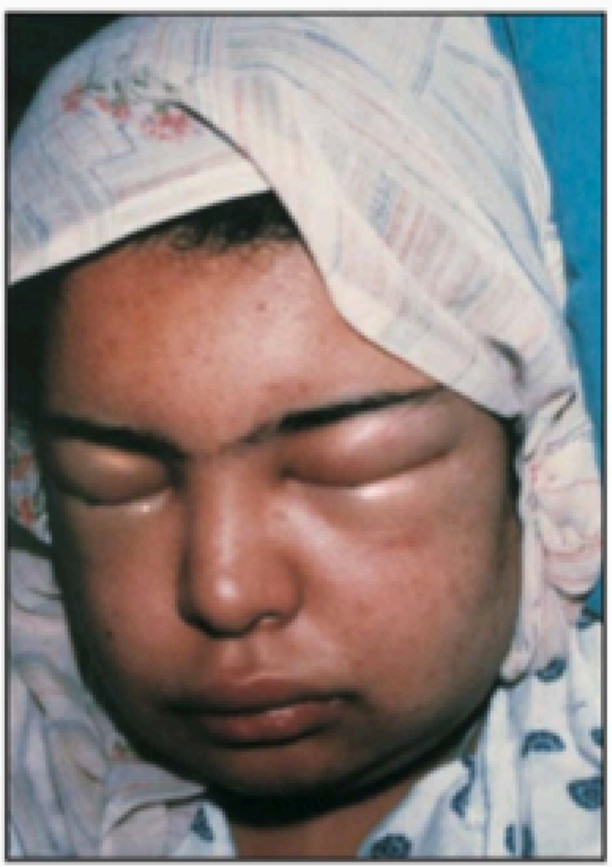
Hereditary Angioneurotic Edema

Presented by: Farah Tahboub

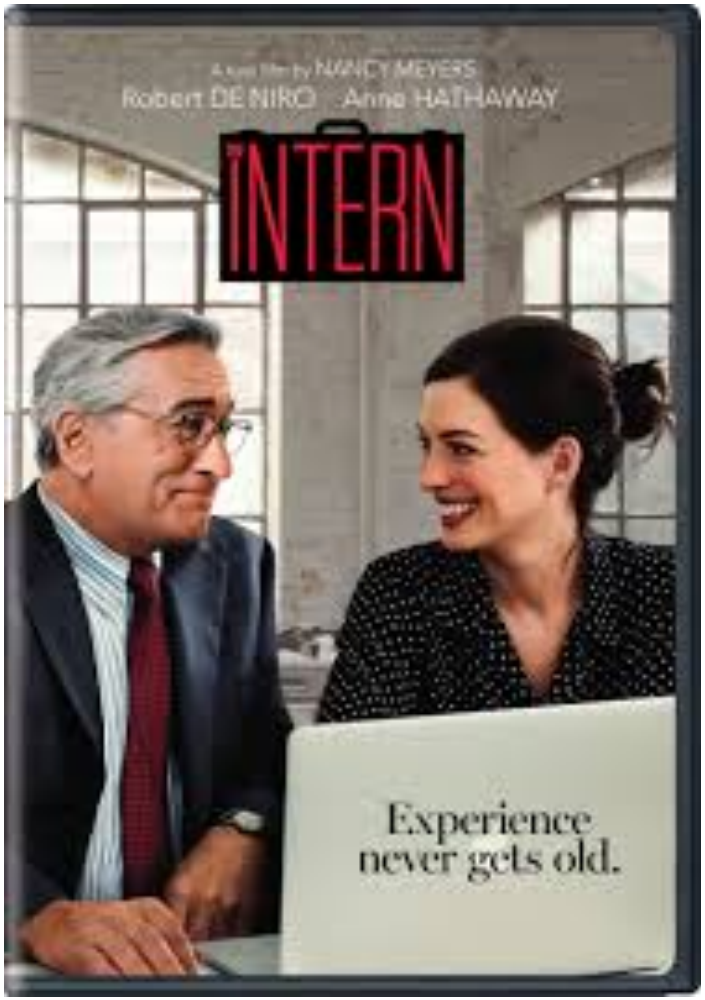


Clinical Case

Richard Crafton was a 17-year-old high-school senior when he had an attack of **severe abdominal pain** at the end of a school day. The pain came as frequent **sharp spasms** and he began to **vomit**. After 3 hours, the **pain became unbearable** and he went to the emergency room at the local hospital.

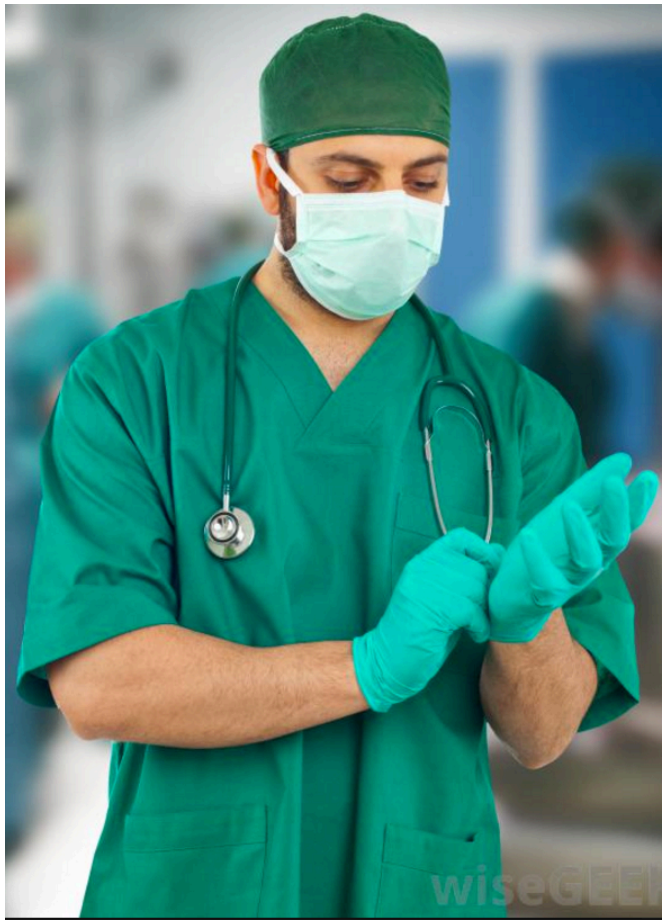
The Intern's findings:

