Cryoglobulinemia – a Cool Disease
Mechanism

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Learning Objectives

• 1. Distinguish between different kinds of cryoglobulins

• 2. Identify mechanisms whereby cryoglobulins cause disease and tissue injury

• 3. Assess the clinical approach to patients with cryoglobulinemia
Disclosures

• None
Case Presentation I

- P.O., 35 year old woman
- Two years of ischemic bowel events (gangrenous cholecystitis, bowel perforations)
- Chronic renal failure
- Multiple bowel surgeries and biopsies
- Limb ischemia with gangrene
Relevant Testing

- Extremely high ESR (>100 mm/hr)
- Cryoglobulins reported twice; and specimens rejected another two times
- IgG1 lambda paraprotein reported twice, considered “MGUS”
- Elevated globulins (total protein 7.5, albumin 2.3)
- Hepatitis C serology negative x 6!
- Rheumatoid Factor negative x 4!
Case Presentation II

• 68 year old man with altered MS, syncope while waiting to be seen in ER
• VS normal
• Great difficulty in drawing his blood despite excellent large antecubital veins
• Large cryo with thermal amplitude 36 deg
• RF titer >1:1,000,000
• Cryo: Monoclonal IgM kappa plus polyclonal IgG
What is a Globulin?
Not this.....
Not these either

• Cold agglutinins
• Globin
Globulins

• From “globular” – spherical, like a globe
• Poorly soluble in aqueous solutions
• Hydrophobic residues face inward
• Tertiary structure highly dependent on tyrosine content
• Some form covalent bridges between subunits
Globulin Structure (IgG2)
Serum Protein Electrophoresis
Gamma Globulins

• The most abundant serum globulins
• These are antibodies – IgG, IgM, IgA mostly
• Each individual molecule is potentially unique
• For IgG, two identical heavy chains, and two identical light chains, connected by disulfide bridges, M.W. ~150,000 daltons
• IgM has 5 IgG-like subunits, M.W. ~800,000
• 60% of light chains kappa, 40% lambda
The variable V-J region of the light chain and the variable V-D-J region of the heavy chain correspond respectively to a variable domain. The constant region CL of the light chain corresponds to one constant domain. The constant region of the heavy chain comprises 4 constant domains CH1 to CH4 (mu and epsilon chain) or 3 constant domains, the CH1 and CH2 domains being separated by the hinge (h) (delta, gamma, and alpha chain).
Immunoglobulins

• Immunoglobulin molecules are made by B lymphocytes undergoing clonal expansion when stimulated
• Each individual immunoglobulin molecule has unique physicochemical properties due to its unique sequence
• For instance, tertiary conformation and solubility differ
• The vast numbers of unique immunoglobulin proteins ordinarily mask the potential for individual Igs to cause difficulties
“Bad actor” Immunoglobulins

• But B lymphocytes occasionally undergo malignant transformation, with production of very large amounts of individual monoclonal immunoglobulins

• The physical properties of these individual antibody molecules may cause clinical problems – namely, precipitation in blood vessels (and vasculitis); or (rarely) hyperviscosity syndrome
Cryoglobulins

• Proteins which precipitate spontaneously in vitro from serum cooled below 37 degrees
• Usually tested at 4 degrees
• Redissolve upon warming of serum
Aaron B. Lerner, M.D., Ph.D 1920-1987
A HOMOMOLECULAR SERUM PROTEIN WITH ANOMALOUS
SOLUBILITIES

By AARON BUNSEN LERNER AND GOODWIN R. GREENBERG

(From the Department of Physiology and Physiological Chemistry,
University of Minnesota, Minneapolis)

(Received for publication, August 8, 1945)

A flocculent material, shown to be a protein, spontaneously precipitated
from the serum of a patient, J. P., at the University of Minnesota Hospitals
during the course of routine blood studies in vitro.

