufe [illegible] hätte, da Complement [illegible] falls keine Lösungen, [illegible] körperchen [illegible] centrifugirt ist, [illegible] Complement [illegible] ringen [illegible] also [illegible] vorhanden [illegible] selbe [illegible] neut [illegible] welches [illegible] Anticomplement [illegible] dieses Ka[illegible] anderen [illegible]

1) Mit diesen Regulationsvorgängen [illegible] interessante Beziehung [illegible] (l. c.) [illegible] vom [illegible]

The illustrated quote is from an article by Paul Ehrlich and J.Morgenroth in the “Berliner Klinische Wochenschrift” from March 1901.

Their deliberations on the facilities of the organism that prevent the immune responses from being directed against their own body was probably the first publication that dealt with autoimmunity as a hazard. The very vivid term “Horror autotoxicus des Organismus” has been quoted many times since then and has also been relativized since the discovery of autoimmune diseases. However, this description remained seminal for the conceptions of the connections between tolerance and autoimmunity for many years.

In two previous papers by the same authors “About Hemolysins” in this journal from the year 1899, investigations and deliberations on induction of tolerance by occupying receptors had already been discussed and postulated. With this, the two decisive pillars of the immune system - tolerance and aggression - had already been introduced and discussed. Despite the tremendous increase in knowledge of the composition, modes of reaction and regulation mechanisms of the immune system in the past hundred years, this is still valid. In particular their prediction that “the formation of tissue autotoxins would be a harmfulness that would frequently and to a great degree threaten the organism more than all exogenous hazards” is still correct. This is a brief

characterisation of the genesis of autoimmune diseases - when the "Horror autotoxicus" has appeared. Ehrlich and his successors in medical science over the next five decades could not really imagine this. It took nearly half a century before it was proven that diseases actually develop and are maintained by autoaggression.

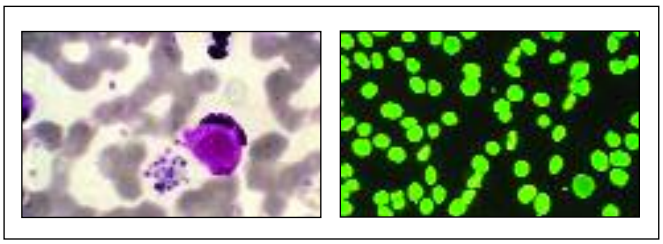

Figure 1 a.

So-called LE cell, which Hargraves (1948) found by chance in the bone marrow and blood of a female SLE patient. This cell is phagocytizing. Here, a leukocyte with a slender, marginal, oblong nucleus, which has ingested and "digested" a large swollen nucleus of a necrotic cell, is shown.

Figure 1 b.

Detection of antinuclear antibodies on HEp-2 cells with indirect immunofluorescence. Antinuclear antibodies form in vivo and in test tubes on the nuclei of necrotic cells. This is the signal for the phagocytizing cells to ingest this nucleus - and an LE cell is formed.

As early as 1948, with the so-called LE cells, Hargraves described an effect of humoral autoantibodies, which was connected with a severe disease that usually had a fatal course. However, it took until 1957 for this to be characterised as an autoantibody in detail. It could be isolated from the 7-s gamma globulin fraction and acted against cellular nuclear components - the antinuclear antibody (ANA) had been discovered (Fig. 1 a and b). Retrospectively interpreted, this detection of LE cells under induction of phagocytosis by antinuclear antibodies was the first indication of the importance of the immune system in apoptosis - the programmed cell death and the degradation of necrotic cell material. The fact that the immune system plays a central role in the organism in the elimination and clearing of necrotic cell material is widely accepted today. This, too, occurs by means of autoimmune responses. Malfuntion of this degradative process, which results in deficient elimination and thus increased concentration of e.g. necrotic nuclear material, are an important factor for the development of SLE and possibly also other autoimmune diseases. We were able to detect a defect in the cellular degradation function for DNA in the cellular immune system as early as 1974. Recent investigations have confirmed the key role this malfunction plays in the development of the disease in many cases.

This antibody tests, which are of main importance for autoimmune diagnostics, were further characterised and specified in the following years. Subsequently, a wide spectrum of antinuclear antibodies against different nuclear antigens has been discovered and described. A fraction of these antibody specificities was associated with extremely different clinical pictures and achieved a major clinical importance as diagnostic criteria for various rheumatic clinical pictures.

ANA	
Antibodies against	Clinical picture
DNA	Systemic Lupus Erythematosus
SSA/SSB	Sjoegren`s-Syndrome
snRNP	Sharp-Syndrome
Scl70	Systemic Sclerosis
Centromere	Crest-Syndrome
Jo1-Ag	Jo1-Antibody-Syndrome
PM Scl	Myositis

Table I

Rheumatic clinical pictures associated with different antinuclear antibodies.

Another important step on the path to discovery and meaning of the autoimmune responses and autoimmune diseases were the investigations on Hashimoto thyroiditis. In this clinical picture as well as in experimentally induced thyroiditides high antibody titres against thyroglobulins and thyroid gland tissue could be regularly determined. However, thyroiditis could not be induced by transferring this antibody to healthy animals. But, if lymphocytes from the diseased animals were transferred to healthy ones, the latter also developed an autoimmune thyroiditis. This was a decisive indication that autoreactive lymphocytes exist and can maintain diseases. On the basis of the insights which were obtained in these animal-experimental investigations on autoimmune thyroiditis, Witebsky formulated his criteria in 1956.

Criteria for an autoimmune disease
(according to Witebsky 1956)

1. Cellular or humoral autoimmune diseases against specific autologous antigens
2. Induction of autoantibodies through immunisation in an animal experiment
3. Tissue lesions in immunised animals corresponding to human organ damage
4. Transfer of the disease via antibodies or cells from diseased animals to healthy ones

The following decades have shown that not all autoimmune diseases could be covered by this definition. Even genetic predisposition, which was shown to be important in the subsequent years, was not considered part of this definition. However, even today there is still no generally accepted and valid definition of this disease group, except for rather obscure descriptions, as the following: ”Autoimmune diseases are characterised by significantly increased and elevated antibodies compared to healthy people.” The reason for these difficulties in definition lies in the complexity of the clinical pictures and organ manifestations, as well as in the different immune reactions and disease courses that are observed in this context.

Intensive investigations of the immune system, its mode of response, and regulation were able to prove that a close relationship and dependency exists between the T and the B cell system - the cellular and humoral immune responses - and that they do not function independently of each other. The interaction between these two systems has determined our conception of the immune system ever since. Their interplay and mutual interference as well as the different pathogenetic importance of these systems for different diseases is the central topic in research on the diagnosis and therapy of autoimmune diseases. Especially the mutual control, the regulation mechanisms, which determine the inhibition and activation of the immune systems, are the subject of intensive investigations. Due to these investigations, the methods of immunodiagnosis are constantly being refined and improved, in particular the development of very specific and effective drugs - the so-called Biologicals - are a result of this research in the last few years. The current progress in these areas is very promising and gives reason to hope for further improved diagnosis and therapies not only for autoimmune diseases.