- Dry mucous membranes of the mouth
- Tender abdomen
- No point tenderness to indicate appendicitis
- No other abnormalities
- Vomit every 5 minutes and said the pain was getting worse



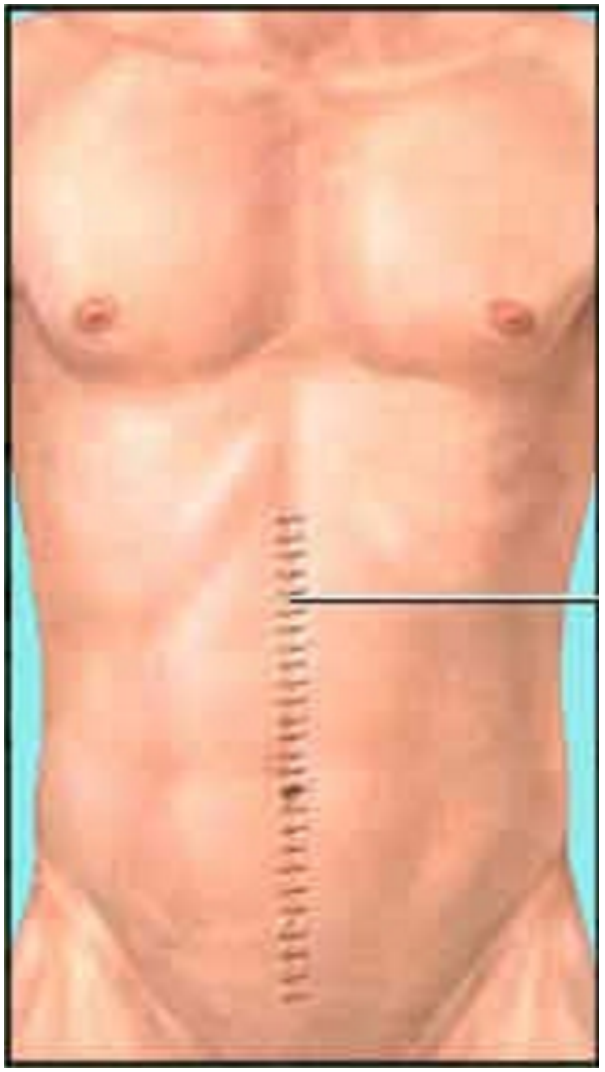
The Surgeon was Summoned

- Acute abdominal condition but uncertain of the diagnosis
- Blood tests showed an **elevated red blood cell** count, indicating **dehydration**
- Proceed with **exploratory abdominal surgery**



Exploratory Abdominal Surgery

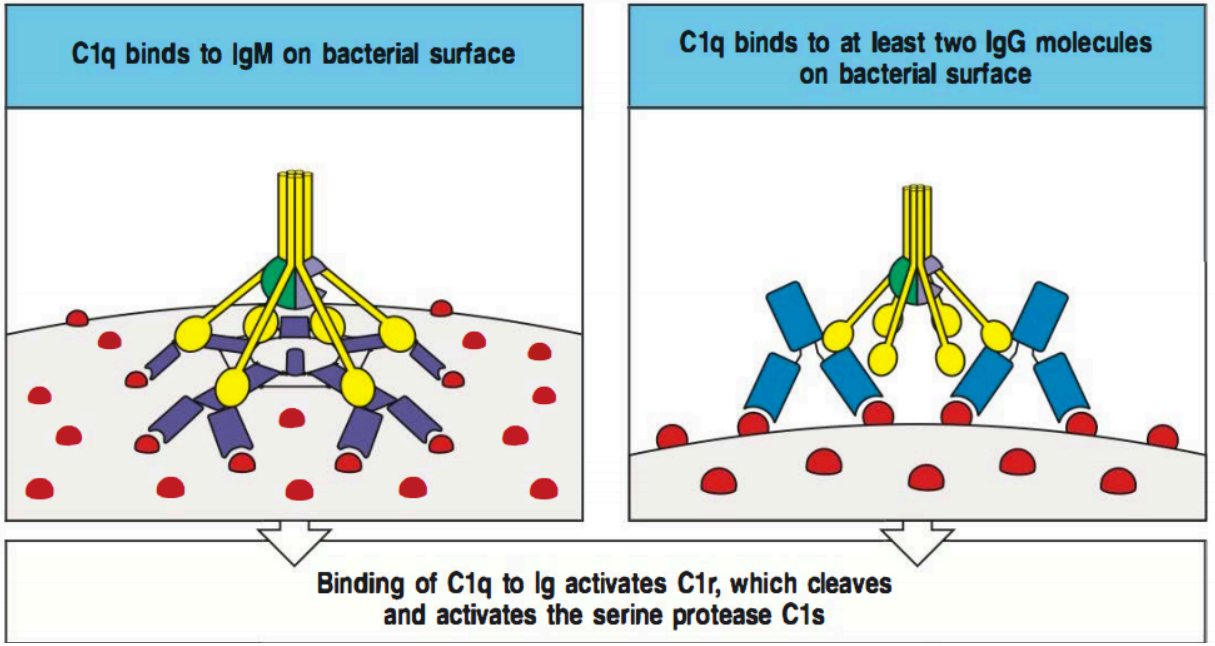
- Large midline incision
- **Moderately swollen and pale jejunum**
- No other abnormalities were noted
- **Richard's appendix was removed** and was normal
- Richard recovered and returned to school **5 days later**



