SOUTHWESTERN MEDICAL SCHOOL

MEDICAL GRAND ROUNDS

THE ROLE OF COLLAGEN AUTOIMMUNITY IN HUMAN DISEASE

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"If by some magic solution one could dissolve all the connective in the body, all that would remain would be a mass of slimy epithelium, quivering muscle, and frustrated nerve cells." (Arcadi)

THE ROLE OF COLLAGEN IMMUNITY IN HUMAN DISEASE

I. INTRODUCTION

One of the major unresolved problems in immunology today is the common occurrence of autoimmune phenomena and their precise role in disease. This issue is particularly puzzling in the case of autoimmune reactions to collagen. Collagenous proteins are widely distributed throughout the body, they can hardly be considered as sequestered antigens, and in addition, they are not particularly strong antigens. There is, however, increasing evidence that cellular and humoral autoimmune responses to different collagen molecules are quite common in human disease. Today, we will attempt to describe some of these autoimmune responses, and their possible role in the induction and modulation of such disparate diseases as relapsing polychondritis, rheumatoid arthritis, and urticarial vasculitis.

II. BIOCHEMISTRY

Collagenous proteins constitute the main macromolecular species of connective tissues. They are probably the most abundant protein in the body, making up to 30 percent of the total protein. It has become apparent in recent years that collagenous proteins are found in many different physical and biochemical forms (1-3), each molecular species tailored to a specific functional need. To be able to mediate the various functional needs, the collagens assume a variety of molecular configurations which, in combination with more conventional protein sequences and polysaccharide chains, result in structural conformations adapted to a particular function. Thus, tendons owe their tensile strength to the collagen fibers arranged in parallel bundles. In cartilage, the collagen fibers appear in the form of a tridimensional meshwork filled with highly hydrated proteoglycan. This arrangement allows for the resilience and elasticity characteristics of articular cartilage.

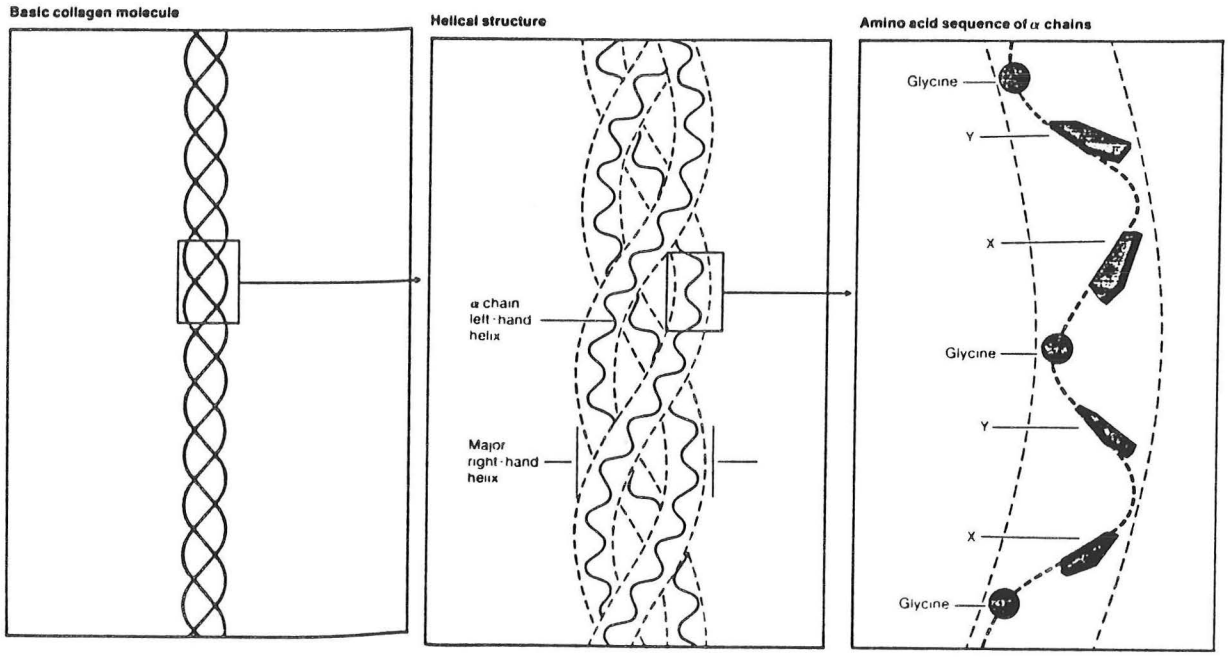
To be considered within the family of collagenous proteins, a protein should have the features listed in table I.