Other important factors that influence autoimmunity and the genesis of autoimmune diseases are the autologous systems and conditions. It has long been known that autoimmune diseases affect women much more frequently than men. Immunoendocrinological investigations, which showed a strong mutual interference of the systems, have been able to clarify the reason of this clinical observation by means of hormone effects to a great extent.

Comparative investigations on older and young test persons showed that the immune system itself is also subject to an aging process. Immune responses and control mechanisms become less precise. There is an increase in detectable autoimmune phenomena without pathological importance with increasing age. Autoimmune phenomena can be detected in up to three percent of the population in young people; for those over 70 years of age this rate increases up to 30 percent and more. Of course this influences manifestations of disease as well as disease courses.

Autoimmune processes
influencing factors

Genetic predisposition (MHC-System)

Age (cumulative autoimmune phenomenons)

Sex (NK cells m > f, Suppressor m ≤ f)

Self-tolerance due to Autoimmunity.

If one transfers Ehrlich's term “Horror autotoxicus” onto the present conception of the immune system, it would now be termed “self-tolerance”. The maintenance of self-tolerance is the central problem which decides on the development or prevention of autoimmune diseases - on illness or health. From this, the central question results: by which mechanisms and controls does the immune system “distinguish” between tolerance and aggression.

For many years Ehrlich's side-chain theory, which he also referred to in the article from 1901 that was presented at the beginning of this paper, determined the existing conceptions of this phenomenon. With the discovery of the selective development of cell clones, the clonal selection hypothesis was formulated by Burnett. The discovery of possibilities of controlling the immune system, its active and reactive components resulted in the development of the network theory by Jerne and more recently to the theory of the idiotypic network. But, none of these theories can include the immune system's entire spectrum of possibilities. However, it is e.g. also conceivable that in different areas of this immune system varying courses and thus also different theories apply. On the contrary, it has been proven that immunocompetence and immunotolerance have already been acquired and programmed in the foetal period and the first few months of life. In this process, cells which react to autologous antigens are suppressed and blocked. B-cell reactivity is also inhibited by appropriate specific suppressor activities of the immune system. The result is the controlled autoimmunity, which however persists in its autoimmune potency.

As early as 1957, Pierre Grabar hypothesised that autoantibodies are continuously present in the organism in low concentrations. This also applies to autoreactive cells. To ensure that this “autoaggressive potency” does not become effective is the task of the suppressing, i.e. tolerance-maintaining, cells and antibodies. However, this is not a static equilibrium, but rather a continuous

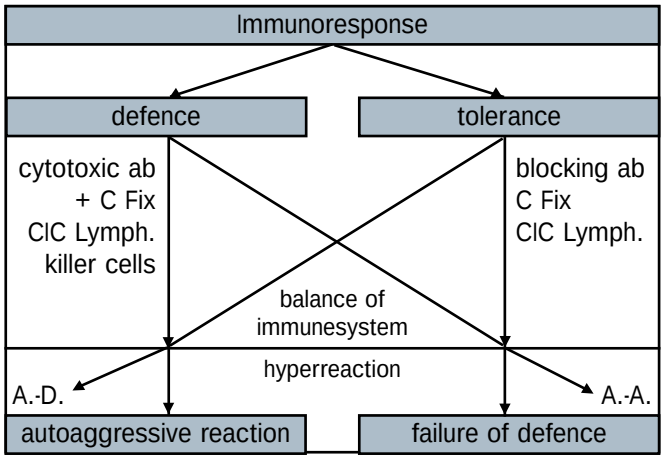

Fig. 2
Shows our conception of the immunological balance between the aggressive and the tolerance-maintaining components schematically. Weakening or failure on one side results in an exaggerated reaction on the opposing side, i.e. to autoaggression or to weakened defence.

dynamic reaction - action and reaction - which can be readily affected by external and autologous influences. As a consequence of inhibition or destruction of individual or numerous "suppressor components", an autoaggressive action can develop without hindrance and attack its own organism. The reason for autoaggressive disease processes thus does not lie in the development of new autoreactive cells and antibodies, but in the partial collapse of the regulating suppressor activity, i.e. in the disturbance of the life-supporting immunological equilibrium.

These insights into these mechanisms and courses of the immune responses have a decisive influence on the development of the diagnosis and also the therapy of autoimmune diseases - conversely, the development, refinement and above all the specification of immunodiagnosis provide important insights into old and new clinical pictures and disease courses as well as therapeutic options.

The triggering factors for the disturbance of the immunological equilibrium can come from very different areas: bacterial, viral or also fungal infections, chemical and biological exogenous toxins, environmental influences as well as psychic stress reactions. It is obvious that some pathogens trigger autoimmune processes more frequently, e.g. Streptococci, Yersinias, but also viral infections, such as the Hepatitis viruses, Cytomegalovirus, Epstein-Barr virus or Parovirus. In these cases, certain factors possibly play a role, such as cross-reactions against identical antigen components, e.g. between bacteria and the organism. As a result of reactions to the bacteria, the tolerance to the same or similar autologous antigens is simultaneously broken down - an exogenously induced autoaggression. In a similar manner, a so-called molecular mimicry is seen as the cause of virally induced autoimmune diseases. In theses cases autologous antigen structures are changed and subsequently considered foreign by the immune system and attacked
A leak of so-called cryptic antigens, i.e. antigenic substances of the body with which the immune system does not normally come into contact, can induce autoimmune responses against these organ components.

Autoimmune Diseases

The immunological equilibrium is disturbed by all of these factors. As a result, the actually protective and life-supporting aggression of the immune system against exogenous pests and poisons becomes a hazard to and a destructive process against its own organism. The weakening or even the breakdown of the humoral and cellular factors that support the tolerance results in autoaggressive diseases (e.g. systemic lupus erythematosus, among others); conversely, in cases involving weakening or failure of the aggressive components of the immune system to an exaggerated tolerance (e.g. immunodeficiencies). This false tolerance is also responsible for an inadequate destruction of abnormal and malignant cells, which in the further course favours or even causes the development of malignant tumours.
Since, as mentioned above, every human being is "autoimmune potent", there is always a latent chance, or better, a hazard of autoaggression as a result of disturbance of the immunological equilibrium. This can proceed in a self-limited manner due to the regulatory mechanisms of the immune system or in an unlimited one due to disturbance of these regulatory mechanisms. The fact that elevated antibody levels as well as autoreactive cells without specific disease processes can be detected in older people with weaker suppressor cell activity is also interpreted as an indication of potential autoimmunity.

