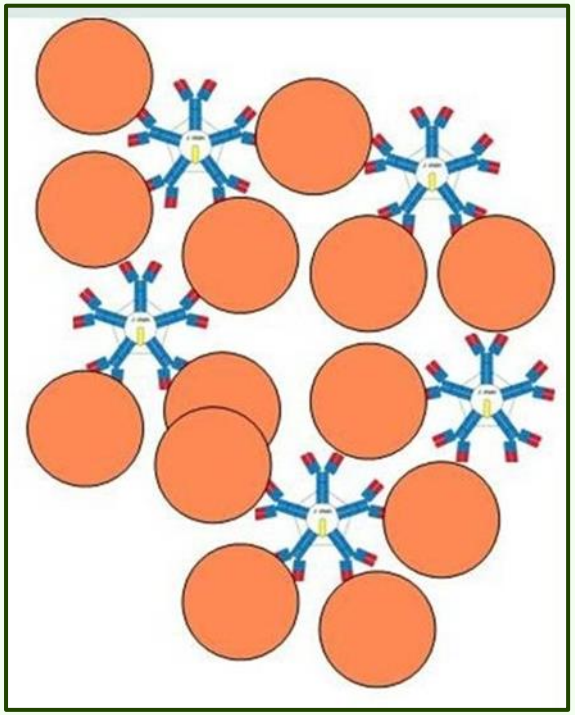

Role of complement in cold agglutinin disease

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What is cold agglutinin disease?

Auto-immune hemolytic anemia (AIHA) *)

*) = Anemia caused by destruction of red blood cells by the immune system

Warm-antibody AIHA (70-75%)

- Primary
- Secondary or associated

Cold-antibody AIHA (25-30%)

- Cold agglutinin **disease** (CAD) (15-25% of AIHA)
- Secondary cold agglutinin **syndrome** (CAS)
  - Acute, infection-associated (*Mycoplasma*, EBV, etc.)
  - Associated with aggressive lymphoma
  - Associated with other malignancies
- Paroxysmal cold hemoglobinuria (PCH)

Mixed warm- and cold-antibody AIHA

What is CAD?

- CAD is a chronic form of autoimmune hemolytic anemia
- The autoantibodies (antibodies against one's own cells) in CAD are termed cold agglutinins.
- Cold agglutinins bind to red blood cells at temperature below normal central body temperature
  - Such temperatures occur normally in face, arms, legs, etc.
- Cold agglutinins can *agglutinate (clump together) red blood cells*

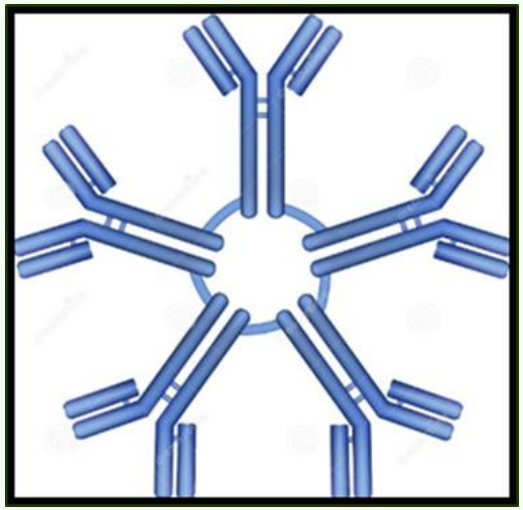
  → explained on next slides
- When bound to the red blood cells, cold agglutinins will *bind complement on the cells and activate the complement system*