TABLE I
BIOCHEMICAL CHARACTERISTICS OF COLLAGENOUS PROTEINS

High glycine content
Aminoacid sequences gly-x-y
Presence of hydroxyproline and hydroxylysine
Characteristic triple helix
Susceptibility to bacterial collagenase

FIGURE 1

SCHEMATIC REPRESENTATION OF THE BASIC COLLAGEN MOLECULE



More than 23 different collagen chains have been described thus far. These chains assemble in triplets in different combinations to yield at least twelve distinctive collagen species (table II). Type I collagen is the most abundant form, constituting most of the familiar collagen fibers found in the dermis, bone, ligaments, etc. Type II collagen is found almost exclusively in cartilage and vitreous. This type is very resistant to proteolytic attack due to the high degree of cross-linking between molecules. Collagen type III is mostly associated with blood vessels in the form of thin fibrils which presumably contribute to the elastic properties of these tissue structures. Type IV collagen is an important constituent of most basal membranes. These molecules form planar structures assembled in a spider-like fashion probably contributing to the peculiar filtration and support characteristics of the basal membranes of different tissues. Collagen type VIII is present in the anchoring fibrils found beneath most epithelial basal membranes. This molecule has recently been identified as the target antigen in patients with epidermolysis bullosa acquisita (4). We have also included in table II two proteins that even though they do not belong to the family of collagens, part of their molecular

structure contain the characteristic features of the collagen triple helix.

C1q forms part of the trimolecular complex of the first component of complement. This interesting molecule is composed of six globular domains and a tail connected by fibrils exhibiting the characteristic collagen-like structure.

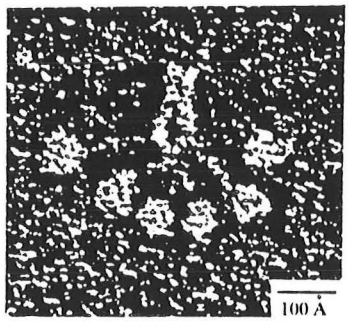
TABLE II

TYPES OF COLLAGENOUS PROTEINS

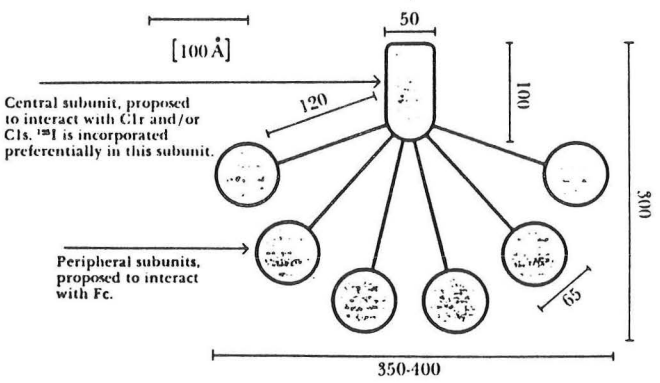
TYPE	DISTRIBUTION	FUNCTION
I	Skin, bone, tendon	Tensile strength
II	Cartilage, vitreous	Resilience
III	Blood vessels, viscera	Elasticity
IV	Basal membranes	Support, filtration
V	Ubiquitous, pericellular	?Adhesiveness
VI	Ubiquitous	Microfibrils
VII	Skin	Anchoring fibrils
VIII	Endothelium	Unknown
IX	Cartilage	?Fiber stabilization
X	Hypertrophic cartilage	?Calcification
XI	Cartilage	?Fiber diameter
XII	Ubiquitous	Unknown
C1q	Blood	Complement component
Acetylcholinesterase		Esterase

FIGURE 2

STRUCTURE OF C1q



At left, lateral view electron micrograph. Note that the central subunit appears to be subdivided longitudinally into two parts. Below, schematic representation derived from electron microscopic and biochemical analysis. The numbers represent average dimensions in angstroms measured on five different preparations. (From Knoebel, H. R., Villiger, W. and Isliker, H.: European Journal of Immunology — submitted for publication.)



III. IMMUNOLOGY

Antibodies to collagen were first reported in rheumatoid arthritis by Steffen et al. over 25 years ago (5). The original observation stimulated a large number of studies, both in humans and animals, which have partially clarified the possible role of cellular and humoral immunity to collagen in human diseases. Some of the earliest workers in the field are now faculty members of this medical school. Jasin and Glynn (6,7) in 1965 demonstrated that it was possible to immunize guinea pigs with synthetic peptides resembling collagen. The lack of crossreactivity with natural collagens observed emphasized the importance of secondary structure of the antigens in determining antibody specificity. Kettman et al.(8) were able to show crossreactivity with natural collagens using a polymer with physicochemical characteristics that were very similar to the natural molecule.

The possible pathogenic role of collagen immunity was greatly clarified by the initial observation of Trentham et al. (9) showing that immunization of rats with purified type II collagen resulted in the development of polyarthritis. The experimental arthritis was associated with high levels of cellular and humoral hypersensitivity to the immunizing antigen. Immunization with types I, III, or denatured collagen II failed to induce the arthritis. The histologic picture of the arthritis resembled that of rheumatoid arthritis including synovial hyperplasia, infiltration of the subsynovium with inflammatory cells, marginal erosions and cartilage fragmentation. Of interest was the observation that a proportion of the animals developed auricular chondritis (10), otospongiosis,vestibular dysfunction and hearing loss (11,12).