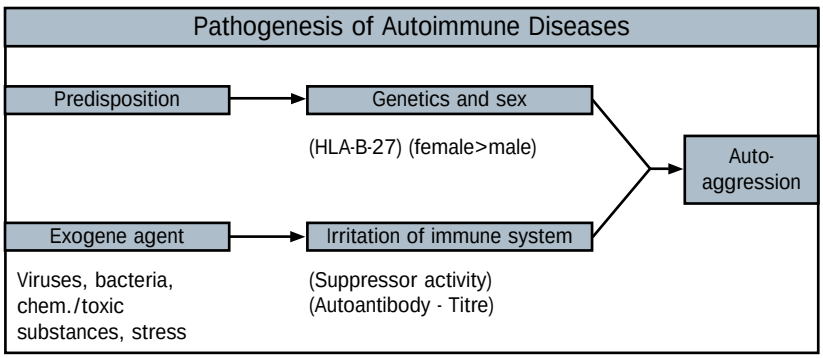

Fig. 3
The factors which play a role in the development of autoimmune disease and also immunodeficiencies are presented.

The spectrum of autoimmune disease has become substantially broadened as a result of our growing knowledge of the immune system and increasingly refined diagnostic methods in the last 50 years. Proceeding from the different manifestations of systemic lupus erythematosus over the organ-specific autoimmune thyroiditides and thyroitoxicoses, type I diabetes mellitus to vasculitides, the phospholipid antibody syndrome, and also arteriosclerosis in recent times.

In the last few years a multitude of new clinical pictures have been defined or newly recognised. This results in an enormous increase in the number of autoimmune diseases, which affect approximately five percent of all adults with increasing tendency. As the autoimmune diseases presented in Tab. III show, nearly all organ systems are affected. There are both diseases selectively restricted to one or more organs (endocrine glands, liver, etc.) as well as systemic generalised clinical pictures (rheumatic diseases, vasculitides, etc.) Accordingly, these clinical pictures as well as the autoantibodies can be classified in organ-specific and systemic (organ-unspecific) autoimmune diseases. Especially the systemic diseases are very different in their clinical expression - severity, progredience, symptomatology - because practically all organs can be affected. Nearly any clinical picture can be caused in this manner. The courses can be relatively mild with long phases of remission and mild symptoms for years and decades or rapidly progressing and not therapeutically influenceable, thus resulting in death. Between these extremes nearly any possible course is conceivable for these diseases.
(Table III)

In this broad disease spectrum with extremely different courses and clinical pictures, for many years and up to the present day the rule was that the exact diagnosis and thus also a successful therapeutic approach frequently could only be made after years of delay and further development of the disease. The inevitable consequences were and unfortunately still are irreversible organ damage and disease states that can barely, or only with use of the strongest drugs, be influenced.
The total development of the diagnostic possibilities in the field of immunology and particularly of autoimmune response will be of decisive importance in the reclassification of old as well as in the discovery of new clinical pictures and their pathogenic courses.

Investigations on the course and on the prognosis of these diseases have shown that the most favourable prognosis is to be expected in cases of the earliest possible diagnosis and therapeutic intervention. For this reason, with regard to the total therapeutic success and the prognosis for the patient, diagnosis is of decisive importance. However, in the initial stages the symptoms are frequently discrete, unspecific or barely perceivable. The first indications of the presence of an autoimmune disease are therefore the result of antibody tests, which thus have central importance in the diagnosis of this disease. The cellular immune responses still do not have any major importance in routine diagnosis despite their great pathogenetic and pathological importance for these clinical pictures.

Autoimmune diseases (selection)
Rheumatology
Rheum. Arthritis (RA), Systemic Sclerosis, Arteriosclerosis, Systemic Lupus Erythematosus (SLE), Antiphospholipid-Syndrome (APS), Vasculitis, Collagenosis
Endocrinology
Thyroiditis, Graves Disease, Diabetes Type I, M. Addison, Autoimmune Polyendocrine Syndromes etc.
Hepatology
Primary Biliary Cirrhosis (PBC), Chronic Aggressive Hepatitis (CAH) etc.
Gastroenterology
Gastritis, Colitis, M. Crohn etc.
Cardiology
Carditis, Postinfarkt/Cardiomyotomy, Coronaritis, Pericarditis.
Pulmonology
Fibrosis, Alveoloitis, Goodpasture-Syndrome, Pleurisy etc.
Haematology
Autoimmune Haematolytic Anemia (AIAH), Thrombocytopenia (ITP) etc.
Neurology
MS, PNP, Guillain-Barré-Syndrome, Myasthenia etc.
Ophtalmology
Uveitis, Iritis etc.
Dermatology
Pemphigus, Pemphigoid LE, Vitiligo, During's disease
Nephrology
Goodpasture-Syndrome, Glomerulonephritis

Table III

The effector mechanisms of the immune system in the different diseases are, in part, different. They can be divided into three groups:

A. Direct antibody effects:
Cytotoxic antibodies, e.g. basement membrane nephritis, ITP
blocking antibodies, e.g. Myasthenia gravis (acetylcholine receptor blockade)

B. Immune complex deposits:
e.g. systemic lupus erythematosus, vasculitides

C. Cytotoxic lymphocytes
e.g. type 1 diabetes, rheumatoid arthritis

Since a causal therapy is not possible in these diseases, it is of great importance to influence the correct effector mechanisms, those which result in organ damage. In this manner it is perhaps possible, at least in an early stage of the disease, to influence the immune process to the extent that perpetuation does not occur, but restoration of the immunological balance is achieved in the most favourable cases. Also with respect to diagnosis and course control of the disease, the relevance of the respective detectable immune phenomena and cell infiltrates is of importance for the pathological process.

Diagnosis of Autoimmune Diseases

In routine diagnosis of autoimmune diseases, the cellular components of the immune system play practically no role at all, despite their indoubtable pathogenetic and pathological importance. In addition to purely practical reasons involving the difficulty of handling of cells and cell reactions in routine diagnostics, this is due to the complexity of the cell reactions. Consequently, routine diagnosis is based exclusively on examination of humoral components. The following components should be mentioned: on the one hand, as unspecific, the determination of immunoglobulins and complement factors as well as the circulating immunocomplexes in rare cases. On the basis of these components, statements on the general immune status and the unspecific mode of reaction of the immune system can be made. In particular they are important in monitoring progression of disease and evaluation of disease activity, e.g. the complement deficiency in cases involving an acute phase of an immune complex nephritis.