The conditions under which a protein spontaneously precipitates from
serum are uncommon. Records of such conditions are even less frequently
met with; only some half dozen reports of such cases have been made (1–6).
Three of these reports were based upon cases in which the serums were
obtained from patients having multiple myeloma. (The precipitated pro-
teins were not of the Bence-Jones type.) The other three reports described
the flocculation of protein from serum of humans suffering either from
chronic rheumatic infectious arthritis and spondylitis, or from liver disease,
and from dogs infected with kala-azar.

Because spontaneous precipitation of protein from serum is a rare
occurrence, it was considered worth while to undertake the isolation and
determination of the physical and chemical characteristics of the protein
that precipitated from the serum of the patient J. P.

Since the clinical aspects of this exceptional case will be reported else-
where,1 suffice it to say that the patient was a 58 year-old white male with
acropurpura of 9 years duration, chronic glomerulonephritis, and congestive
heart failure.

Isolation

A 320 ml. sample of the patient’s blood was allowed to clot at 37° and
220 ml. of serum were decanted. Upon cooling the serum to 2°, a flocculent
precipitate formed. This was centrifuged at 0° and the supernatant fluid
poured off. To the precipitate were added 120 ml. of 0.9 per cent sodium
chloride. By warming to 37°, all but a minor portion (Fraction A) of the
substance dissolved. The solution was centrifuged at 37° with the resulting
removal of the few red cells from the fraction precipitated in the cold. This
process of purification was repeated three times. In each case a small
amount of material insoluble at 37° was formed (Fractions B, C, and D).2

1 To be published by Dr. C. J. Watson.
2 It should be noted that an increased volume of saline did not affect the solution of the insoluble portions.
the protein, the values at these points were determined by suspending known weights of protein in the sodium chloride solution and slowly warming the mixture in a water bath until complete solution occurred. Solubilities at the lower temperatures were determined after 24 hour equilibration, centrifugation at the same temperature, and analysis of the supernatant solutions.

As is shown in Fig. 3, a 0.93 per cent solution of the protein in distilled water showed no precipitate at 2°. However, in 0.085 M (0.5 per cent) sodium chloride at that temperature, the protein was almost completely insoluble. As the temperature was increased, a marked increase in solubility occurred.

Salted-Out Constants—The relationship between the solubility and ionic strength can be represented by the equation (8 p. 604), log \( S = B - K_s \mu \), where \( S \) = the solubility of the protein in gm. per liter, \( \mu \) = ionic strength, \( K_s \) = the slope of the curve and for a given protein and salt is independent of temperature and pH, \( B \) = the logarithm of the solubility of the protein in solutions of 0 ionic strength and is dependent on temperature and pH. For the protein studied here, \( K_s \) for ammonium sulfate solutions = 2.0 and for dilute sodium chloride solutions is somewhere between 25 and 35. The value of approximately 30 for \( K_s \) in dilute sodium chloride solutions is much greater than any previously calculated salting-out con-

![Fig. 3. Relation between solubility and temperature in 0.5 per cent NaCl solution](image-url)
Some clinical features of cryoglobulinemia

Figure 4 Systemic cryoglobulinaemic vasculitis (A) Membranoproliferative glomerulonephritis associated with HCV-related type II cryoglobulinaemia. A glomerulus shows proliferative changes and subendothelial deposits within capillary loops (pink). These le...

Manuel Ramos-Casals, John H Stone, Maria C Cid, Xavier Bosch

The cryoglobulinaemias


http://dx.doi.org/10.1016/S0140-6736(11)60242-0
Why Do Cryoglobulins Cause Vasculitis?