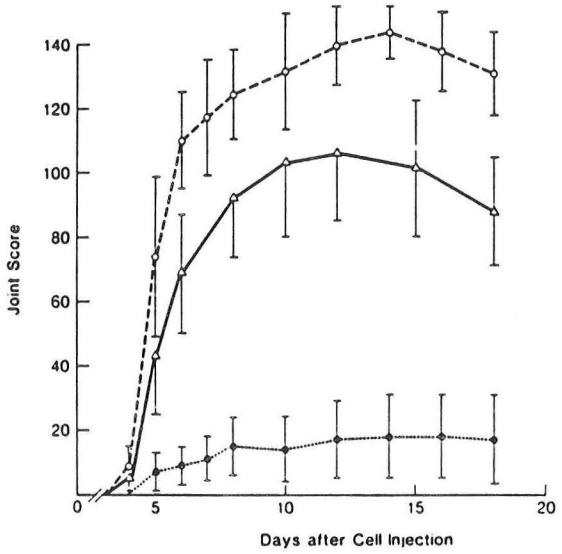
Although the exact mechanism by which arthritis develops is not yet completely understood, there is good evidence that antibodies to collagen appear to play an important role. A transient arthritis has been passively transferred with purified collagen antibodies (13). Immunofluorescence studies have localized collagen antibodies and complement to the superficial areas of articular cartilage (14). Moreover, it has been shown that complement depletion results in amelioration of the active arthritis or suppression of the passively transferred disease (15,16).

Impressive evidence for a modulating role of collagen II antibodies in inflammatory arthritis has been presented by Taurog et al. (17). In these studies, striking synergy was shown between adjuvant arthritis and infusion of collagen II antibodies or active immunization with type II collagen. Figure 3 shows the results of an experiment in which naive rats were

passively infused with lymphocytes derived from animals with adjuvant disease and increasing amounts of collagen II antibodies. Notice the striking increase in arthritis severity resulting from the administration of the antibody.

FIGURE 3

SYNERGY BETWEEN ADJUVANT ARTHRITIS AND COLLAGEN ANTIBODIES



From(17)

III. RHEUMATOID ARTHRITIS

The animal studies described above were prompted by earlier work showing that collagen immunity was not uncommon in patients with rheumatoid arthritis(RA). Serum antibodies were present in a relatively small proportion of patients, and in most studies, wide crossreactivity with denatured collagen type II and other collagen types were reported (18-20). Of greater pathogenic importance however, were the studies demonstrating the presence of collagen antibodies and immune complexes in the majority of synovial fluids obtained from patients with RA (21,22). Moreover, cellular hypersensitivity against collagen has been detected in the circulating blood cells of RA patients (23), and in cells obtained from rheumatoid synovial membranes (24). B lymphocytes with specificity to collagen II are also well represented in rheumatoid synovium. A recent study has

demonstrated local anti-collagen antibody synthesis in synovial tissue explants cultured in vitro (25). To complete the picture, studies from our laboratory have demonstrated the presence of immunoglobulin and complement tightly bound to the superficial areas of rheumatoid articular cartilage (26), in the same anatomical location found in the cartilage of rats with collagen-induced polyarthritis.

TABLE III

COLLAGEN ANTIBODIES IN SERA AND SYNOVIAL FLUIDS

	Number	Collagen Antibodies Percent positive Native	Denatured
SERA			
Rheumatoid arthritis	30	13	30
Control	13	0	0
SYNOVIAL FLUIDS			
Rheumatoid arthritis	17	53	71
Inflammatory	8	12	12
Osteoarthritis	13	0	0

TABLE IV

IMMUNOGLOBULIN AND COMPLEMENT DEPOSITS IN HUMAN JOINT COLLAGENOUS TISSUES

Disease	Number	Percent
Rheumatoid Arthritis	42	83
Trauma	16	0
Osteoarthritis	26	23
Inflammatory	9	22

To investigate the antibody specificity of the immune complexes sequestered in rheumatoid cartilage and osteoarthritis, extracts were obtained from articular cartilage specimens from 16 patients with RA, 11 patients with osteoarthritis, and 6 normal controls. IgM-Rheumatoid factor was found in 13 of 16 rheumatoid cartilage extracts but in none of 11 osteoarthritic and 6 normal control extracts. More than 60% of the rheumatoid cartilage extracts were positive for native and denatured type II collagen antibodies. We also showed that 50% of the osteoarthritic specimens also contained significant titers of collagen antibodies (27).