In the routine diagnosis of the autoimmune diseases, autoantibody tests - organ-specific and organ-unspecific - play a decisive role. Organ-specific autoantibodies indicate a disease of an organ as a rule. However, particularly antibodies against endocrine glands can also be directed against different organs (e.g. islet cells, thyroid gland, suprarenal cortex) without all these organs being diseased to the same extent. Conversely, organ-specific antibodies normally indicate systemic autoimmune diseases, such as systemic lupus erythematosus, other connective tissue diseases or vasculitides.
(Table IV)

Clinical/diagnostical relevant autoantibodies	
SYSTEMIC	ORGAN-SPECIFIC (ab against)
ANA (antinuclear antibodies) against: dsDNA SSB (La) SSA (Ro) ScL 70 Centromere Sm snRNP Jo1-antibodies	TPO (Thyroid Peroxidase)
	Adrenal cortex
	AMA Mitochondria, M2, M4, M8, M9,
	LKM (Liver, kidney)
	PCA (Parietal cells)
	SMA (Smooth muscle)
ANCA against: (Antineutrophilic cytoplasmic antibodies) MPO (Myeloperoxidase) PR3 (Proteinase 3)	Skeletal muscle
	GMB (Glomerular basement membrane)
	Pemphigus (Dermal epidermal borderline)
RF (Rheumatoid factor) antibodies against: IgM IgG IgA Citrullin	Heart muscle (Sarkolemma)
	Acetylcholine Receptor-Ab
	Blood cells
	Erythrocytes
	Leukocytes
APLA (Antiphospholipid-antibodies) against: Cardiolipin ß2 Glycoprotein Prothrombin	Thrombocytes)

Table IV

The majority of the detectable antibodies are more likely to be considered as markers for underlying autoimmune diseases, which are only indirectly involved in the pathological process via immune complex formation or influencing cellular immune response or even not verifiably involved. However, this does not reduce their importance in diagnosis, but can result in irritations or misinterpretations in observations of the course of a disease. While autoantibodies that are directly involved in the pathological process can be well correlated with the disease activity based on their titre level, this is frequently not the case for other antibodies.

The basement membrane antibodies in Goodpasture syndrome, the Pemphigus antibodies in cases involving Pemphigus Vulgaris as well as antibodies against thrombocytes in ITP and erythrocytes in the autoimmunohemolytic anaemia belong to those antibodies which act directly cytotoxic. The antibodies against the

acetylcholine receptor in Myasthenia gravis also act directly but via receptor blocking. In systemic lupus erythematosus, vasculitides and other systemic diseases, the antibodies are indirectly involved in the pathological process via immune complex formation and deposits. In type I Diabetes, other endocrine autoimmune diseases and also in rheumatoid arthritis, cytotoxic cells play a primarily pathological role; whereas the detectable autoantibodies are to be assessed as diagnostic markers for ongoing autoimmune processes.

In clinical routine autoantibodies are predominantly detected by means of enzyme-linked immunoassays and indirect immunofluorescence. In special test procedures, radioimmunoassays and immunoblots are used. Today investigative methods from the pioneer period of autoimmune diagnostic, such as the complement fixation reaction, hemagglutination, immunodiffusion are only used in special cases but not in every day clinical routine.

Problematic Nature of Autoantibody Tests

The clinical value of autoantibody tests is extremely dissimilar in the diagnostics of different autoimmune diseases. It is therefore of great importance to correctly allocate or weight, respectively, the positive - or also negative - autoantibody findings.

Since the beginning of immunodiagnosis, an additional problem has been the reproducibility and standardisation of the investigative methods. This was and is - as different comparative investigations performed very recently have shown - a problem that has not yet been definitively solved and that can presumably also not be solved with the methods currently in use. This is the result of the multiplicity of the antibody populations, different binding properties, varying influenceabilities resulting from serum and reagent factors and differing antigen preparations.

Comparative studies, which have been repeatedly conducted over the last several years, as well as international consensus investigations have shown that test systems produced by different manufacturers, in part, also with different lots made by the same manufacturer still obtain different results. Even the introduction of WHO standards in individual test systems was only able to produce a slight improvement, but still no decisive stabilisation, in this situation. Meticulous quality controls by the manufacturer as well as regular internal laboratory quality controls and comparative studies on the same samples with different lots are thus the prerequisite for a reproducible and clinically relevant diagnosis. As a rule this is only ensured in specialised laboratories with supervision by appropriately trained immunologists, rheumatologists or haematologists. More specific formulations of problem complexes and studies should thus only be conducted in such institutions.

CLINICAL VALUE OF AUTOANTIBODIES WITH REGARD TO THE RESPECTIVE AUTOIMMUNE DISEASE

Disease	Antibody	Sensitivity	Specificity
SLE	ANA positive	XXXX	X
	anti-dsDNA	XXX	XXXX
	anti-Sm	X	XXXX
	anti-ribosomal RNP	X	XXXX
	anti-PCNA	X	XXXX
	anti-Histone	XXX	X
	anti-U1-RNP	X	X
	anti-SS-A (Ro)	X	X
	Anti-SS-B (La)	X	X
Drug induced LE	ANA positive	XXXX	X
	anti-Histone	XXX	XX
MCTD (Sharp-Syndrome)	ANA positive	XXXX	X
	anti-U1-RNP	XXXX	XXXX
Sjoegren's Syndrome	ANA positive	XXX	X
	anti-SS-A (Ro)	XX	XX
	anti-SS-B (La)	XX	XX
	α-Fodrin IgG/IgA	XXX/XXX	XXXX/XXXX
	IgA-RF	XXX	XX
	IgM-RF	XXX	X
Systemic Sclerosis	ANA positive	XXXX	X
	anti-Centromere	XX	XXXX
	anti-Scl-70	X	XXXX
	anti-nucleolar (Fibrillarin)	X	XXXX
Poly/Dermatomyositis	ANA positive	XX	X
	anti-Jo-1	X	XXXX
Anti-Phospholipid-Syndrome	anti-Cardiolipin plus β2-Glycoprotein I	XXXX	XX
Rheumatoid Arthritis	IgA-RF	XXX	X
	IgM-RF	XXX	X
	IgG-RF	XXX	XX
	Citrullin	XXX	XXXX
	anti-Keratin	XX	XXXX
	anti-Histone	XX	X
M. Wegener	cANCA PR3	XXX	XXX
		XXX	XXXX
Panarteriitis nodosa	pANCA MPO	XX	XXX
		XXX	XXX
X= up to 25%	XX= up to 50%	XXX= up to 75%	XXXX= up to 100%

It is important for the clinical physician to be familiar with these difficulties and to take them into consideration. Additionally, different methods for detecting the same antibody are, in part, not compatible in their clinical relevance. For example the results for DNA antibodies obtained by ELISA, indirect immunofluorescence on Crithidia luciliae and radioimmunoassay are clearly different with regard to sensitivity and specificity and thus also with regard to diagnostic relevance.

In Tab. V some clinical pictures from the group of rheumatic disease with the tests for the different autoantibodies are presented. The weighting of these autoantibody tests for diagnostics are indicated in terms of their varying sensitivity and specificity. The latter is naturally of great importance for the interpretation and should therefore be known for every autoantibody interpretation.

Perspective

Every new insight and discovery opens new, unknown fields. This is particularly true for such a complex, broadly branched system, which is involved in nearly all organ processes and reactions, as the immune system. Disease and healing courses without involvement of the immune system are inconceivable. Studies on the processes and effects of the immune system on the organism repeatedly lead to new insights in old clinical pictures or else also diseases that are to be redefined.

The latter applies, e.g., to the antiphospholipid syndrome (APS), which was described on the basis of the phospholipid antibody reactions and their effects on the vascular system. Its conspicuous and, in part, dramatic manifestations also in young female patients with mild or severe strokes, pulmonary embolisms and other thrombo-embolic events are a good example. In addition, the high spontaneous abortion rate, which has been observed in cases involving detection of this antibody, shows the clinical relevance of such an antibody test. In female patients with connective tissue diseases or primary APS, early controls before and in the course of pregnancy are now possible and therapeutic measures can be initiated in accordance with the immunological findings. As a consequence, the spontaneous abortion rate in these patients could be clearly reduced.