• The immunoglobulins undergo at least partial change of state in vivo, usually in cool (acral) areas

• The deposition of immunoglobulin in vascular tissue favors the activation of complement and of Fc-receptor bearing inflammatory cells (neutrophils, mononuclear phagocytes, and others)

• But we really don’t understand this fully...
Hypothetical pathogenetic mechanisms of vascular damage in mixed cryoglobulinaemia


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A 51-year-old woman with chronic hepatitis C virus (HCV) infection and type II cryoglobulinemia reported fatigue, pain in her ankles, and recurrent crops of superficial vasculitic lesions on her legs.
Fig. 3  Vasculitic manifestations are the most frequent percentage-wise in type II mixed cryoglobulinemia and inversely related with the cryocrit.
Cryoglobulin Testing – An area in need of improvement

• The test is humble (store serum at 4 deg C for 5-7 days, observe for precipitate)
• Rigid restrictions on collection conditions lead to very high rate of sample rejection
• Improperly collected samples may lead to false negatives – but not to false positives!
Work up of Cryoglobulins

• Wash cryoglobulin in cold PBS
• Redissolve cryo in warm PBS
• Perform immunodiffusion or electrophoresis, followed by immunofixation
Figure 11: Immunofixation on the cryoprecipitate. Monoclonal IgG kappa
IgM Cryoprecipitation and Anti-Immunoglobulin Activity in Dysgammaglobulinemia Type I

John B. Winfield, Philip L. Cohen, Linda Bradley, Fred D. Finkelman, Robert A. Eisenberg, Richard Wistar, Jr., and John K. Whisnant

Departments of Medicine and Pediatrics, University of North Carolina, Chapel Hill, North Carolina 27514, and Department of Medicine, Uniformed Services University of Health Sciences and Naval Research Institute, Bethesda, Maryland 20014
Biologic and Clinical Significance of Cryoglobulins

A Report of 86 Cases

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FRANCOISE DANON, M.D.
MICHEL KLEIN, M.D.
MAXIME SELIGMANN, M.D.
Paris, France

Eighty-six patients with cryoglobulinemia repeatedly underwent complete immunoochemical and clinical evaluation during the course of their disease. Immunoochemical analysis of the purified cryoglobulins allowed us to classify them into three groups. Type I cryoglobulins are made of isolated monoclonal immunoglobulin: IgM (11 cases), IgG (7 cases), IgA (2 cases) or Bence Jones protein (1 case). Type II cryoglobulins are mixed cryoglobulins with a monoclonal component possessing antibody activity towards polyclonal IgG. These cryoglobulins were mainly IgM-IgG (19 cases), sometimes IgG-IgG (2 cases) or IgA-IgG (1 case). Type III cryoglobulins (43 cases) are mixed polyclonal cryoglobulins, i.e., composed of one or more classes of polyclonal immunoglobulins and sometimes nonimmunoglobulin molecules such as beta,2C or lipoprotein. Most of these type III cryoglobulins are also immunoglobulin-anti-immunoglobulin immune complexes. This classification enabled us to establish correlations between the biologic findings and the clinical features as well as the underlying diseases.

Cutaneous and vasomotor symptoms were most severe in patients with type I and II cryoglobulins. The usual clinical picture in patients with type II or III cryoglobulins consisted of chronic vascular purpura and mild Raynaud's phenomenon. Renal and neurologic involvement were more frequent in patients with type II and III cryoglobulins, and were of major prognostic significance. In our series, immunoproliferative and autoimmune disorders were the most frequent diseases associated with cryoglobulinemia. The former were associated with type I or II cryoglobulins and the latter mainly with type III cryoglobulins. Of note is that idiopathic cryoglobulinemia accounted for nearly 30 per cent of the cases despite repeated careful clinical evaluation and a mean follow up of 9 years.