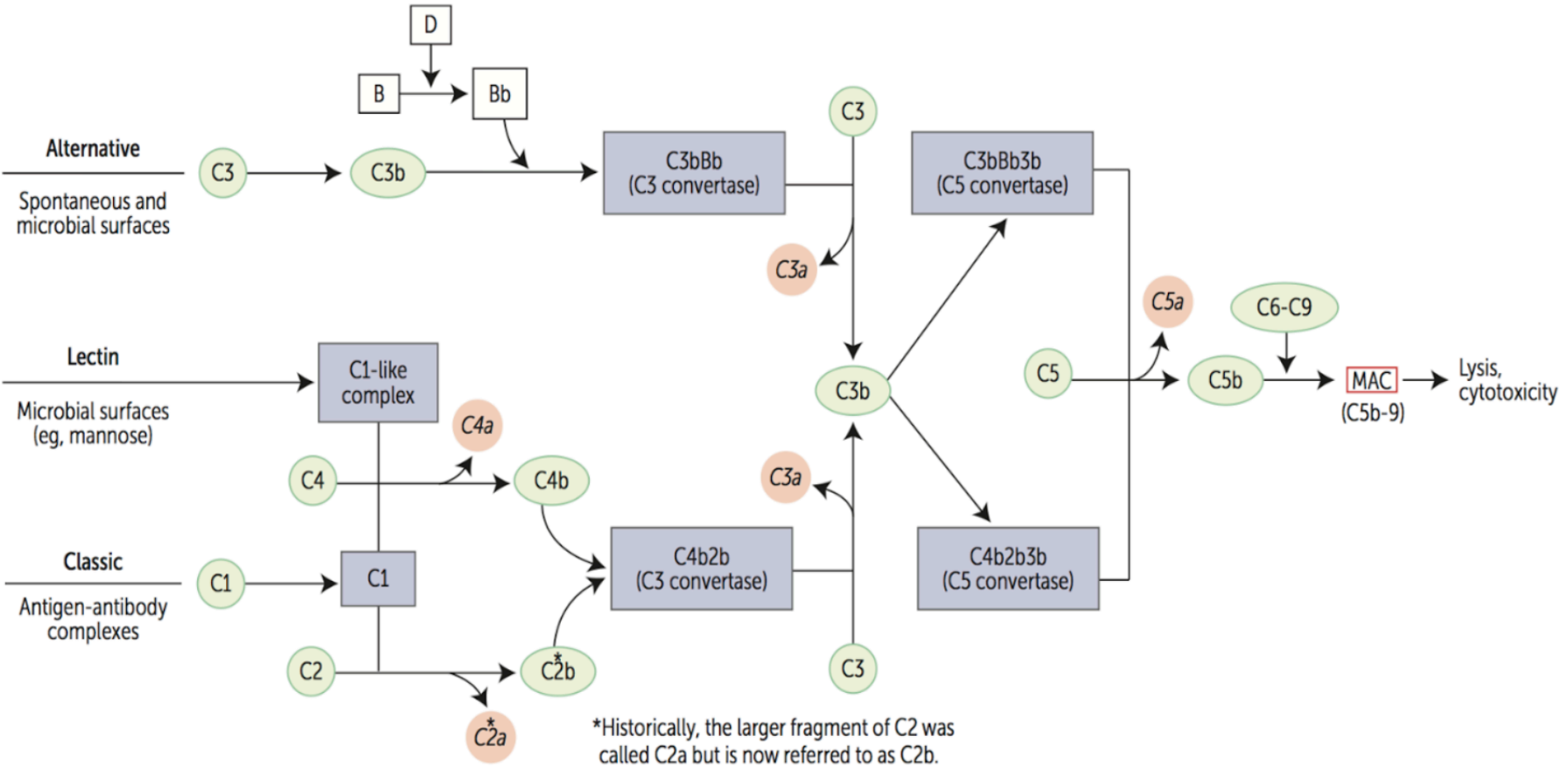
Complement is normally activated by one of three routes:

- **The classical pathway:** triggered by antigen:antibody complexes or antibody bound to the surface of a pathogen
- **The mannan-binding lectin pathway**: activated by cytokines released by macrophages
- **The alternative pathway**: complement is activated spontaneously on the surface of some bacteria