Even well known and widespread clinical pictures, such as arteriosclerosis, are being given new “autoaggressive” aspects as a result of new insights into their immunopathogenesis. In addition to the previously known risk factors for this clinical picture, an ever-increasing number of chronic inflammatory responses, which result from autoimmune processes and which take place, e.g., on vessel walls, are coming to the fore. The vasculitides are a definitive example of this. With this, a clinical observation, which has been described for many years, has been confirmed, which had long-since led to a discussion of the immunopathogenesis of arteriosclerosis: An above average number of patients with autoimmune diseases - from SLE to rheumatoid arthritis - fall ill, in part even at an early age, with arteriosclerosis and develop coronary heart disease (CHD). These complications are the most frequent causes of death for these clinical pictures. An explanation for this can now be found in the immunopathological processes described above.

Autoimmune processes are also being discussed in connection with a number of other diseases. Among them are, e.g., psoriasis, epilepsy, schizophrenia, endometriosis, alopecia, duodenal ulcers. These clinical pictures also illustrate, as do the previously known autoimmune diseases, the broad area of conflict of the autoimmune diseases.
In addition to the diagnosis and definition of new autoimmune diseases, the therapeutic approaches, based on our growing insights into the immune system and autoimmune responses, are a fascinating and no less important field. After the glucocorticoids and the cytotoxic immunosuppressives, the selective targeting of immunological processes and inflammatory responses by means of blockade or antibodies against cytokines, the messenger and control substances of the immune system, is very promising and its therapeutic application in some clinical pictures has been impressively successful up to now.

The antibodies against the so-called tumour necrosis factor alpha were the first step. This cytokine is, e.g., released at the beginning and during the course of inflammatory processes, and has also been made responsible for the loss of weight in tumour patients. The neutralisation of this tumour necrosis factor (TNF) thus blocked the real, damaging inflammatory process, which leads to the destruction of organ structures and cells.

Besides soluble receptors for these cytokines, in particular monoclonal antibodies against different cytokines have been developed, such as Interleukin 6, Interleukin 15. Additionally, monoclonal antibodies against cell antigens or receptors, such as anti-CD20 and CTLA4 IgG1 as well as the inhibition of the C5 degradation blockade are meanwhile under development or have already been introduced in therapy. Monoclonal antibodies against B cells also open completely new therapeutic options. Already very successfully used in cases of B cell diseases and transplantations, here too, very promising studies are being conducted on their therapeutic application in cases involving connective tissue diseases and other autoimmune diseases. According to current estimation, this is only a small segment of the large field of the additional drug-therapeutic options that will result from the further development of and new insights into immunological processes.

Another therapeutic approach uses the normal products and regulation mechanisms of the immune system. The administration of large doses of immunoglobulins results in a down-regulation of the pathological immune process and thus to an "immunoregulation" in the direction of a restoration of the immunological balance. In this context, the effects on the different components of the immune system are very complex. Not only immunoglobulin production, cytokines and phagocytosis are influenced, but also the reactivity of cellular immune components are affected.

In addition, the further development of "blood washing"(hemodialysis) or plasmaphresis for immunoadsorption is a very promising therapy concept. It is based on the specific elimination of damaging components of the immune process. On the one hand, a general depletion of the antibody reservoir of the organism can be achieved in this manner. On the other hand, by using special antibody-coated filter columns, in addition selective pathological antibody fractionations, cytokines, individual cell populations or other damaging substances which maintain the pathological process can be filtered out. The particularly fascinating and tempting thing about the last two therapy options, in particular, lies in their "lack of toxicity" - in contrast to drug treatment, in which the therapeutic principle is a properly dosed toxicity and thus simultaneously also involves a corresponding risk.

The diagnosis and therapy of autoimmunological diseases is thus based increasingly on specific antibody detection as well as on the preparation of and treatment with monoclonal antibodies. At present, an end to this development is not in sight. In this context, hopes lie not only in the field of autoimmune diseases or of the immunodeficiency, but also in tumour therapy. Monoclonal antibodies or also cytotoxic T cells, which react to tumour antigens and cell components, can also prevent tumour growth and result in the destruction of tumour cells.

However, the diagnosis of autoimmune diseases and also their clinical control can still not be fulfilled for any of these clinical pictures by a single parameter. In this context, in addition to the immunological investigation results, in particular, the clinical findings, which in many autoimmune diseases of the group of rheumatic diseases are defined by disease-specific criteria, must be taken into consideration. To evaluate the disease course, activity indices, which are also a combination of immunological findings and clinical examination results, are used. Of course, additional laboratory chemical, histological and roentgenological examinations, which depend on the clinical picture and organ involvement, must also be considered.

An early and exact diagnosis is the basis for the early and successful therapeutic approaches in cases involving autoimmune diseases. Both in the diagnosis and in the therapy, autoantibodies play an increasing decisive role and are, as the basis for further development, indispensable with an importance that cannot be estimated today.

SLE: Tracking down therapeutic antibodies

Systemic Lupus Erythematosus (SLE) is one of the most common rheumatological diseases. Prevalence of SLE is 1:2500.
The prognosis for the patient depends on a major degree on whether the kidneys are also attacked by glomerulonephritis (Lupus nephritis), as this severe complication can lead to kidney failure. Glomerulonephritis affects 30 - 50 % of patients, so up to 1 of 5000 patients suffers from Lupus nephritis.
Organ damage is mediated by immune complexes containing autoantibodies against double-stranded DNA (anti-dsDNA) and the concentration of IgG anti-dsDNA correlates with the occurrence of glomerulonephritis in SLE patients.
As SLE is still unaddressed by specific therapeuticals, Cyclophosphamide is used as a powerful but unspecific immune suppressive drug in therapy, especially in the severe progression with the participation of organs as a successor of a therapy with cortisol. The disadvantage: Cyclophosphamide has serious side effects.
Together with the team of Dr. Torsten Witte, Hannover Medical School, AESKU is now on the trail of fresh possibilities for the therapy of SLE, which will enable a specific treatment and minimize side effects.
Because of first promising results AESKU has already patented an in vivo therapy implementing therapeutic antibodies for glomerulonephritis.