In 10 per cent of the cases, acute and severe symptoms necessitated emergency treatment with plasmapheresis and chemotherapy which allowed a satisfactory initial remission in all but one patient. Conversely, no treatment was definitively effective in patients with chronic symptoms such as vascular purpura.
Fig. 1 Composition of distinct types of cryoglobulin. Type I cryoglobulin consists of monoclonal immunoglobulins (typically IgM; left). Type II cryoglobulins consist of complexes of monoclonal immunoglobulins with rheumatoid factor (RF) activity (typically...
<table>
<thead>
<tr>
<th>Cyroglobulin Type</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td>31 (34)</td>
</tr>
<tr>
<td>IgG κ monoclonal</td>
<td>15</td>
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<tr>
<td>IgM κ monoclonal</td>
<td>15</td>
</tr>
<tr>
<td>IgG λ monoclonal</td>
<td>1</td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td>50 (56)</td>
</tr>
<tr>
<td>IgM κ monoclonal + IgG polyclonal</td>
<td>47</td>
</tr>
<tr>
<td>IgM λ monoclonal + IgG polyclonal</td>
<td>1</td>
</tr>
<tr>
<td>IgG κ monoclonal + IgG polyclonal</td>
<td>1</td>
</tr>
<tr>
<td>IgA κ monoclonal + IgG polyclonal</td>
<td>1</td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Other types</strong></td>
<td>7 (8)</td>
</tr>
<tr>
<td>IgM κ monoclonal + IgG κ monoclonal</td>
<td>4</td>
</tr>
<tr>
<td>IgM κ monoclonal + IgG λ monoclonal</td>
<td>1</td>
</tr>
<tr>
<td>IgM λ monoclonal + IgG κ monoclonal</td>
<td>1</td>
</tr>
<tr>
<td>IgM κ monoclonal + IgG λ monoclonal + IgG polyclonal</td>
<td>1</td>
</tr>
</tbody>
</table>

Trejo et. al. Medicine 2001
Rheumatoid Factor
Rheumatoid Factor

• Large part of IgM repertoire is RF
• Scavenger autoab with higher avidity for complexed IgG (antibodies bound to antigen)
• High levels in chronic inflammatory states (e.g. RA, SBE, osteomyelitis)
• RF high levels in some B cell cancers
Idiotypes and Rheumatoid Factor

• 60% of cryo-associated monoclonal RFs are Wa idiotype (now known to be VH I-69/Kv325)
• 30% are Po (VHIII/Kv325)
• This is remarkable! There are over 100 VH genes and nearly 100 VK genes!
• Somatic mutations in VH and VK
• These must be important Ig genes!
Edward C. Franklin, M.D. 1929-1982
BACKGROUND. Type II cryoglobulinemia is a vasculitis characterized by cryoglobulins consisting of complexes of polyclonal IgG and monoclonal IgM rheumatoid factors. The cause of these immune complexes is unknown, though both the hepatitis B (HBV) and C (HCV) viruses have been suspected.

METHODS. We studied 19 patients with Type II cryoglobulinemia for markers of HCV and HBV infection. Quantitative HCV antibody and RNA studies were performed on whole serum, cryoprecipitates, and supernatants.

RESULTS. Eight patients (42 percent) had HCV antibodies, and 16 (84 percent) had HCV RNA. Of the 19 patients, 5 (26 percent) had HBV markers, but only 1 had evidence of active HBV infection. Control serum samples from nine patients with Type I cryoglobulinemia were negative for HCV antibody and HCV RNA. There was a close, although not exclusive, association of one type of rheumatoid factor (WA) with HCV RNA. HCV antibody and HCV RNA were concentrated approximately 10-fold and 1000-fold, respectively, in the Type II cryoglobulins examined.

CONCLUSIONS. Type II cryoglobulinemia is strongly associated with concomitant HCV infection and a high rate of false negative serologic tests. HCV virions and HCV antigen-antibody complexes are concentrated in the cryoprecipitates, most commonly in association with the WA type of rheumatoid factor, suggesting a role for HCV in the pathogenesis of mixed cryoglobulinemia.

Department of Medicine, Massachusetts General Hospital, Boston.
<table>
<thead>
<tr>
<th>Disease Classification</th>
<th>No. of Patients (%) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>331 (75)</td>
</tr>
<tr>
<td>HCV</td>
<td>321/443 (73)</td>
</tr>
<tr>
<td>HBV</td>
<td>15/443 (3)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>29/153 (19)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>94 (24)</td>
</tr>
<tr>
<td>Primary Sjögren syndrome</td>
<td>40 (9)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>30 (7)</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Primary antiphospholipid syndrome</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Horton arteritis</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Dermatomyositis-polymyositis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Henoch-Schönlein disease</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hematologic disease</td>
<td>33 (7)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Myelodyplasia</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Waldenström disease</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Castelman disease</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Thrombocytopenic thrombotic purpura</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Other diseases</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Essential cryoglobulinemia</td>
<td>49 (11)</td>
</tr>
</tbody>
</table>

Abbreviations: See previous tables.