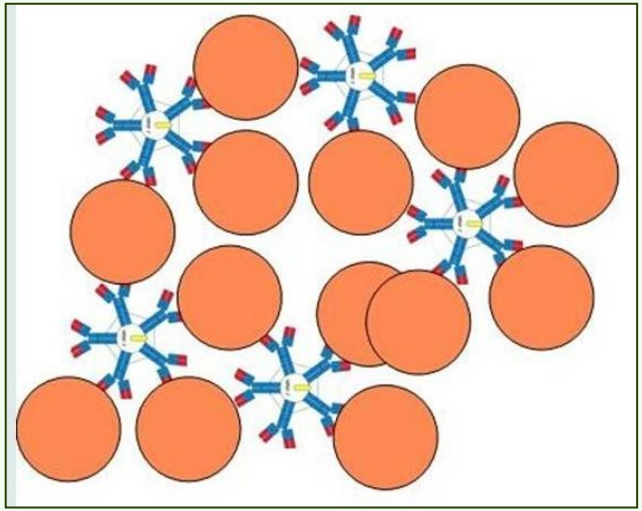
  → further explained later

We produce different classes of antibodies

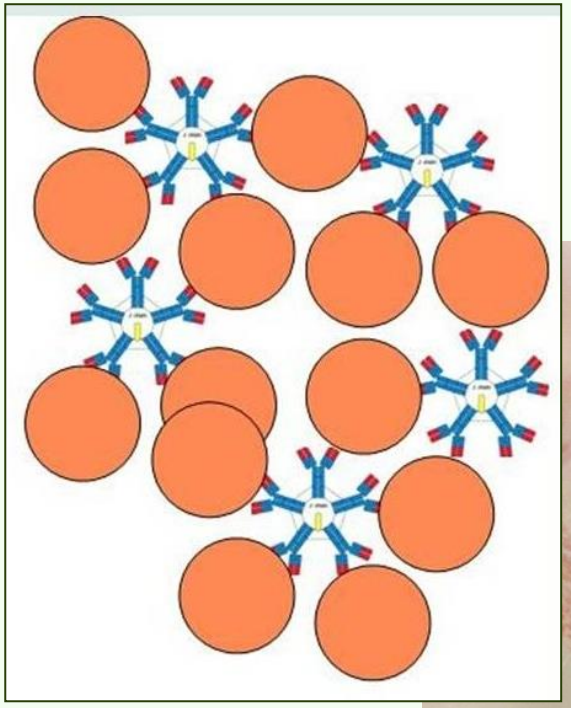
- Antibody classes (main groups): IgG, IgM, IgA, IgD, IgE
- These antibody classes differ from each other in structure (design of the molecule) and function
- Cold agglutinins are of the IgM class