Therapeutic Application of IgM Autoantibodies

The latest research activities by the Wendelsheim research team, in cooperation with clinical working groups in Hannover and Prof. Dr. Klaus Hemke and others Munich, have shown that the development of kidney disease depends on the extent to which certain autoantibodies typical for the disease, the so-called anti-dsDNA antibodies, are present in a patient's body.
These studies clearly demonstrate that the presence of IgM anti-dsDNA negatively correlates with the development and severity of glomerulonephritis (1)+(2). It has therefore been hypothesized that the presence of IgM anti-dsDNA may protect against immune complex-mediated organ damage.
In joint experiments with Dr. Torsten Witte and his team at Hannover Medical School it was actually possible to show this hypothesized protective effect of IgM dsDNA antibodies in a murine lupus model and to delay the onset of kidney disease and the mortality rate using a form of these autoantibodies.
Mice treated with a murine monoclonal IgM anti-dsDNA antibody showed a delayed onset of proteinuria and a prolonged survival rate compared to control mice. In addition, a markedly reduced glomerular IgG deposition in kidney sections of treated mice has been observed.
These results demonstrate that IgM anti-dsDNA protects against immune complex-mediated organ damage in murine lupus and may also explain why human SLE patients with IgM anti-dsDNA are partially protected against glomerulonephritis (3). These data are encouraging to clarify the mechanism of therapeutic benefit of IgM anti-dsDNA and may provide new specific therapeutic approaches of SLE.
The research teams in Wendelsheim and Hannover now begun to look in further detail at the mechanisms of the therapeutic effect of IgM anti-dsDNA antibodies.
The objective is the development of antibodies which when used specifically as a therapeutic or prophylactic measure with SLE patients can prevent the development of kidney disease with Lupus Erythematosus without the patients having to suffer the side-effects of those drugs currently available.

(1) IgM anti-dsDNA antibodies in systemic lupus erythematosus: negative association with nephritis. Witte et al., Rheumatol Int. 1998; 18: 85-91.
(2) Clinical Significance of anti-dsDNA Antibody Isotypes: IgG/IgM ratio of anti-dsDNA antibodies as a prognostic marker for lupus nephritis. Förger F, Matthias T, Oppermann M, Becker H, Helmke K. Lupus 2004, 13: 36-44
(3) These results have been presented at the EULAR (European League against Rheumatism) Congress in Berlin from June, 9-12, 2004 and at the 7th International Congress on SLE in New York from May, 9-13, 2004 and are published in the Annals of the Rheumatic Diseases, July 2004, Vol 63, Supplement 1.German-Israeli research cooperation opens up new opportunities in the diagnosis and therapy of autoimmune diseases

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APS: From the diagnosis to the prognosis

Together with renowned researchers at the University of Tel Aviv in Israel, AESKU is now on the trail of fresh possibilities for the therapy and diagnosis of autoimmune diseases.
Professor Yehuda Shoenfeld, head of the Center for Autoimmune Diseases at Tel Aviv University, holder of the world's first professorship for autoimmunity and scientific head of the AESKU.INSTITUTE, and Miri Blank, head of the research laboratory in Tel Aviv, spent their 3-week research trip in Wendelsheim conducting further research into the autoimmune disease antiphospholipid syndrome, together with the AESKU team.
Antiphospholipid syndrome (APS) causes not only the typical changes in the skin, but can also cause venous and arterial cardiovascular problems, which lead to thromboses, neurological damage and to recurring spontaneous miscarriages.
With new forms of laboratory tests such as those being developed and produced by AESKU.DIAGNOSTICS on the basis of its own research, APS can be successfully diagnosed. The consequences for the individual patient could, however, barely be predicted to date.
The objective of the research activities in cooperation with the Israeli working group is to refine the test possibilities such that in the form of a prenatal screening they can give an early indication whether a young woman with APS actually has to reckon with the possibility of a miscarriage. The corresponding preventive measures can then be taken.

In the middle of everywhere

A critical time factor in the development of new diagnostic methods and therapeutics is the networking between research, development and production. This is why the company AESKU has a unique corporate structure, uniting research into the development, therapy and diagnosis of autoimmune diseases under one roof. Research results can thus be implemented as innovative products remarkably quickly. The ideal framework for the company's research activities, for product development and product, as well as for further growth, is offered by the technology center "Mikroforum" in Wendelsheim, Germany.
At the end of his research trip Yehuda Shoenfeld corrected his first impression - Wendelsheim, he said, is not, as he initially thought, "in the middle of nowhere", but rather "in the middle of everywhere".

Background information, studies and more are available under: www.aesku.com

The German-Israeli team at work: Dr. Sascha Pfeiffer, Dr. Ingrid Wies, Dr. Torsten Matthias, AESKU und Prof. Yehuda Shoenfeld, Dr. Miri Blank, Tel Aviv University (from left to right).

On the trail of fresh possibilities for the prognosis of APS: Dr. Torsten Matthias, AESKU, and Prof. Yehuda Shoenfeld, Tel Aviv University (from left to right).

Premiere: AESKU.AWARD for life contribution to autoimmunity

The 4th International Congress on Autoimmunity in Budapest November 3-7, 2004 opened with a premiere: The AESKU.AWARD for life contribution to autoimmunity was granted for the first time during the opening session on the first evening.
This year three of the pioneers in research in the field of autoimmune diseases have been rewarded for their work: Donato Alarcon Segovia, Ian R. Mackay and Noel R. Rose.
In the course of the past decades the award winners have made a major contribution to research into the causes of autoimmune diseases.

Introduced by Yehuda Shoenfeld, congress chairman and holder of the world's first professorship for autoimmunity at Tel Aviv University, Donato Alarcon Segovia, National Institute of Medical Sciences and Nutrition, Mexico, DF, Mexico, spoke about "Shared autoimmunity, a new concept" during the opening session.
Noel R. Rose, Departments of Pathology and Molecular Microbiology and Immunology, John Hopkins Medical Institutions, Baltimore, MD, USA, reported also introduced by Yehuda Shoenfeld, on "The transition from benign to pathogenic autoimmunity: the myocarditis model".
Last but not least Ian R. Mackay, Department of Biochemistry and Molecular Biology, Monash University, Clayton, Victoria, Australia, who was introduced by the chairman M.E. Gershwin from the University of California School of Medicine, USA, held a short lecture about "Autoimmune epitopes: autoepitopes".

The AESKU.AWARD for life contribution to autoimmunity does not only want to show the importance of research on autoimmune diseases, it also aims to establish the significant field of autoimmunity as an independent research area and to foster interdisciplinary cooperation.
AESKU continuously invests in research and development to create new opportunities that improve diagnosis and therapy of autoimmune diseases substantially. Therefore the research team also contributed to the scientific program together with research partners from renowned universities.

Detailed information about the award winners, their research work und about new future trends in diagnosis and therapy of autoimmune diseases presented during the 4th International Congress on Autoimmunity in Budapest will be published in the next issue of AESKU.SCIENCE.

AESKU.AWARD for life contribution to autoimmunity

1. AESKU Autoimmune Workshop

What is the clinical picture and disease pattern for various autoimmune diseases, how can the laboratory contribute to a secure diagnosis, which parameters should be tested, and how meaningful are the resulting figures - these questions were at the focus of the 1st AESKU Autoimmune Workshop in Wendelsheim on 13th September 2004.
Following the welcome by Petra Löffler, Sales Manager Germany, and a brief presentation of the company by managing director Dr. Torsten Matthias, 27 participants from all over Germany gathered information on the latest trends in autoimmune diagnostics. Addresses by leading clinical and laboratory experts provided up-to-date knowledge on the antiphospholipid syndrome (APS), celiac disease, Crohn's disease, collagen diseases and autoimmune liver diseases. The program was supplemented by the presentation of new automation techniques for ELISAs in the laboratory of the company AESKU.DIAGNOSTICS.