FIGURE 4

RHEUMATOID FACTOR BOUND TO CARTILAGE

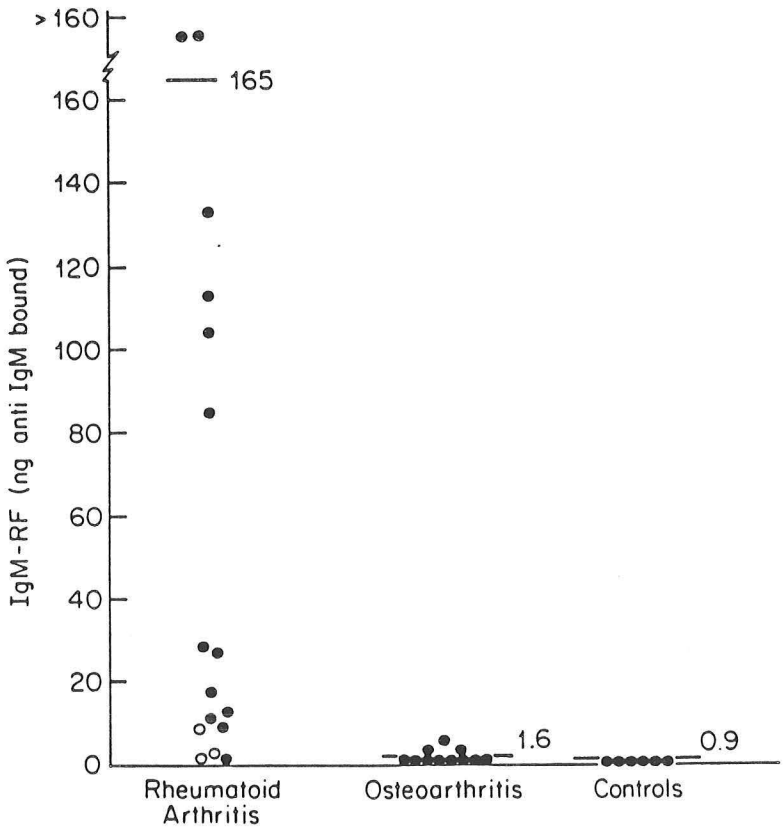


FIGURE 5

COLLAGEN II ANTIBODIES BOUND TO CARTILAGE

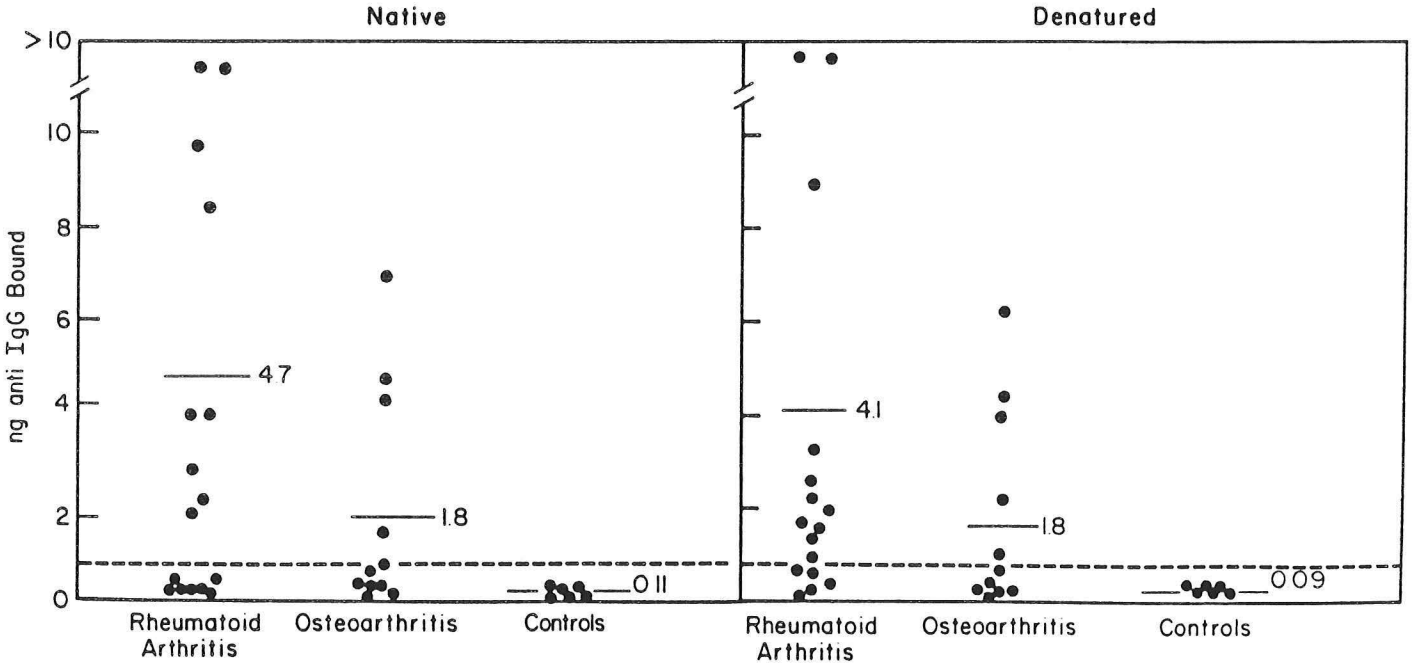


TABLE V

COLLAGEN ANTIBODIES BOUND TO CARTILAGE

Disease	Native	Denatured
Rheumatoid arthritis	9/16	10/16
Osteoarthritis	5/11	6/11
Normal controls	0/6	0/6

Many lines of evidence suggest that autoimmune phenomena play a key pathogenic role in rheumatoid inflammation. The findings discussed suggest that collagen may be at least one of the autoantigens involved in this process. Collagen antibodies are capable of inducing arthritis in animals as previously discussed. Moreover, infusion of human serum containing high titers of collagen antibodies in mice induced a transient polyarthritis (28). Immunization of monkeys with type II collagen results in the development of a chronic polyarthritis very similar to RA (29,30). Finally, Solinger et al. have shown that cellular immunity to collagen is linked to the major histocompatibility complex (31). High responses were associated with HLA-DR4, a haplotype found in over 70% of patients with RA.