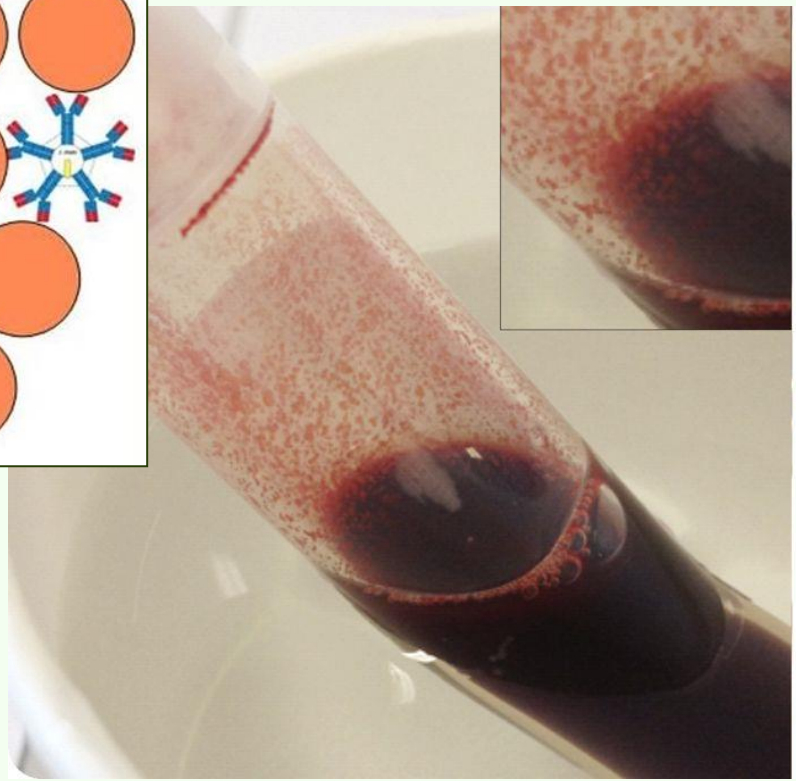
IgM
Cold agglutinin

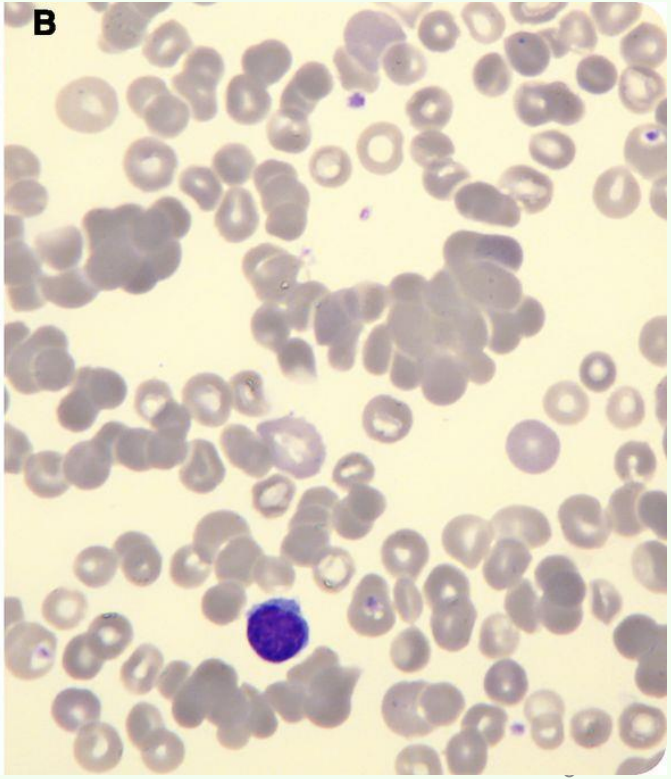




Red blood cell agglutination in CAD

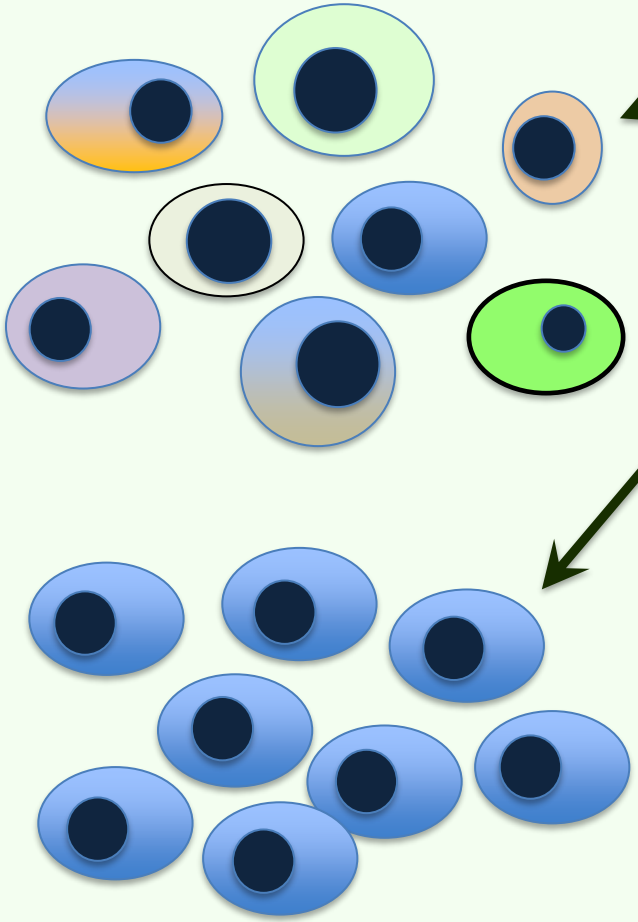






How are the cold agglutinins produced in CAD?

CA are produced by clonal B-lymohocytes



Normal (polyclonal) cells

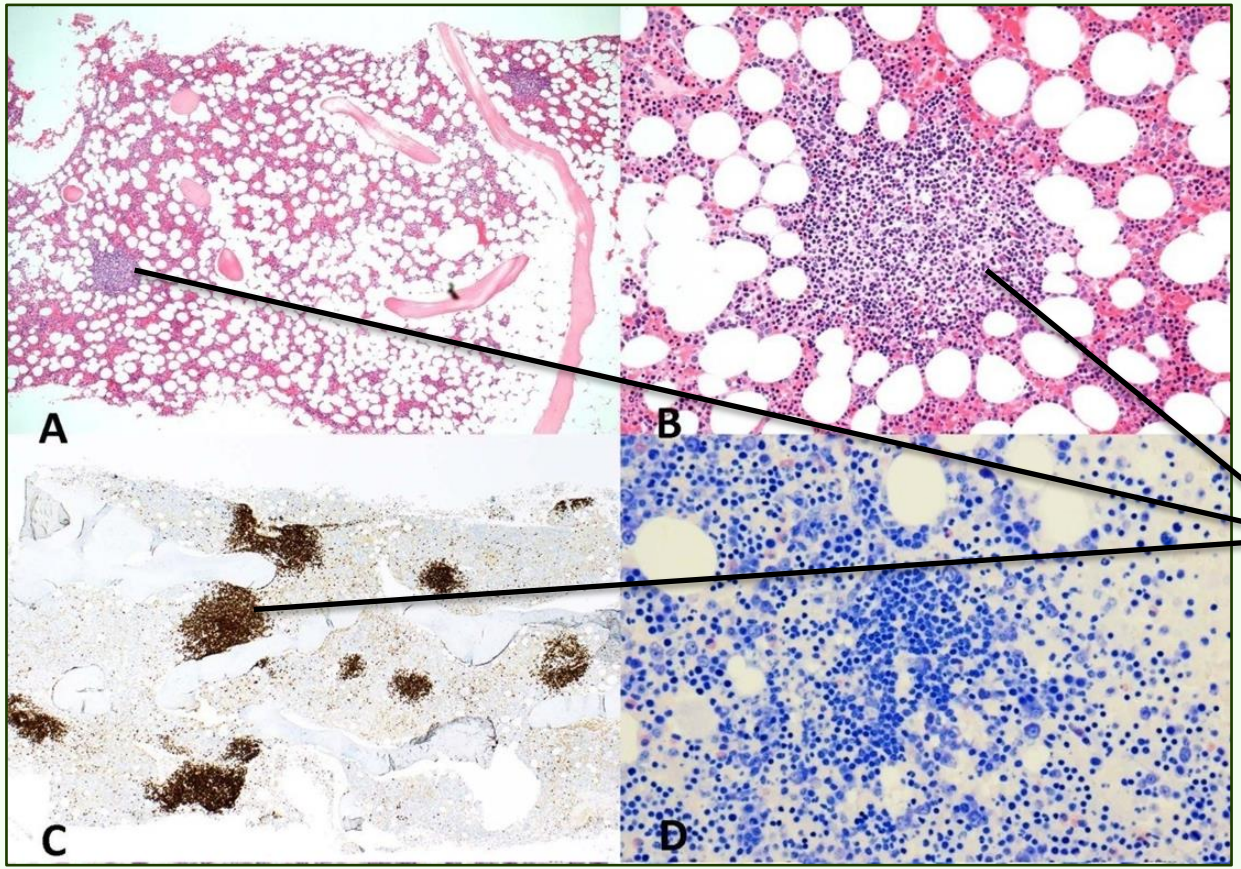
- are all slightly different from one another (diversified)

Clonal (monoclonal) cells

- are all exactly like
- have identical properties
- All of them descend from 1 (one) cell

The cells that produce cold agglutinins in CAD are clonal, antibody-producing cells, located in the bone marrow