*The numbers of each category may add up to more than 443 due to overlapping of different etiologies.

†Twelve of 15 HBV patients showed HCV coinfection.

‡Twenty-two of 29 HIV patients showed HCV coinfection.
# Immunological Manifestations of Cryoglobulinemia

*(Spanish Series)*

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Patients Tested</th>
<th>No. (%) Positive Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CH50</td>
<td>283</td>
<td>201 (71)</td>
</tr>
<tr>
<td>RF</td>
<td>232</td>
<td>139 (60)</td>
</tr>
<tr>
<td>Low C4</td>
<td>283</td>
<td>142 (50)</td>
</tr>
<tr>
<td>ANA</td>
<td>349</td>
<td>143 (41)</td>
</tr>
<tr>
<td>Low C3</td>
<td>283</td>
<td>72 (25)</td>
</tr>
<tr>
<td>ASMA</td>
<td>346</td>
<td>68 (20)</td>
</tr>
<tr>
<td>APCA</td>
<td>347</td>
<td>35 (10)</td>
</tr>
<tr>
<td>Anti-thyroglobulin</td>
<td>175</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Anti-microsomal</td>
<td>176</td>
<td>12 (7)</td>
</tr>
<tr>
<td>RNP</td>
<td>160</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Ro/SS-A</td>
<td>187</td>
<td>26 (6)</td>
</tr>
<tr>
<td>ANCA-MPO</td>
<td>91</td>
<td>5 (6)</td>
</tr>
<tr>
<td>La/SS-B</td>
<td>187</td>
<td>9 (5)</td>
</tr>
<tr>
<td>AMA</td>
<td>347</td>
<td>16 (5)</td>
</tr>
<tr>
<td>LKM-1</td>
<td>342</td>
<td>14 (4)</td>
</tr>
<tr>
<td>ANCA-PR3</td>
<td>92</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Sm</td>
<td>163</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

Abbreviations: see previous tables. ASMA = antismooth muscle antibodies; APCA = antiparietal cell antibodies; AMA = antimitochondrial antibodies.
Back to Case I -- Relevant Testing

- Extremely high ESR (>100 mm/hr)
- Cryoglobulins reported twice; and specimens rejected another two times
- IgG1 lambda paraprotein reported twice, considered "MGUS"
- Elevated globulins (total protein 7.5, albumin 2.3)
- Hepatitis C serology negative x 6!
- Rheumatoid Factor negative x 4!
Case I, continued

- Type I cryoglobulinemia due to B-cell proliferative disorder leading to large amounts of circulating IgG lambda protein with physical property of precipitating in tissues
- Rx’d with myeloma regimen
Response of Type I Cryoglobulinemia to Intensive Rx
Back to Case II, the Man Whose Blood Could Not be Drawn

• Mixed cryoglobulin – patient is making large amounts of monoclonal rheumatoid factor, possibly from Hep C infection
• Clinical effect is hyperviscosity syndrome, with CNS manifestations
• Did well post plasmapheresis (technically difficult) and alkylating agent
Why Does Hepatitis C Infection Generate Monoclonal RFs?

- Dominant clone concept
- Preference for genotype 1
- Not all develop cryos
- Role for CD81 (TAPA, tetraspanin regulates B-cell activation)
- Role for LDL receptor?
- Role for class B scavenger receptor?
Key Role for E2 Glycoprotein in RFs?