In spite of the strong circumstantial evidence implicating collagen autoimmunity in the pathogenesis of RA, it is clear that not all collagen antibodies are pathogenic. Indeed, cellular and humoral immunity to collagen has been detected with variable frequency in many diseases where chronic connective tissue injury and collagen degradation constitute a prominent feature (Table VI). The suggestion that the emergence of collagen antibodies may be secondary to collagen degradation does not exclude the possibility that one or more of the antibody subpopulations may play a prominent role in the facilitation of tissue injury and in the maintenance of chronic and progressive cartilage damage. Recent studies by Terato et al. indicate that this may indeed be the case (32). These authors found that although collagen antibodies from immunized mice contained subpopulations reacting with several antigenic sites in the molecule only one site contained in a small peptide was able to generate antibodies that induced the polyarthritis. These observations lead to the concept of collagen "arthritogenic epitopes" and/or of subpopulations of "arthritogenic" antibodies to type II collagen.

TABLE VI

DISEASES ASSOCIATED WITH COLLAGEN IMMUNITY

Disease	References
Rheumatoid arthritis	(18,19)
Osteoarthritis	(27,33)
Gout	(33)
Ankylosing spondylitis	(33)
Systemic lupus erythematosus	(33,34)
Scleroderma	(35)
Relapsing polychondritis	(36,37)
Urticarial vasculitis?	(34,38)
Goodpasture syndrome	(39)
Epidermolysis bullosa acquisita	(4)
Leprosy	(40)
Thromboangiitis obliterans	(41)

Collagen immunity may well be involved in a primary fashion in the second group of diseases listed in the table above. In the remaining time we will discuss briefly the clinical and immunologic features of the first three.

V. RELAPSING POLYCHONDRITIS

Relapsing polychondritis is a relatively uncommon disease characterized by widespread but spotty inflammatory involvement of cartilaginous tissues and sensory organs such as the eye, the middle and inner ears, and the vestibular apparatus.

This condition affects equally both sexes. It is more common in third to fifth decades of life, but several patients have been reported in children and in the elderly. The clinical course is highly variable, with periods of exacerbation and remissions, and occasionally the disease may be self-limited. The clinical features of the disease are listed in table VII. Onset is usually acute during the initial and subsequent attacks, often preceded by a febrile episode. The most common initial manifestation usually includes involvement of the cartilaginous portion of the ear pavilion which become swollen purplish-red and

very tender. The soft earlobes are always spared. The external auditory canal may swell and become partially or completely obstructed; hearing may be significantly impaired. Involvement of the inner ear may result in serous otitis, obstruction of the eustachian tube and further hearing impairment. Labyrinthitis may produce Meniere's type vertigo.

TABLE VII

CLINICAL FEATURES OF RELAPSING POLYCHONDRITIS

Clinical Manifestation	Presenting %	Cumulative %
Auricular chondritis	39	85
Hearing loss	9	26
Vertigo	4	13
Nasal chondritis	24	54
Saddle nose	18	29
Laryngotracheal chondritis	41	71
Ocular symptoms	19	51
Fever	20	39
Arthritis	36	52
Aortic regurgitation	0	4
Mitral regurgitation	0	2
Aneurism	0	4
Increased ESR	74	82
Anemia	50	55

Modified from Michet et al.(42)

The respiratory tract is also commonly involved. The nasal cartilage becomes inflamed during the first or subsequent attacks,often resulting in the characteristic nasal bridge collapse or "saddle-nose". One of the most serious complications of this disease is that of laryngotracheal involvement. Symptoms may include hoarseness, mild cough, and local tenderness. In more severe instances, inflammation of glottis and larynx may necessitate emergency tracheostomy. Not infrequently, the trachea and bronchial tree may become involved, resulting in severe dyspnea, asphyxia and/or secondary infection. In these circumstances, tracheostomy may not be effective, owing to the development of widespread tracheobronchomalacia and multiple strictures or collapse even down to the smallest bronchi. Occasionally, further respiratory impairment may be caused by inflammatory involvement of the costo-sternal cartilages.

The arthropathy of relapsing polychondritis is characterized by simple arthralgia or mild asymmetric joint swelling, affecting large and small peripheral joints as well as parasternal and sacroiliac articulations (43-45). The vertebral column and feet are usually spared. It may occasionally mimic rheumatoid arthritis, with widespread, symmetrical, erosive disease (46).