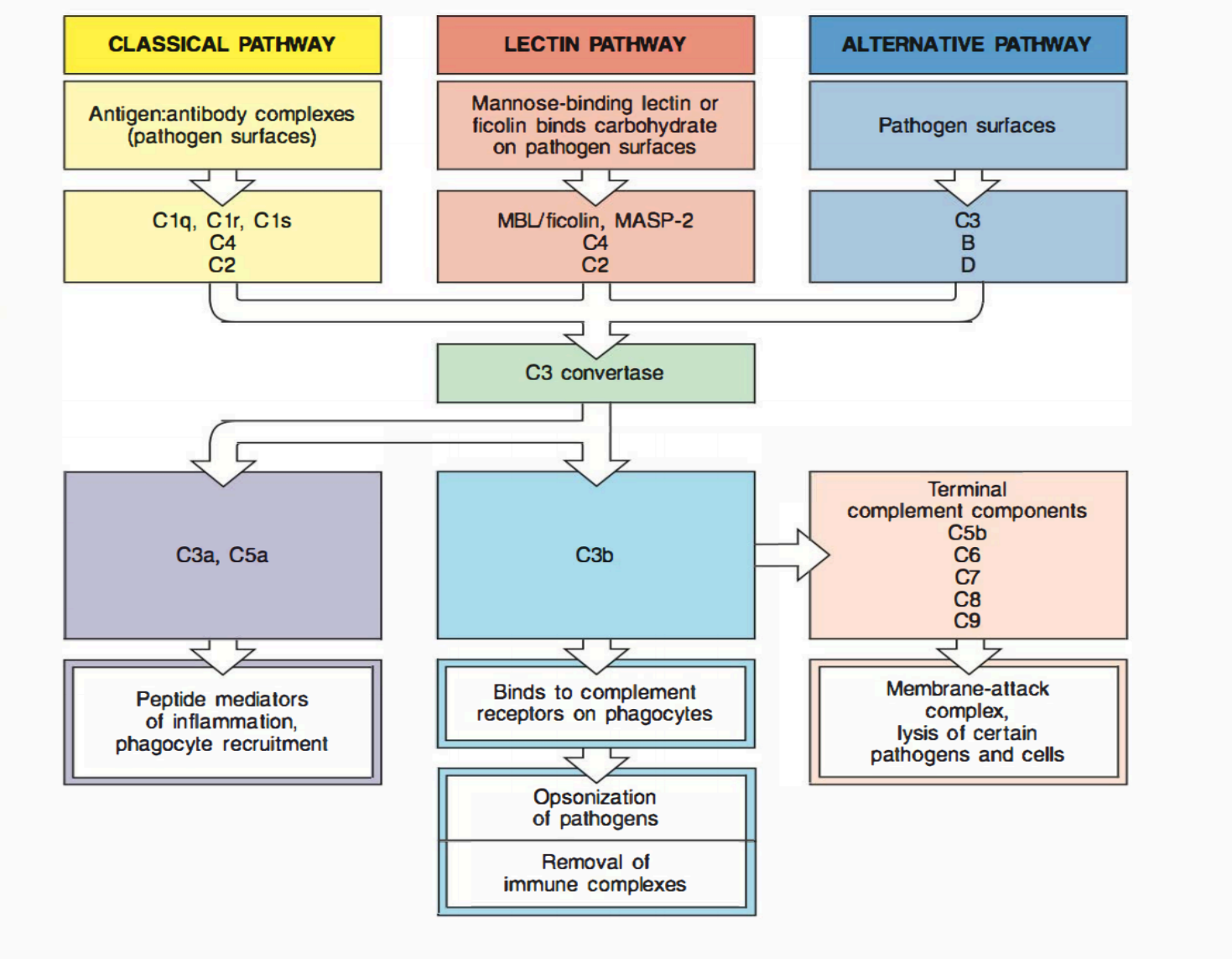
The Classical Pathway: C1



The Classical Pathway

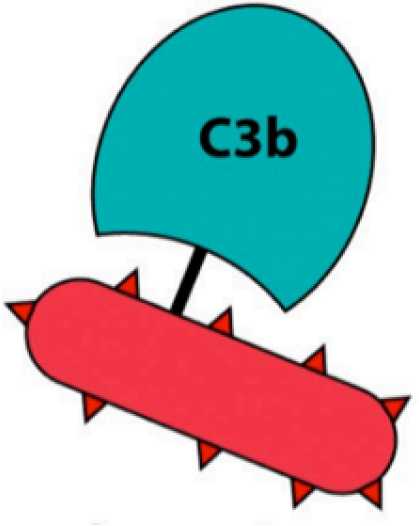


C3 Convertase (serine protease) generation by all three pathways



C3b

- The principal effector molecule for compliment
- Large cleavage fragment of C3, major opsonin
- If active C3b, or the homologous but less potent C4b, accidentally becomes bound to a host cell surface instead of a pathogen, the cell can be destroyed
- Rapid hydrolysis of active C3b and C4b prevents the binding to host cells

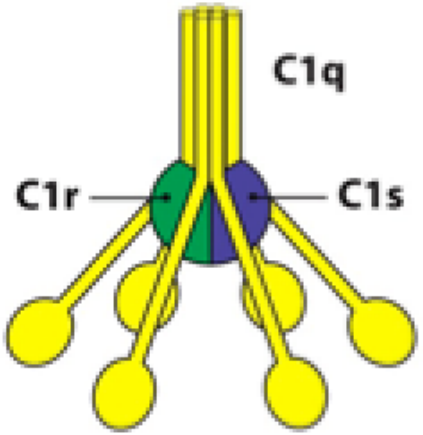


C1 Inhibitor (C1INH)

- Regulatory proteins provide protection against inappropriate activation of complement
- The most potent inhibitor of the classical pathway
- Belongs to a family of serine protease inhibitors (called serpins) that together constitute 20% of all plasma proteins.
- C1INH contributes to the regulation of serine proteases of the clotting system and of the kinin system