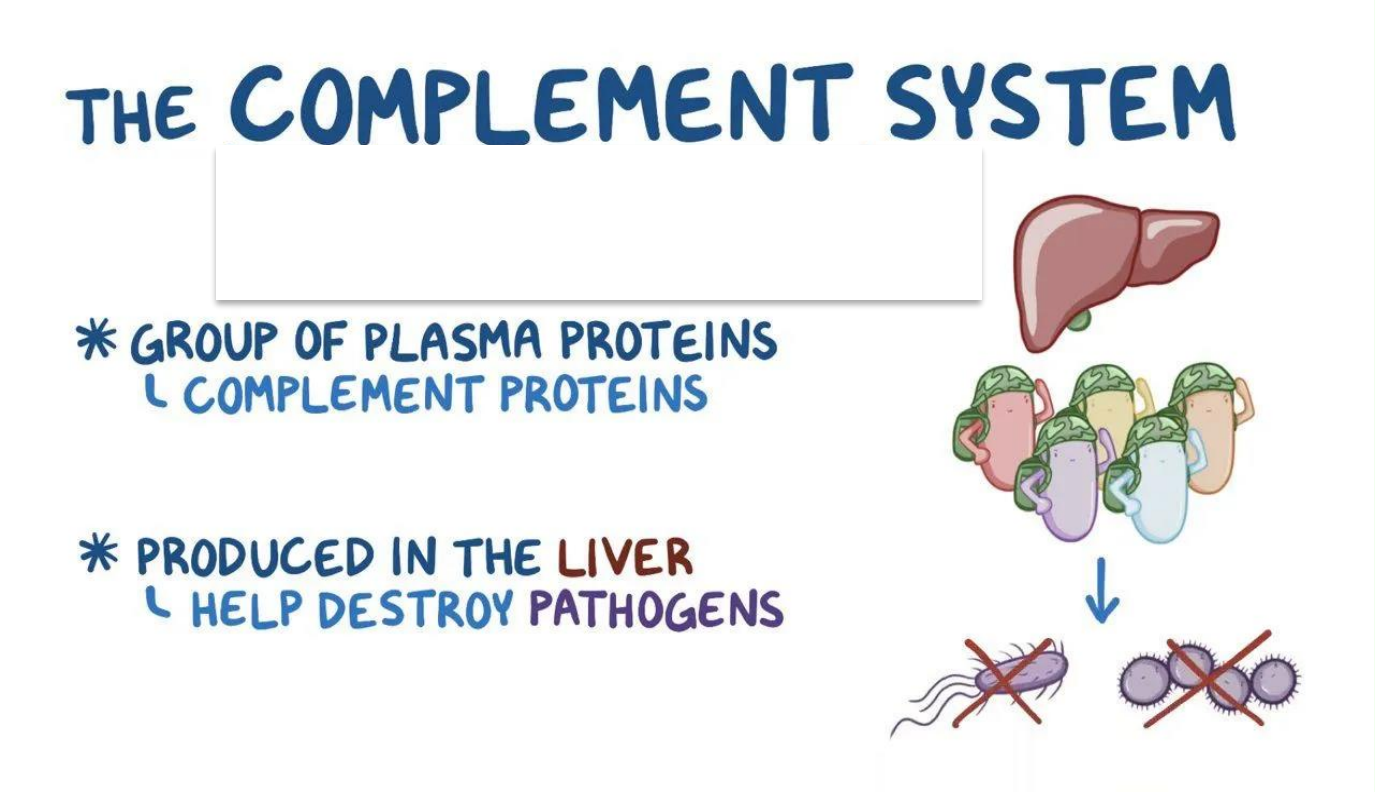
“CA-associated lymphoproliferative bone marrow disorder”



Groups of cold agglutinin-producing clonal cells

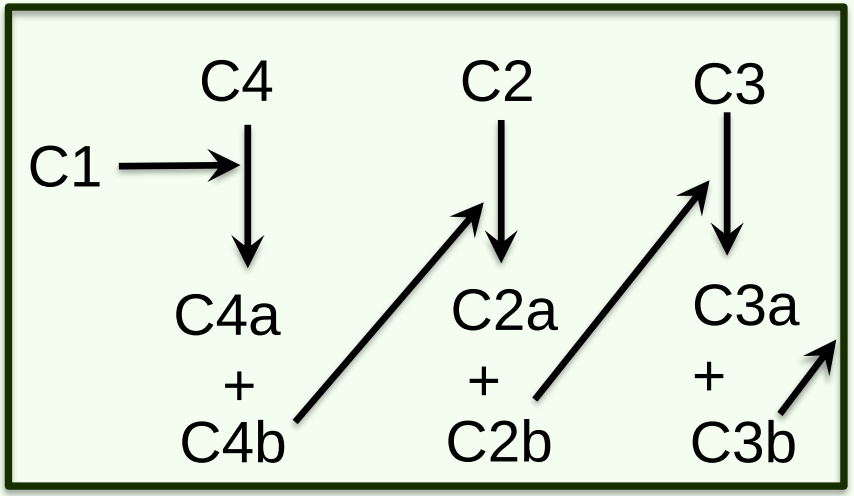
What is complement
and what does complement do in CAD?