Aortic insufficiency is another life-threatening complication occurring in about 10 to 15% of cases. The lesion is due to progressive dilatation of the aortic ring and ascending aorta, rather than to inflammation of the valve leaflets (47,48). This pattern of involvement helps in the differential diagnosis from other causes of aortic regurgitation such as rheumatic fever, rheumatoid arthritis, ankylosing spondylitis, or Reiter's syndrome (49).

Eye involvement may be seen in 50% of the cases. The lesions include episcleritis, conjunctivitis and less frequently, iritis. These fluctuate according to the activity of the disease, rarely leaving serious sequelae. However, occasional proptosis, cataracts, or even blindness have been reported (50).

Routine laboratory tests are usually nonspecific. During the active period, there may be increased erythrosedimentation rate, moderate leukocytosis and anemia. Occasional positive rheumatoid factor, antinuclear antibody, and antithyroid antibodies tests may be positive. This is due to the not uncommon association of relapsing polychondritis with other autoimmune diseases (table VIII).

TABLE VIII

DISEASES ASSOCIATED WITH RELAPSING POLYCHONDRITIS

Disease	Patients*
Systemic vasculitis	11
Rheumatoid arthritis	8
Systemic lupus erythematosus	6
Overlap syndrome	2
Ankylosing spondylitis	3
Reiter's syndrome	1
Hashimoto's thyroiditis	4
Hematologic syndromes	6

*From a total of 112 patients. Modified from (42)

Although most patients with this disease are diagnosed early because of their characteristic presentation and pattern of involvement, a few other conditions should be considered in the differential diagnosis, particularly because of the frequent overlap with other autoimmune processes (table IX).

TABLE IX

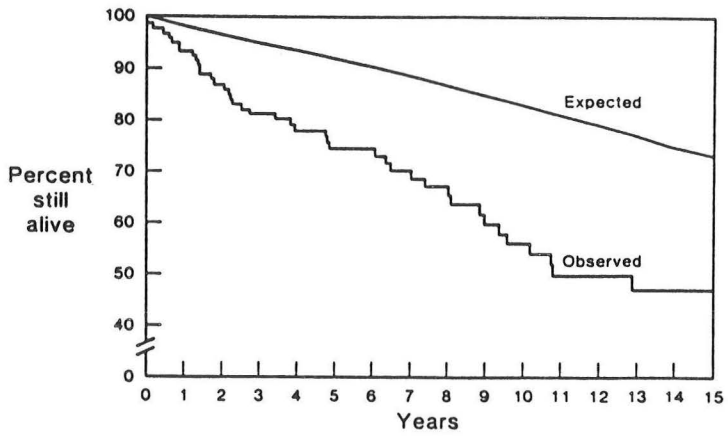
DIFFERENTIAL DIAGNOSIS OF RELAPSING POLYCHONDRITIS

Bacterial perichondritis
Trauma
Frostbite
Rheumatoid arthritis
Wegener's granulomatosis
Lethal midline granuloma
Cogan's syndrome
Syphilis

In spite of its smoldering, intermittent course, relapsing polychondritis is not a benign disease. In a study from the Mayo Clinic involving 112 patients, 5 and 10 year survival rates after diagnosis were 74 and 55% respectively (42). Surprisingly, the most common causes of death were not those attributable to airway involvement. Infection, related to corticosteroid therapy, vasculitis, and malignancy were the most frequent causes.

FIGURE 6

SURVIVAL RATE IN RELAPSING POLYCHONDRITIS



From Michet et al. (42)

TABLE X

CAUSES OF DEATH IN RELAPSING POLYCHONDRITIS

Cause of death	Patients*
Infection	12
Vasculitis	7
Malignancy	5
Aortic aneurism	3
Celiac artery thrombosis	1
Gangrene	1
Pulmonary embolism	2
Cardiac surgery	1
Lupus myocarditis	1
Acute respiratory failure	2
Renal failure	2
COPD	2
Aplastic anemia	1
Gastric ulcer	1

*From 112 patients. Modified from (42)

The histopathologic features of relapsing polychondritis are specific for this disease (48,51). The perichondrium shows focal or diffuse infiltration by mononuclear inflammatory cells, with occasional polymorphonuclear leukocytes and plasma cells. The inflammatory infiltrate is usually associated with adjacent cartilage changes which include loss of metachromasia and dissolution of this tissue from the periphery inward. These changes are similar to the histopathologic picture found in rheumatoid arthritis in areas of articular cartilage covered by pannus.

The exact pathogenic mechanisms involved in the generation of cartilage damage in this disease are not well understood. However, there is compelling evidence that autoimmune reactions to cartilage components, particularly type II collagen may play a prominent role. We have already seen that animals immunized with collagen II develop auricular lesions similar to the human counterpart. There are several reports of positive cellular immune reactions against cartilage components in such patients (52,53). Moreover, granular deposits of immunoglobulin and complement have been consistently detected in affected cartilage (54,55) with a staining pattern similar to that obtained with indirect staining using collagen II antisera. Finally, several

studies have shown the presence of serum antibodies to collagen in the majority of patients with active, untreated disease (36,37,56,57). It may be argued that the emergence of collagen antibodies is secondary to cartilage degradation. However, longitudinal studies suggest that the antibodies make their appearance early in the disease, and their titers follow disease activity closely, so that soon after initiation of treatment with corticosteroids they disappear from circulation.