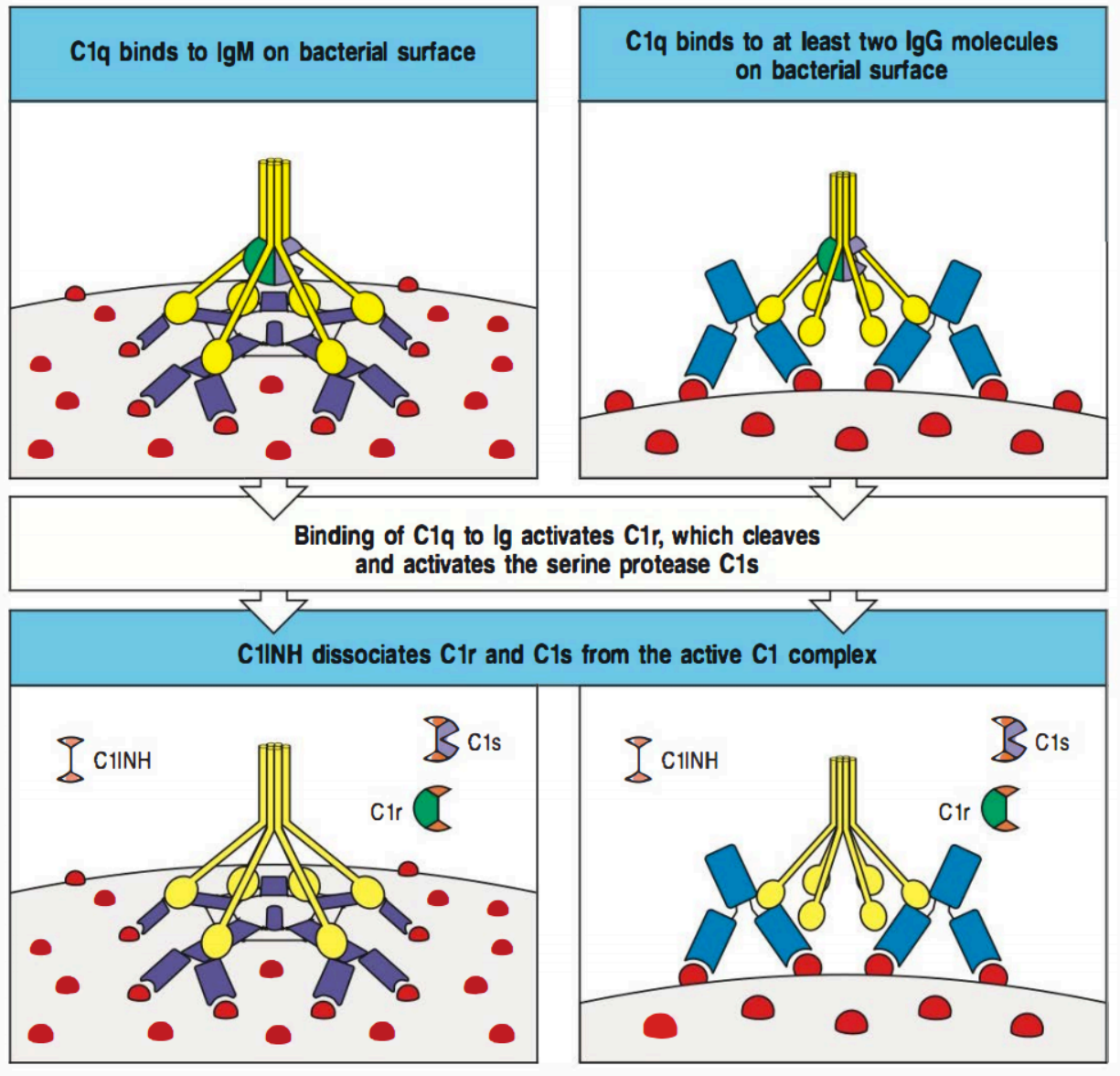
C1INH Mechanism of Action

- C1INH intervenes in the first step of complement pathway
- C1INH inhibits C1r and C1s by providing them with a bait site in the form of an arginine threonine bond that they cleave



- C1r and C1s attack the bait site, they bind C1INH and dissociate from C1q limiting the time they can cleave C4 and C2 to generate the C3 convertase.

- There are two C1r and two C1s molecules so four molecules of C1INH are needed



Another way to activate C1

- C1 can spontaneously activate at low levels without binding to antigen: antibody complex
- Triggered further by plasmin
- Plasmin: is a protease of the clotting system, which is normally inhibited by C1INH

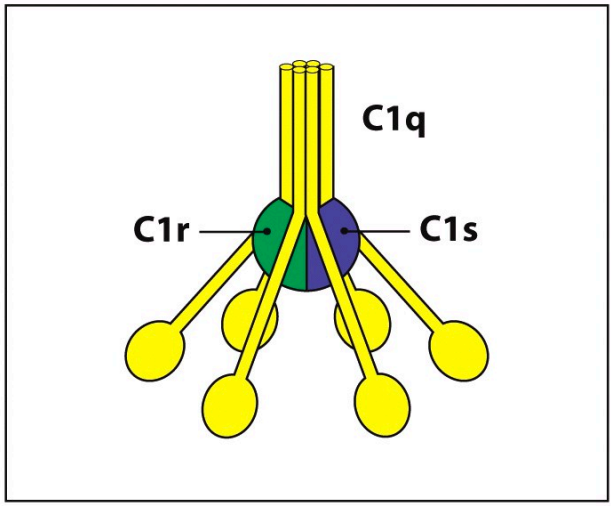


Figure 2.42 The Immune System, 3ed. (© Garland Science 2009)