- Complement is part of the immune system
- Complement consists of more than 50 proteins



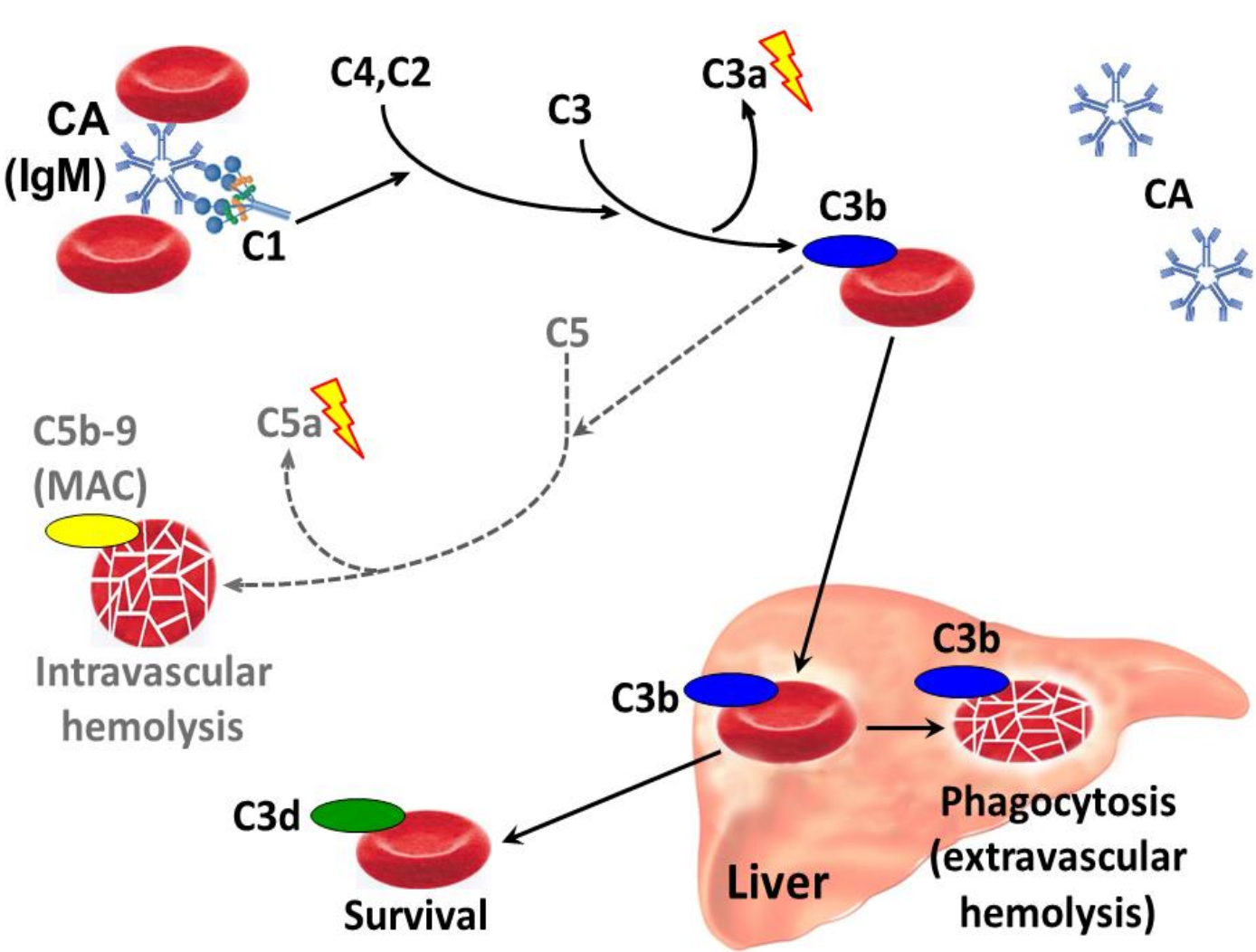
- The word «complement» implies that it «complements» the immune system – «helps the antibodies in doing their job».

- The complement system consists of more than 50 proteins
- These proteins can bind to cell surfaces or microbial surfaces
- Complement proteins are activated in a serial way,



- which means that a complement protein can split the next complement protein and, thereby, form an active substance,
- which can then split the next complement protein and form another active substance,
- which can then split the next…….etc. etc.

Complement mediated hemolysis in CAD



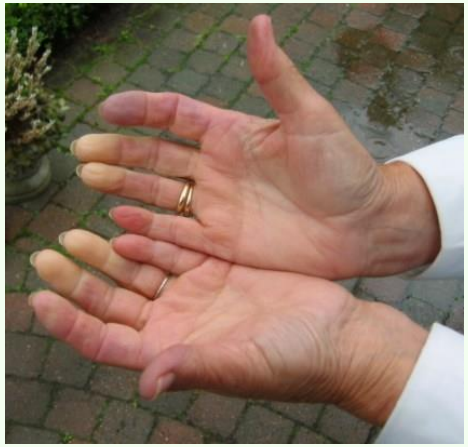
What are the results of this process?