Treatment of relapsing polychondritis consists primarily of corticosteroid administration. Disease activity is usually controlled with prednisone doses ranging from 20 to 60 mg/day. As the attack subsides, a daily dose of 10 to 15 mg/day may be sufficient to control inflammation. Therapeutic responses in this disease may be delayed, therefore, prednisone administration should not be discontinued prematurely. There are only isolated reports of therapeutic responses in cases of corticosteroid-refractory disease with dapsone (58) or immunosuppressive agents (59).

VI. URTICARIAL VASCULITIS

In 1973, McDuffie et al. (60) described four patients with a syndrome characterized by urticarial rash, joint pain, necrotizing vasculitis, and hypocomplementemia. In addition, two of these patients had evidence of renal involvement. In the past 15 years,numerous reports have described the association of urticarial lesions with vasculitis (61,62). In some cases, clinical and serological investigations have disclosed underlying conditions such as mixed cryoglobulinemia, serum sickness, viral hepatitis, infectious mononucleosis, etc. There are some patients, however, with chronic, recurring urticarial rash and vasculitis which appear to have a distinct syndrome not associated with the conditions mentioned above.

The clinical features of hypocomplementemic urticarial vasculitis are listed in table XI.

TABLE XI

CLINICAL FEATURES OF HYPOCOMPLEMENTEMIC URTICARIAL VASCULITIS

Skin Rash
Urticaria
Angioedema
Vasculitis
Arthralgia-Arthritis
Abdominal pain
(Renal disease)
(COPD)

These patients are usually female. Although they present with a syndrome resembling systemic lupus erythematosus, they do not fulfill the clinical criteria for this disease. Antinuclear factors may be positive in low titers, but they usually have negative tests for antibody to native DNA.

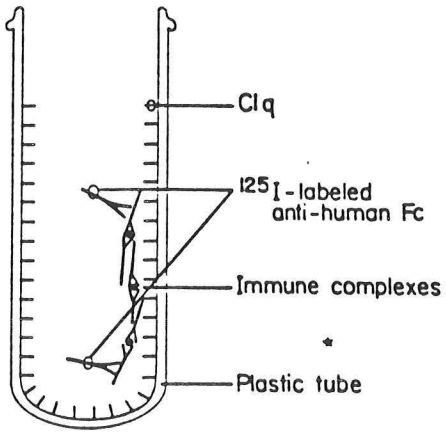
The skin rash has an urticarial appearance, and it is associated with pruritus or a burning sensation. The lesions are transient, lasting 24 to 72 hours, and they leave no sequelae except for occasional hyperpigmentation. Hemorrhagic skin lesions and angioedema may be seen in some patients. Biopsy of the skin lesions show a picture compatible with leukocytoclastic vasculitis. Arthralgia, joint swelling, or both are present during the active periods in the majority of patients. As a rule, these patients do not develop deforming arthritis, although occasional cases have been reported with Jaccoud's-like changes in the small joints of the hands (61,63). About 25% of the patients develop abdominal pain, sometimes associated with nausea, emesis, and diarrhea. Of interest is the high prevalence of renal disease in these patients, which in some series may reach as high as 60% (61). Kidney function is only moderately impaired in most cases. Kidney biopsies have not revealed a consistent pattern of involvement; histology has shown cases with focal necrotizing vasculitis, focal and diffuse glomerulonephritis, interstitial nephritis, and mesangial sclerosis. At least one study emphasizes the frequent association of urticarial vasculitis with significant chronic obstructive pulmonary disease (COPD) in patients who smoke (63). Eight of ten smokers out of a group of 16 patients had evidence of COPD, 1 of whom died of this complication. In three patients, severe COPD developed at a young age after relatively low pack-year cigarette smoking histories. These authors concluded that

"the lung disease resulted from the interaction of two major factors: smoking and an immunologically mediated process that has not been identified".

One of the constant laboratory features of this disease is the finding of low total hemolytic and individual complement component levels (60-63). In addition, tests for soluble immune complexes are usually positive. One of the most common tests for the detection of immune complexes takes advantage of the ability of C1q to interact with immunoglobulin aggregates (figure 7). Several investigators have reported the presence of immunoglobulin material precipitating with C1q in over 50% of the sera from patients with urticarial vasculitis (60,63-65). Early studies indicated that the material reactive with C1q was an unusual monomeric IgG which bound this complement component via the Fc portion of the molecule, and not with the antibody combining side, such as a conventional antibody would (66). However, recent investigations have failed to confirm these results. Moreover, it has been shown that close to 50% of patients with systemic lupus erythematosus (34,67) and the patients with urticarial vasculitis (68) have IgG antibodies to C1q that behave in a conventional fashion. Presumably, this antibody is responsible for the previously reported C1q precipitins in these diseases. The reason why urticarial vasculitis has been included in this discussion is that the anti-C1q antibodies react with the collagenous portions of C1q, thus providing the rational for a dual role for this antibody in the generation of immune complexes and perhaps as a pathogenic factor in the induction of arthritis (69).