Hereditary Angioneurotic Edema

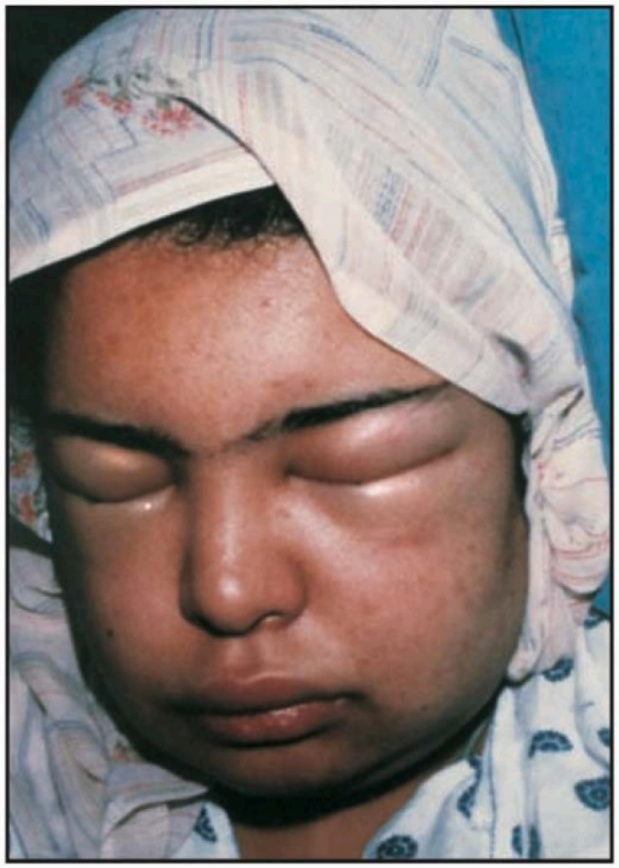


Fig. 31.3 Hereditary angioedema. Transient localized swelling that occurs in this condition often affects the face.

Is a **rare** autosomal dominant disease caused by a deficiency in C1 inhibitor, and causes rapid swelling in the face, gastrointestinal tract, upper airways and extremities

Hereditary Angioneurotic Edema

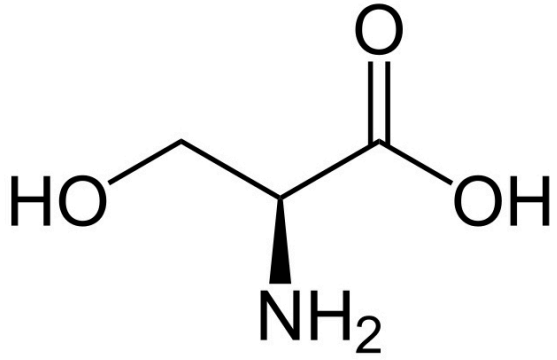
- Recurrent episodes of circumscribed swelling of the skin, intestine, and airway
- **Intestinal swelling:** causes severe abdominal pain, and obstructs the intestine so that the patient vomits
- **Swelling in the Colon:** severe watery diarrhea may occur
- **Swelling in the larynx:** is the most dangerous symptom, because the patient can rapidly choke to death

Triggers of Swelling Episodes

- Trauma
- Menstrual periods
- Excessive exercise
- Exposure to extremes of temperature
- Mental stress

Attacks are associated with activation of four serine proteases normally inhibited by C1INH

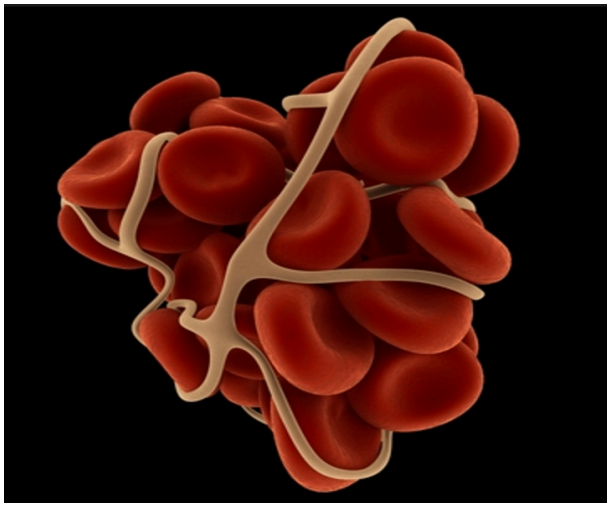
- Factor XII (which directly or indirectly activates the other three)
- Plasmin
- C1s, C1r
- Kallikrein