1. Red blood cell agglutination →

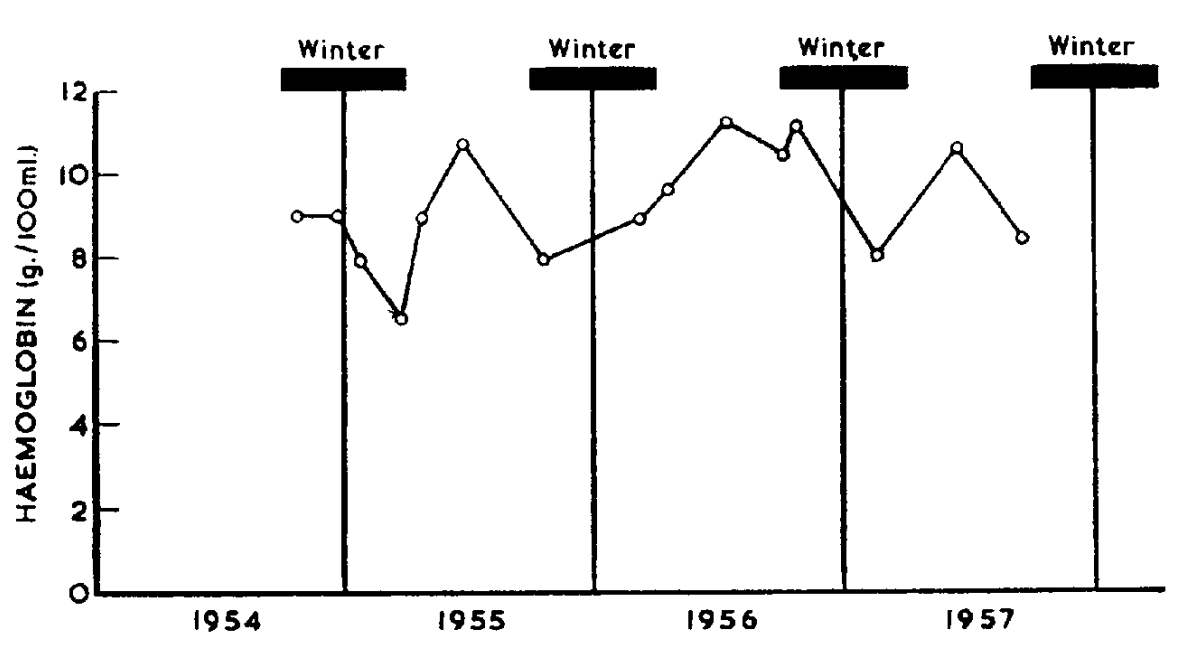
- Cold intolerance (Bluish/dark skin discoloration, Raynaud phenomena) (40-90%)

2. Complement activation →

- Hemolytic anemia
- Worsening of hemolytic anemia on cooling
- Worsening of hemolytic anemia in febrile infection
- Fatigue



Seasonal variation in a British patient with CAD



Dacie, 1957

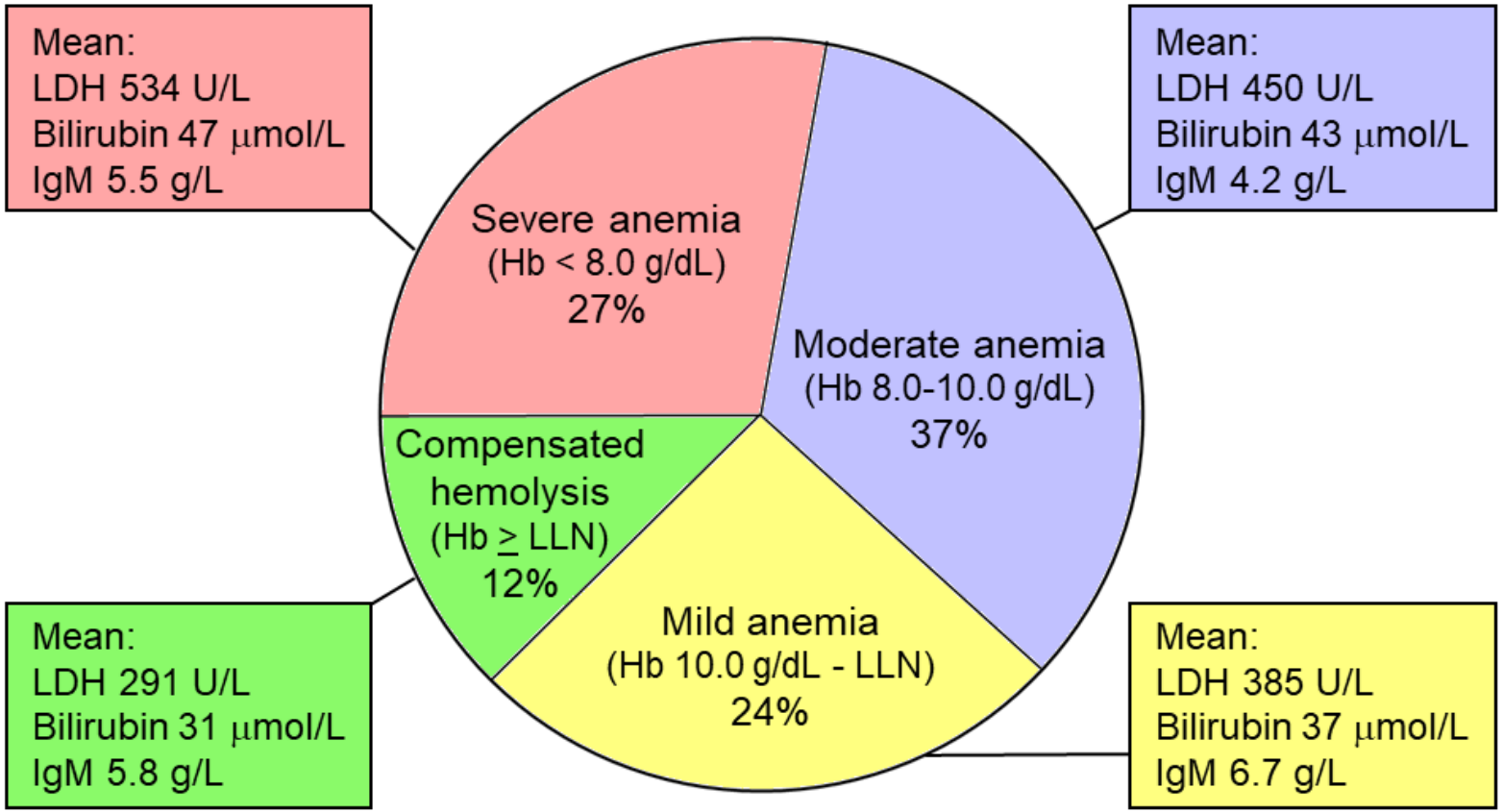
…but hemolysis is persistant all year round