- The mechanism by which HCV induces non-organ-specific autoantibodies may involve the enhancement of B-cell activation through the binding of the E2 envelope glycoprotein to the CD81 activatory co-receptor and the activation of the innate Toll-like receptor (TLR) 7 by viral RNA.
Figure 1 Serum soluble B lymphocyte stimulator (BLyS) concentration is elevated in hepatitis virus C (HCV)-induced mixed cryoglobulinaemia (MC)-vasculitis and B cell non-Hodgkin's lymphoma (B-NHL). Serum soluble BLyS concentration measured by an enzyme-linked immunosorbent assay sandwich method, comparing mean{+/-}SEM values of healthy volunteers (n = 7, control), patients with chronic HCV without MC-vasculitis (n = 15, HCV+), patients with HCV-induced MC-vasculitis (n = 8, HCV+ vasculitis) and patients with HCV-induced B-NHL (n = 7, HCV+ B-NHL). p < 0.05
Principal sites for the production and the activity of B-cell activating factor belonging to TNF family (BAFF) in HCV-related cryoglobulinaemic patients

ETIOPATHOGENESIS OF MIXED CRYOGLLOBULINEMIA

Unknown environmental co-factors

HCV, HBV, other infections

Viral antigens

Host factors: genetic, autoantigens, sex hormones

Autoreactive T-cells

Poly-oligoclonal B-cell expansion

Autoantibodies, RF, IC, cryoglobulins

B-cell

T(14;18) translocation

Bcl2 overexpression

Other genetic aberrations (c-myc, Bcl6, p53, etc.)

Autoimmune disorders
hepatitis, porphyria c.t., arthritis, sicca s., nephritis, thyroiditis, lung fibrosis, diabetes, cardiomyopathies

Mixed cryoglobulinemia
(cryogl. vasculitis)

B-cell lymphomas
Hepatocellular carcinoma
Thyroid cancer

Mixed cryoglobulinemia
(cryogl. vasculitis)
Therapeutic Strategies of Mixed Cryoglobulinemia Syndrome (1)

1. Chronic HCV infection
   - Poly-oligoclonal B-cell expansion
   - Production of different autoantibodies, RF, CIC, mixed cryoglobulins
   - Monoclonal B-cell proliferation
   - B-cell NHL
   - Attempt at HCV eradication (IFN+RIBA)

2. Immunosuppressors CPX, RTX
   - Chemotherapy

3. LAC-diet plasma exchange
   - Corticosteroids

Cryoglobulinemic Vasculitis
Figure 1 Complete response rate of hepatitis C virus-associated cryoglobulinaemia vasculitis with rituximab combined with Peg-interferon-\{alpha\}2b-ribavirin. Arrows indicate the number of weekly rituximab infusions and the duration of antiviral treatment.
Type III Cryoglobulinemia

• Much less of a problem clinically than I or II
• Cryoglobulins consist of immune complexes
• Usually the antigen in the complex is unknown
• Seen in SLE (DNA reported as antigen), other connective tissue diseases, some infectious diseases
We report the presence of serum cryoimmunoglobulins in patients with attacks of a newly described epidemic arthritis--Lyme arthritis--and in some patients with a characteristic skin lesion--erythema chronicum migrans--that sometimes precedes the onset of the arthritis. Seven patients who had cryoimmunoglobulins at the time of the skin lesion have developed arthritis; four patients without them have not. The cryoglobulins in patients with the skin lesion consisted primarily of immunoglobulin M (IgM); those in patients with arthritis often included both IgM and IgG. These findings support the hypothesis that a common origin exists for the skin and joint lesions and suggest that circulating immune complexes may have a pathogenetic role in Lyme arthritis.
CONCLUSIONS

• Pathogenesis of cryoglobulinemia due to Hepatitis C remains puzzling
• Something about chronic infection with this RNA virus provokes an exaggerated RF response by a very limited repertoire of VH and VL genes
• The RF contributes in a material way to the pathology of the disease
• Type III cryoglobulinemia is less worrisome and generally reflects circulating immune complexes
Conclusions

• We need to do a better job in detecting and characterizing cryoglobulins
• Rituximab a useful new Rx for mixed (type II) cryoglobulinemia (but not for type I)
• Most types of cryoglobulinemia will respond well to therapy