APS and antiphospholipid antibodies

Dr. Christian Fischer, Bioscientia Institut für Laboruntersuchungen Ingelheim GmbH, opened the event with his address on the antiphospholipid syndrome (APS) and the associated antiphospholipid antibodies. He described the classification of APS on the basis of case studies, the immune pathogenesis, and the possibilities of laboratory diagnostics of APS.
APS can already be diagnosed with new forms of antiphospholipid ELISA laboratory tests, which specifically demonstrate the characteristic antiphospholipid antibodies. According to Christian Fischer there is a lack of predictive laboratory values as well as parameters that are associated with the course of the disease. Peptide mimotopes and monoclonal antiphospholipid antibodies can contribute to the standardization of the chemical analysis. Knowledge of the binding properties and of the precise binding regions of the antibodies could possibly close the diagnostic loopholes.

Diagnostic approach in the event of suspected celiac disease and Crohn's disease

In his subsequent address Prof. Dr. Dr. Jürgen Stein, University Clinic Frankfurt, presented the clinical patterns of celiac disease and Crohn's disease, the factors in their emergence and development, and the possibilities for clinical and serologic diagnosis. The differential diagnosis of these diseases, and in particular chronic inflammatory bowel diseases (IBD), among which rank Crohn's disease and ulcerative colitis, is extremely difficult. This is why, stated Jürgen Stein, intensive cooperation between clinical and laboratory diagnostics is required for a clear diagnosis.

Autoimmune liver disease

In her speech Dr. Ingrid Wies, AESKU.DIAGNOSTICS, covered considerable ground, from a presentation of the various autoimmune liver diseases, through a discussion of the significance of a swift and secure diagnosis, to the presentation of the latest research findings in diagnostics and therapy.
There may be various causes of liver diseases. Alongside various forms of intoxication, viral and bacterial infections, autoimmune diseases also play a significant role. A secure differential diagnosis is extremely important as the wrong diagnosis and therapy can have serious consequences. If, for instance, immunosuppressive agents are used with a viral liver disease, the consequences for the patient can be disastrous. Liver diseases with an autoimmune background may be easily differentiated using antibody profiles.

Prof. Dr. Dr. Jürgen Stein, Dr. Torsten Matthias, Dr. Christian Fischer and Paul Ballieux in discussion (from left to right)

Collagen diseases

Dr. Martin Welcker, a resident rheumatologist in Munich, looked at the symptoms and diagnosis of collagen diseases in the final presentation of the day.
Rheumatologists, said Martin Welcker, are confronted with a very wide range of clinical pictures in practice, from arthritis, through rheumatoid diseases, to carcinomas, and endeavour to make progress on the basis of meaningful laboratory results. The number of autoimmune diseases in itself is very large. In his address he highlighted numerous parameters which could indicate inflammatory diseases with an autoimmune background.

Automation of autoimmune diagnostics

"In passing", as it were, the participants were able to gather information on the latest possibilities for the automation of autoimmune diagnostics in the address by Paul Ballieux, Grupo Grifols, and on the advantages of the TRITURUS system. The TRITURUS system is an immunoassay system which is outstanding thanks to its high degree of precision and accuracy, incredible flexibility and user-friendly software. Thus it is the ideal platform for the fully automated processing of ELISA-Tests in the laboratory. Together with the wide AESKULISA® product range, TRITURUS forms an ideal team, said Paul Ballieux.
A tour of the laboratories of AESKU, in which all the products are developed and manufactured, rounded off the day.

The first but not the last time!

The response by the participants to the first workshop was extremely positive. It was evidently highly interesting and motivating for the participants to not just become familiar with the laboratory diagnostics for the diseases, but also with the possible consequences for patients.
The feelings of all were summed up by one attendee from Dresden: "It was a long journey, but it was well worthwhile."
And that's why work has already started on next year's event!

As the response was extremely positive but the number of participants unfortunately limited, the addresses made at the 1st AESKU Autoimmune Workshop will be available in full in German and English in a series of 4 articles on the AESKU homepage from December onwards.
If you are interested in taking part in the next Autoimmunity Workshop don't hesitate to contact us
phone:+49 (6734) 9627-0 ; e-mail info@aesku.com

MEDICA 2004: New diagnostic opportunities

AESKU continuously invests in research and development to create new products that broaden the range of diagnostic opportunities continuously; the *AESKULISA*® product line now offers more than 100 different assays for a fast and reliable diagnosis of autoimmune diseases.

Numerous new highlights are presented at MEDICA 2004 in Düsseldorf this year.

- A new generation of tTg ELISA´s increasing the sensitivity in the diagnosis of Coeliac disease markedly.
- The new kit *AESKULISA*® Parietal cell for the quantitative and qualitative determination of IgG autoantibodies against parietal cells for the diagnosis of pernicious anemia and for the early diagnosis of type A gastric lesions.
- *AESKULISA*® Prothrombin: a highly specific marker for foetal loss related to APS.
- The new assay *AESKULISA*® Annexin V-GM that contributes to an improved diagnosis of APS especially in female patients at risk for obstetric complications.
- *AESKULISA*® Laminin, a useful tool for the diagnosis of recurrent abortion and infertility associated with endometriosis.
- *AESKULISA*® RA/CP Detect: a novel and highly specific marker which employs synthetic citrullinated peptides from human immunoglobulin G for the diagnosis of rheumatoid arthritis.

AESKU also introduces a new testing system offering decisive time advantages for patients, treating physicians and laboratory staff when every minute counts in autoimmune diagnostics. AESKU.Seven-Up requires only 3 times 7 minutes for the entire test sequence. Despite its speed, the system provides not just qualitative but also quantitative results.

AESKU.DIAGNOSTICS	MEDICA 2004	Hall 3, Booth 03/H34

Autoimmune diagnostics and automation - the ideal partnership

AESKU.DIAGNOSTICS, Wendelsheim, and the Diagnostic Division of the Spanish company Grifols International have now concluded a distribution partnership for the German and the U.S. market, so as to open up new possibilities for laboratory automation in the field of autoimmune disease diagnostics.

The success factor for immunoassays (ELISA) is, according to recent market studies, the clear suitability for laboratory automation, which opens up the possibility to cut costs, optimize processes and enhance quality. AESKU.DIAGNOSTICS thus now offers two ideal partners for the automation of autoimmune diagnostics from one source:

- Its own *AESKULISA*® product line, which, with more than 100 CE-marked ELISA tests, represents the widest range of ELISA tests for autoimmune diagnostics, and
- TRITURUS, the immunoassay analyser from the company Grifols, which is outstanding thanks to its high degree of pre cision and accuracy, incredible flexibility and user-friendly software.