CAD in Norway and Lombardy, Italy

Patients diagnosed with CAD

	Population, million	Prevalence, cases/million inhabitants	Incidence, cases/million inhabitants/ year	Outdoors temperature, °C, yearly average
Norway	5.32	20.5	1.9	6.0
Lombardy, Italy	7.0	5.0	0.48	13.1

How bad is the anemia?



What does the complement involvement mean for treatment?

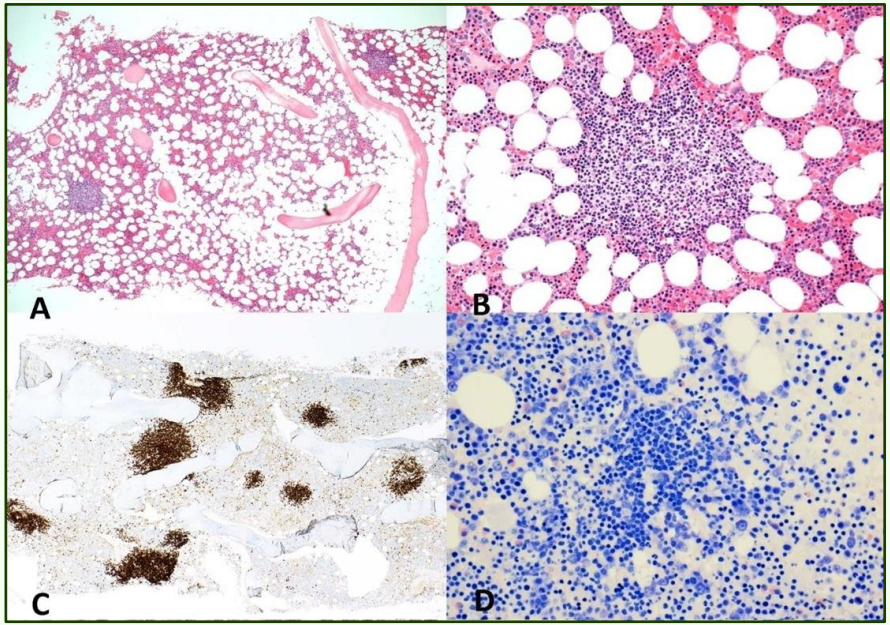
Drug therapy is not always needed

- Counselling patients
  - Warm clothing
  - Particular protection of hands/feet/head/ears
- Counselling doctors / health care professionals:
  - Keep patient warm
  - Avoid infusion of cold liquids
  - Early treatment of any febrile bacterial infections
  - Transfuse if indicated, but observe specific precautions!
  - Avoid blood products with a high complement content
- CAD should not be treated with corticosteroids