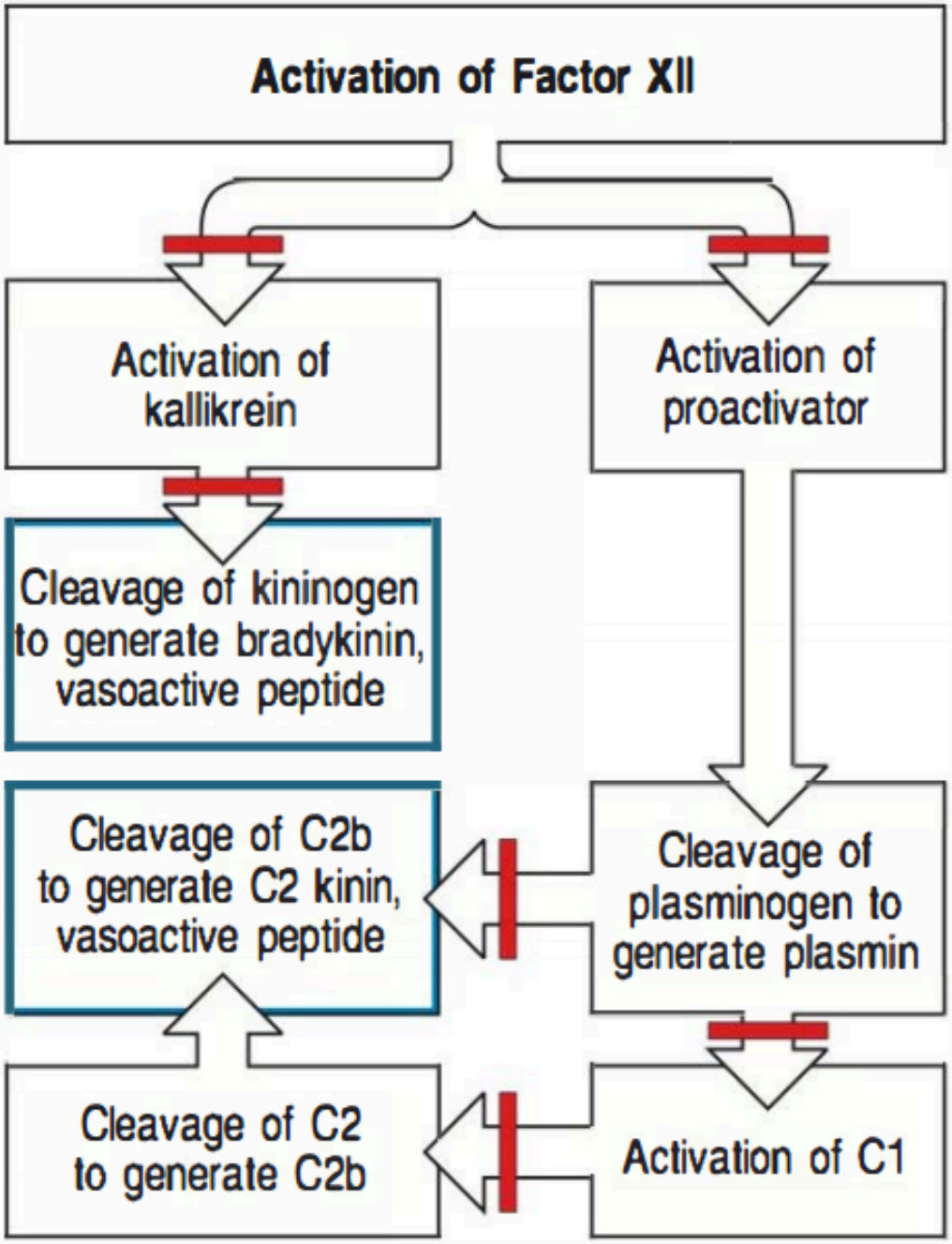


Serine

Factor XII

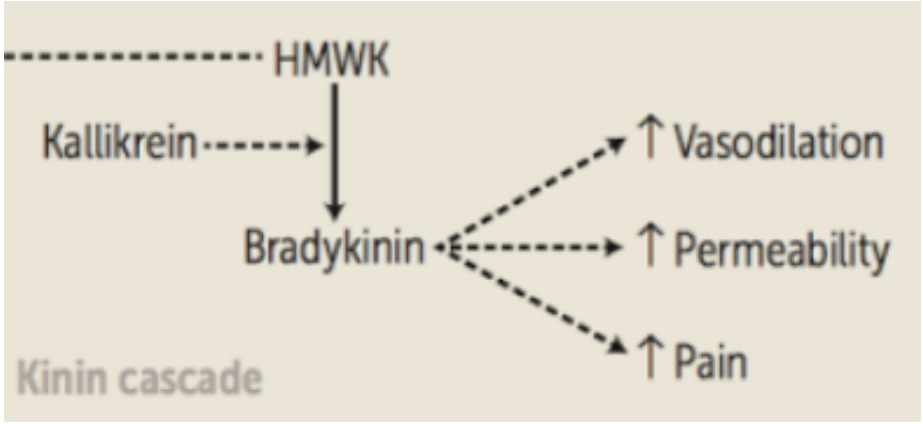
- Activated by injury to blood vessels
- Initiates the kinin cascade
- Activates kallikrein which generates bradykinin
- Indirectly activates plasmin
- Plasmin activates C1
- Plasmin cleaves C2a to produce C2 kinin




Activation of Factor XII
Activation of kallikrein
Activation of proactivator
Cleavage of kininogen to generate bradykinin, vasoactive peptide
Cleavage of C2b to generate C2 kinin, vasoactive peptide
Cleavage of plasminogen to generate plasmin
Cleavage of C2 to generate C2b
Activation of C1

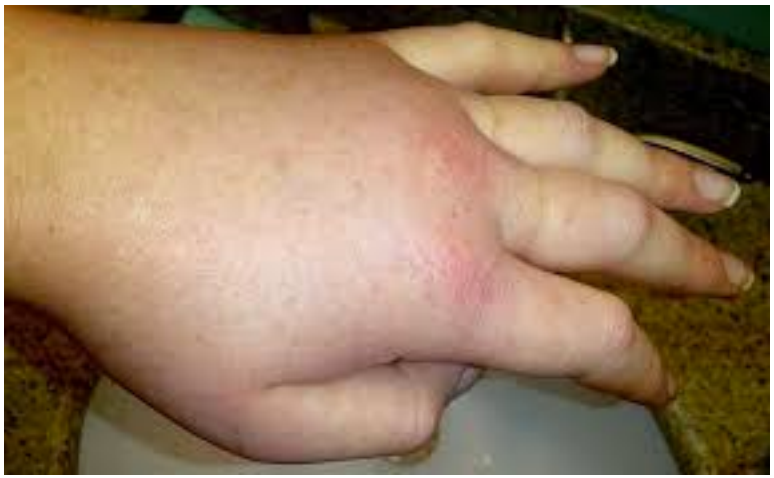
Bradykinin and C2 Kinin

- Bradykinin and C2 kinin increase the permeability of postcapillary venules by causing contraction of endothelial cells and create gaps in the vessel wall -> Edema