The *AESKULISA*® product line was specifically adapted to automation during the development stage. The inimitable "unique but equal" concept, which ensures all tests have a common structure, even if they are used to determine different parameters in patient serum, has already established the product range in many European countries as the ideal partner for automated autoimmune diagnostics.

TRITURUS, an immunoassay analyser, which is outstanding thanks to its high degree of precision and accuracy, incredible flexibility and user-friendly software, forms the ideal platform for the fully automated processing of ELISA tests in the laboratory. Thanks to its flexibility TRITURUS is suited to serologic laboratories of all kinds and sizes.

Further information is available at all times at MEDICA 2004 in Düsseldorf at the AESKU.DIAGNOSTICS booth, hall 3, booth 03/H34, or in the internet under: www.aesku.com.

Ideal partners for the automation of autoimmune diagnostics: the *AESKULISA*® product line and TRITURUS.

AESKU - Networking for a better diagnosis and therapy of autoimmune diseases

AESKU aims at autoimmunity research in a new quality. Therefore the company continuously invests in research and development to create new opportunities for improved therapy and diagnosis of autoimmune diseases substantially. With this aim in view AESKU has two goals.

First of all, AESKU`s main focus is to establish autoimmunity as an independent research faculty. One of the most important tasks is to bring together all fields of autoimmunity research to an interdisciplinary approach, which will be the basis for a new quality of results.

Secondly, AESKU aims at combining research on pathomechanisms, diagnostics and therapy so that all these fields can interactively provide each other with new impulses. The use of synergistic effects will serve the research on autoimmune diseases as well as the aim to gain better diagnostics and therapies.

Unique network structure shortens time to market

A critical time factor in the development of new therapeutics and diagnostics is a good network of communication and exchange between research, development and production. Therefore AESKU cooperates closely with renowned scientific institutions and scientists on the one hand, and, on the other hand, it has a lively exchange of information with industry.

Scientific cooperation provides the scientific background for the development of innovative drugs and diagnostics as well as opportunities for new therapies. Economic cooperation with different industry partners enables a quick and direct realization of promising research results in order to serve for improved health care.

The company AESKU itself has a unique corporate structure, uniting research on development, therapy and diagnosis of autoimmune diseases under one roof. Three different divisions each with their own particular focus - AESKU.DIAGNOSTICS, AESKU.THERAPY and AESKU.INSTITUTE - work closely together and cover the interdisciplinary research. Moreover, AESKU has developed and produced from the very beginning the world's largest product range of innovative laboratory tests for the swift and secure diagnosis of autoimmune diseases. Research results can thus be implemented as innovative products remarkably quickly.

AESKU.DIAGNOSTICS: Dedicated to a better diagnosis

AESKU.DIAGNOSTICS is an ISO certified company (DIN EN ISO 9001:2000, DIN EN ISO 13485:2003), which produces and distributes more than 100 CE marked ELISA kits for diagnostics of autoimmune diseases: the *AESKULISA*® product line. The deve-

lopment and production has a strong focus on manufacturing antigens, mainly recombinant, in the company's own laboratories. Unique features of the *AESKULISA*® product line are identical test procedures and protocols enabling easy automation and a high sample turnover, especially in larger laboratories.
In order to maintain the high quality of the *AESKULISA*® products AESKU.DIAGNOSTICS participates regularly in national and international quality control assessment schemes (INSTAND e.V., Germany. UK NEQAS and RCPA, Australia).
Moreover, a major goal of AESKU.DIAGNOSTICS is to develop specific testing systems for those diseases which lack specific diagnosis systems by now. Additionally, the company concentrates on creating new possibilities for diagnosis which are safer, easier, faster and, most of all, more efficient than the ones currently in use.

Two recognized innovations should be mentioned as an example. For the development of a new type of diagnostic for the Sjoegren`s syndrome, the alpha-fodrin-ELISA, Dr. Torsten Matthias, founder of AESKU received the Innovation Award 2001. The alpha Fodrin ELISA is patented, it is the first test system for Sjoegren`s syndrome which follows the therapy of the disease and which is highly specific. It replaces the need for a painful taking of lip biopsy which was so far the only procedure for a reliable diagnosis of this disease.
A new Prothrombin-ELISA for the prenatal diagnostics of early foetal loss can give a predictive indication whether a young woman with APS actually has to reckon with the possibility of a miscarriage.

Moreover, together with the University of Munich AESKU worked successfully on the clinical significance of anti-dsDNA antibody isotypes for the differentiation of systemic lupus erythematosus (SLE). It was shown that anti-dsDNA autoantibodies of subclass IgM in patient's sera seem to be predictive for the development of lupus nephritis, a severe complication of SLE. Calculation of IgG/IgM ratio revealed to be a prognostic marker for lupus nephritis and therefore can replace kidney biopsy for diagnosis (Foerger F, Matthias T, Oppermann M, et al. Lupus (2004) 13: 36-44).

AESKU.DIAGNOSTICS: Focused on alternative therapies

AESKU.THERAPY concentrates on the research and development of new, alternative therapies, which will enable a more specific treatment of individual diseases with less adverse effects than existing methods. Hence it takes part in the foundation of a center of excellence for alternative therapies of autoimmune diseases in Germany.
First projects: a new in vivo therapy for lupus nephritis and a therapy center for extracorporeal therapy, in which removal of pathogenic substances is applied.
At this stage AESKU.THERAPY is the first company worldwide which has developed and patented an in vivo therapy for renal damage which frequently accompanies systemic lupus erythematosus (lupus nephritis).

AESKU.INSTITUTE: Committed to interdisciplinary research on autoimmunity

The AESKU.INSTITUTE, founded in 2003, is dedicated to research on pathomechanisms of autoimmune diseases with a strong alliance to the key aspects of activity of AESKU.THERAPY and AESKU.DIAGNOSTICS, namely therapy and diagnosis. Therefore the institute cooperates in different research projects closely with renowned scientific institutions namely with the Universities of Hannover, Munich and Tel Aviv.
The first scientific head of the Institute is Prof. Yehuda Shoenfeld from the University of Tel Aviv, who holds the first chair of autoimmunity worldwide. The chair was created by the AESKU and implemented in March 2003. A top-class advisory board including a Nobel price winner serves as a consulting agency on voluntary basis and also looks after the assessment of projects. This guarantees future orientated research, reliable results and fast economic utilization. Besides research, the institute will hold and host national and international conferences on autoimmunity as well as workshops and seminars.
The AESKU.INSTITUTE is also open to cooperate with other companies active in the field of autoimmune diseases. Located in the technology center "Mikroforum" in Wendelsheim, Germany, it offers an ideal framework for research activities and product development.

At the same time the three AESKU companies team up in order to gain and realize new insights in the field of autoimmune diseases. This guarantees real and efficient interdisciplinary cooperation without bureaucratic hindrance. As each company within the holding can use all available resources, it is able to react directly and quickly to new demands that can result from latest research. The direct and smooth transfer of knowledge enables each separate field to give fresh impetus to the other and serve as an important interface between industry and fundamental research. The interdisciplinary approach enriches the scientific possibilities in Germany with an important and also internationally competitive facility.

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