Steps in the disease process → Targets for therapy

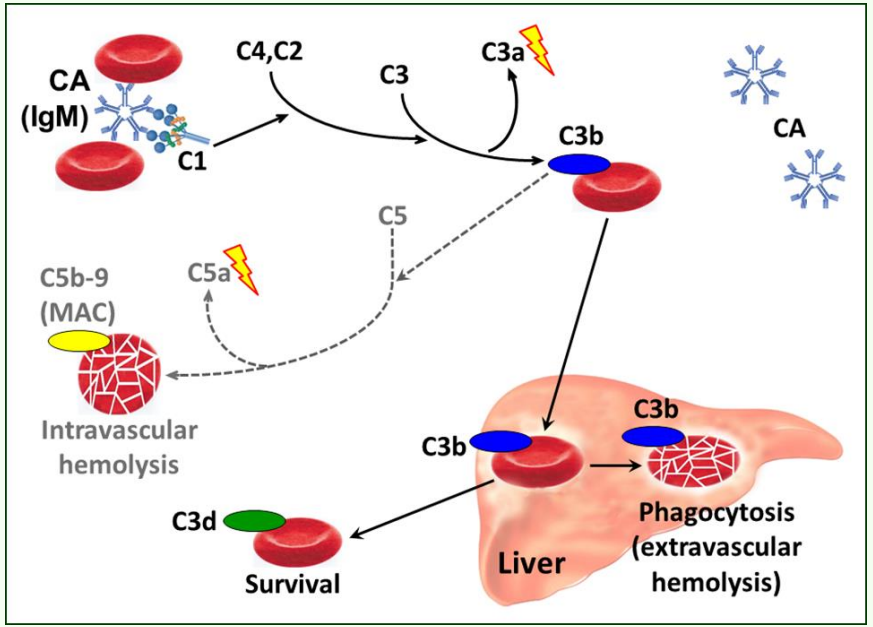
1) Clonal B-cells

→ a target for treatment



2) Complement activation

→ a target for treatment



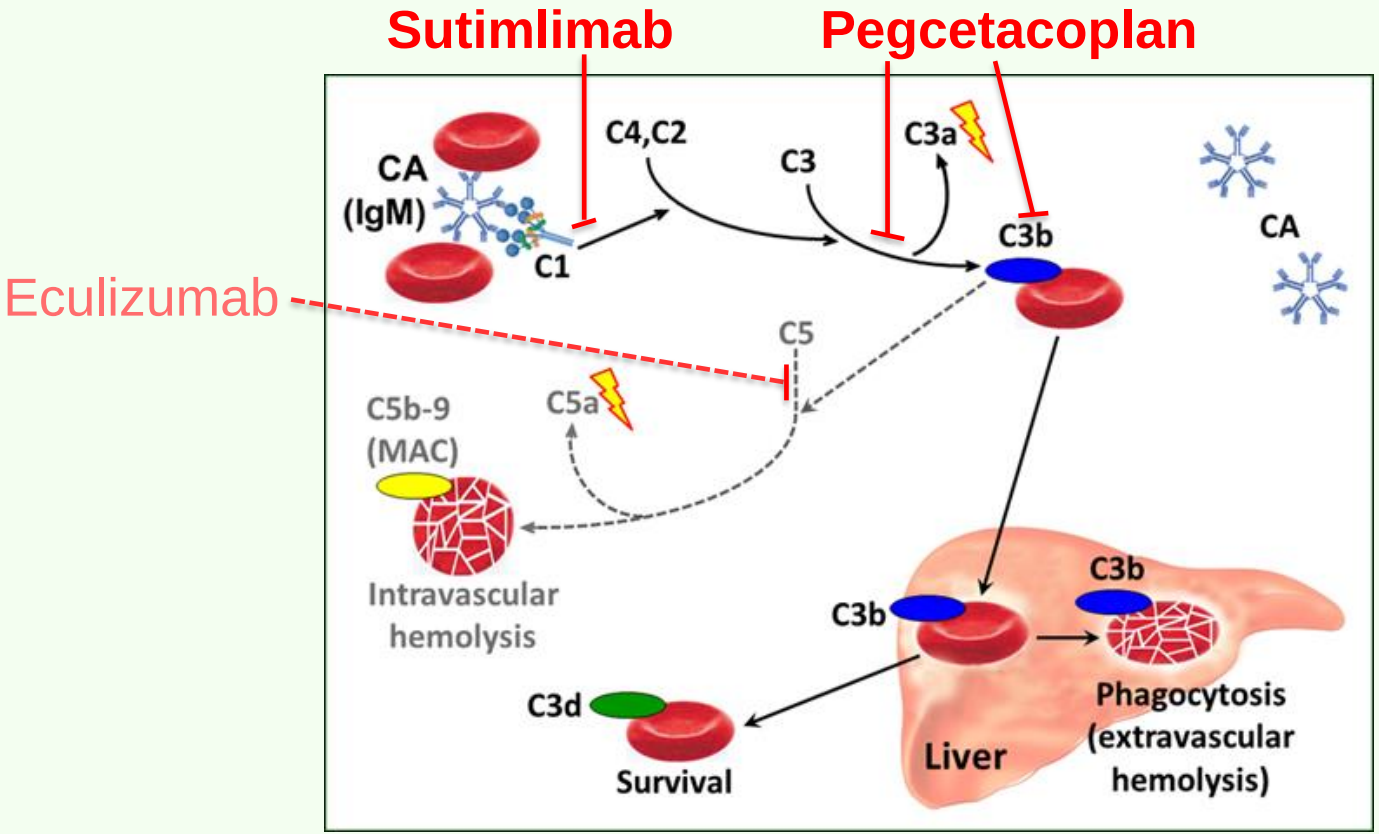
1. Therapies directed at the clonal B-cells

- Rituximab
- Rituximab plus bendamustine
- Bortezomib

These treatment options have been highly beneficial for many patients, but they leave some unmet needs:

- the failure rate
- some adverse effects
- long time to response in many patients

2. How can we take advantage of the complement involvement?



Some complement inhibitors studied in CAD

- Sutimlimab is a C1 inhibitor designed for intravenous infusion.
- Sutimlimab has been approved in the US by FDA. In Europe, an application for EMA approval is awaiting decision.

- Pegcetacoplan is a C3 inhibitor designed for subcutaneous infusion.
- Pegcetacoplan is not yet available for use in CAD outside clinical trials, but has now entered a phase 3 trial.

- More experimental treatment options are in the pipeline, but possible clinical use is farther ahead.
- Patients with CAD who need treatment may benefit from participation in clinical trials.

Thank you for your attention

&
Greetings from beautiful South-West Norway