FIGURE 7

SOLID-PHASE C1Q ASSAY



From RC Williams, Jr (70)

VII. GOODPASTURE SYNDROME

The clinical features of Goodpasture syndrome have been described in detail in a recent Medical Grand Rounds by Dr. J.H. Helderman (71). We will only deal here with the recent identification of the Goodpasture antigen to the globular domain of collagen type IV.

TABLE XII

CLINICAL FEATURES OF GOODPASTURE SYNDROME

Glomerulonephritis
Hemorrhagic pneumonitis
Anti-basal membrane antibodies

Goodpasture syndrome is the entity in which the "Koch postulates of autoimmunity" have been established most firmly. The following points make a strong case for a direct pathogenic role of the anti-basal membrane antibody: 1) the presence of linear immunoglobulin staining of glomerular and alveolar basal membranes (72); 2) circulating anti-glomerular basal membrane antibodies in 90% of patients (73); 3) positive correlation between clinical improvement and antibody titer (74,75); 4) the disease can be reproduced in animals by immunization with basal membranes (76) or with passive transfer of serum containing basal membrane antibodies (77); 5) passive transfer of human antibodies to subhuman primates reproduces the disease (78).

TABLE XIII

ROLE OF ANTI-GBM ANTIBODY IN GOODPASTURE SYNDROME

Linear staining of basal membranes
Anti-GBM serum antibody
Antibody titers correlate with disease activity
Reproduction in animals by active immunization
Passive transfer with animal or human serum

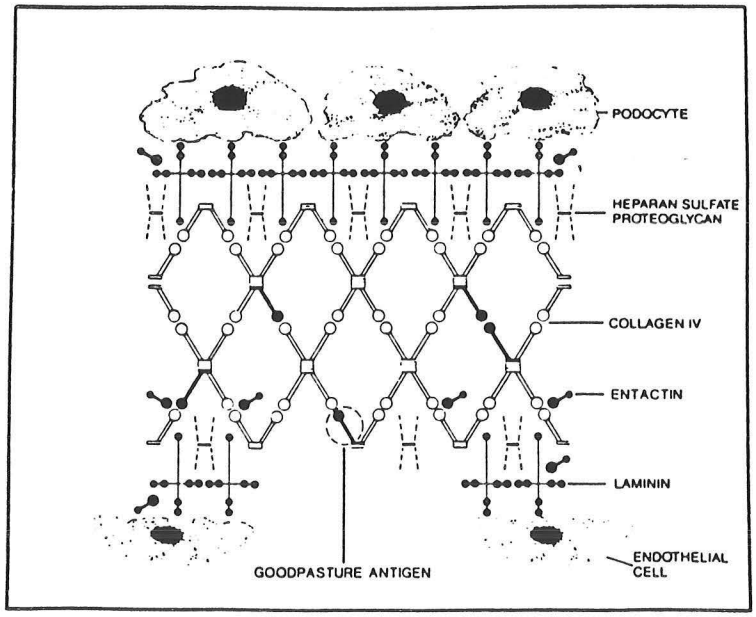
It should be pointed out that the presence of anti-GBM antibodies is not specific for Goodpasture syndrome. Antibodies to multiple basal membrane components have been identified in patients with systemic lupus erythematosus, poststreptoccocal glomerulonephritis (79), IgA nephropathy (80), and Chagas disease (81).

The epithelial basal membranes are complex structures composed of several different macromolecules: type IV collagen, laminin, proteoglycan, and entactin. A schematic view of its molecular organization is seen in figure 8. In the diseases listed above, the antibody responses are directed against laminin, proteoglycan, and the 7S domain of collagen IV. It has been recently established that the main antigenic site in Goodpasture syndrome is the globular NC1 domain of the molecule (39,82,83).

In some sense, these findings parallel the concept of "arthritogenic epitopes" discussed in the section dealing with autoimmunity to type II collagen. In the case of Goodpasture syndrome one particular antigenic determinant of the macromolecule appears to have a key pathogenic role.

FIGURE 8

MOLECULAR ORGANIZATION OF EPITHELIAL BASAL MEMBRANES



From Hudson et al. (84)

VIII. OVERVIEW

The evolution of our knowledge regarding the pathogenic role of collagen immunity in human disease reflect the macrocosm of autoimmunity in general. After the demolition of the dogma of "horror autotoxicus" when it was realized that autoimmune phenomena were not only commonplace, but perhaps part and parcel of normal homeostatic mechanisms, much of work done in this area was devoted to establish a direct pathogenic role to this or that particular autoimmune reaction. Along the way, we have learnt that not all autoimmune reactions are created equal. The task of the clinical and experimental immunologist is to extricate from the multiple autoantigenic specificities recognized by the immune system in disease, the few that may be directly responsible for the mediation of tissue injury. In this way, it may be possible to develop the "magic bullets", that is, specific immunosuppressive agents directed against one particular pathogenic antigenic determinant.

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