Dehydration and Edema

- Movement of fluid from the vascular space into another body compartment such as the gut causes the symptoms of dehydration as the vascular volume contracts
- Pain is also due to the edema and obstruction



Summary of Hereditary Angioneurotic Edema

- Caused by deficiency in C1INH
- C1INH inhibits the following serine proteases:
  1. C1r, C1s: which are responsible for activating the classical complement pathway
  2. Factor XII: activates coagulation and kinin pathway, and indirectly or directly activates the other three
  3. Plasmin: activates C1 and generates C2 kinin
  4. Kallikrein: generates bradykinin, vasoactive peptide

The Intern's findings:

- Dry mucous membranes of the mouth
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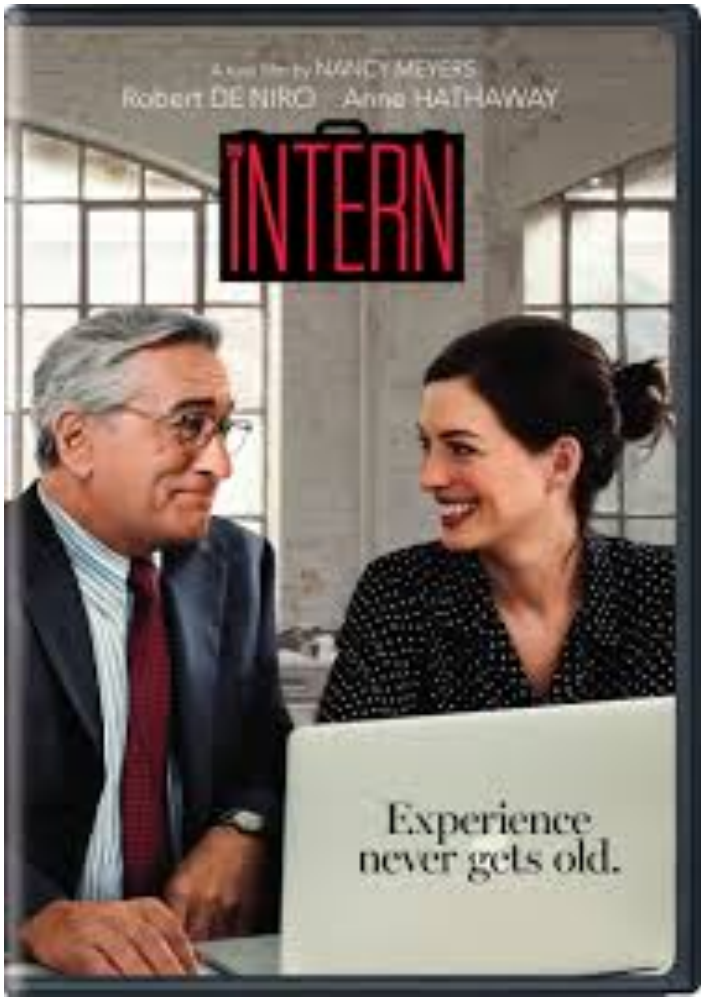

What Richard had not mentioned to the intern or to the surgeon was that, although he had never had such severe pains as those he was experiencing when he went to the emergency room; he had **had episodes of abdominal pain since he was 14 years old.** No one in the emergency room asked him if he was taking any medication, or took a family history or a history of prior illness. If they had, they would have learned that **Richard's mother, his maternal grandmother, and a maternal uncle, also had recurrent episodes of severe abdominal pain, as did his only sibling, a 19-year-old sister**.

As a newborn, Richard was **prone to severe colic**. When he was 4 years old, a bump on his head led to **abnormal swelling**. When he was 7, a blow with a baseball bat caused his entire left forearm to swell to twice its normal size. In both cases, the swelling was **not painful, nor was it red or itchy, and it disappeared after 2 days**. At age 14 years, he began to complain of **abdominal pain every few months**, sometimes accompanied by **vomiting** and, more rarely, by **clear**, **watery diarrhea.**

Richard's mother had taken him at 4 years of age to an immunologist, who listened to the family history and immediately **suspected hereditary angioedema**. The diagnosis was confirmed on measuring key complement components. **C1INH levels were 16% of the normal mean** and **C4 levels were markedly decreased**, while **C3 levels were normal.**

When Richard turned up for a routine visit to his immunologist a few weeks after his surgical misadventure, the immunologist, noticing Richard's large abdominal scar, asked what had happened. When Richard explained, **he prescribed daily doses of Winstrol {stanozolol)**. This caused a marked diminution in the frequency and severity of Richard's symptoms. When Richard was 20 years old, **purified C1INH became available**; he has since been infused intravenously on several occasions to alleviate severe abdominal pain, and once for swelling of his uvula, pharynx, and larynx. The infusion **relieved his symptoms within 25 minutes.**

Richard subsequently **married and had two children**. The **C1INH** level was found to be **normal** in both newborns.

Questions???

Thank You!