Fontes:
Janeway's Immunobiology
Abbas: Imunologia Celular e Molecular
Bellanti Immunology IV
Literatura corrente

Reações de Hipersensibilidade Tipos II e III

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Na guerra nunca existem soldados sem ferimentos
José Narosky

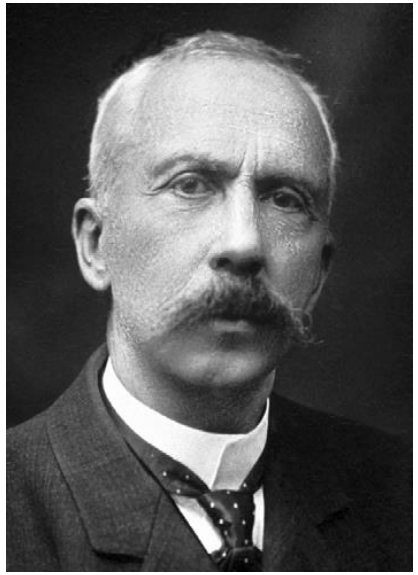
Desenvolvimento do conceito de hipersensibilidade immune – Aspectos históricos

Final do século 19: **a resposta immune é perfeita** e incapaz de causar mal ao hospedeiro

- "Fenômeno de Koch": dano tecidual em animais infectados com Mtb quando são inoculados com bacilos de Mtb
  - Koch atribuía o fenômeno a excesso de alguma toxina bacilar e não a resposta excessiva do hospedeiro ao Mtb
- Emil von Behring; Charles Richet e Jules Hericourt: descrevem respostas severas a segundas doses de toxinas que, de tão baixas, não causavam efeito algum em animais virgens de exposição às toxinas
  - Animais eram "hipersensíveis" .... à toxina.

1902 - Richet e Paul Portier desconfiam que a resposta immune era a causa da hipersensibilidade

Prova: mostram que o soro de animais imunizados e hipersensíveis transferia a hipersensibilidade a animais virgens de exposição



Anafilaxia
Ana = oposto
Phylaxis = proteção

Charles Richet 1850-1935
Prêmio Nobel de 1913 pela descoberta da anafilaxia

Anafilaxia: a reação por vezes letal de um indivíduo pré-sensibilizado a um antígeno a uma segunda e pequena dose do mesmo antígeno

1903 - Maurice Arthus: injeções repetidas de soro de cavalo em coelhos resultam em infiltrado neutrofílico, hemorragia e necrose no local das injeções.

1906 - Clemens von Pirquet e Bela Schick: sintomas similares, porém sistêmicos em pacientes que receberam soro de cavalo anti-diftérico

- DOENÇA DO SORO

von Pirquet demonstrou que imunidade e hipersensibilidade eram causadas pelo mesmo mecanismo

Alergia para designar reatividade alterada

Allos = outro

Ergon = trabalho

"Anergia para designar falta de reatividade

Hipersensibilidade:

...uma resposta imune normalmente benéfica que passa a ser a causa de doença

... antígenos alvejados na resposta podem ser estranhos ao organismo ou próprios; muitas vezes são inócuos

...A damage to host mediated by preexisting immunity to self or foreign antigen

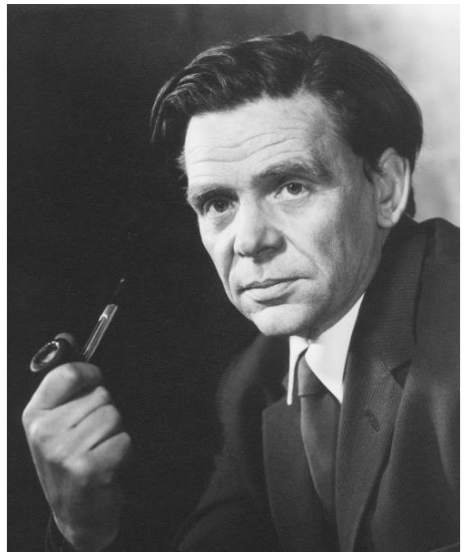
FATORES ASSOCIADOS A ALERGIA

- Fatores genéticos
- Idade
- Aleitamento materno
- Fatores emocionais
- Poluentes e exposição ambiental
- Infecções
- Estilo urbano
- Microbiota

The Gell-Coombs classification of hypersensitivity reactions

.... connotation of deleterious responses with no known function in homeostasis

Robin Coombs



Phillip Gell

Types of hypersensitivity reactions

Type I:	anaphylactic or immediate
Type II:	cytotoxic
Type III:	Immune complex
Type IV:	cell mediated or delayed

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Type IVa	Th1 cell-mediated reactions macrophage activation	Type 1 diabetes and contact dermatitis (with IVc)
Type IVb	Th2 cell–mediated reactions eosinophilic inflammation	Persistent asthma and allergic rhinitis
Type IVc	Cytotoxic T cell-mediated (perforin/granzyme B involved)	Stevens-Johnson syndrome and TEN
Type IVd	T-cell-mediated neutrophilic inflammation	AGEP and Behcet disease

Source: Adapted from Ref. 2.
AGEP = acute generalized exanthematous pustulosis; TEN = toxic epidermal keratinocytes.

Classifications of hypersensitivity reactions should describe diseases in terms of **immunopathological origin** and/or **mechanism of injury**

J. Descotes, G. Choquet-Kastylevsky:
Gell and Coombs's classification: is it still valid?

The four 'types' of hypersensitivity reactions of the Gell-Coombs classification describe the **strategies that the body uses in order to combat classes of infectious agents**

T.V. Rajan
A re-interpretation

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Extracellular, indigestible agents, such as *Mycobacterium tuberculosis*, Schistosome eggs	Not included	Formation of granulomas that encapsulate and isolate the pathogen. Driven by innate immunity ('foreign body') or type 1 (*M. tuberculosis* infections) or type 2 (Schistosome eggs) cytokines	Sarcoidosis?

TYPE II HYPERSENSITIVITY REACTIONS

Gell-Coombs:
Type II hypersensitivity reactions are characterized by antigen-antibody interactions, resulting in the local production of … C5a, … recruitment of … PMNs and subsequent tissue injury

T.V. Rajan:
Strategy used by the mammalian organism to deal with small extracellular pathogens that can be successfully ingested and subsequently killed by PMNs.

Type II hypersensitivity reactions are host-destructive only when they occur inappropriately:

… more intensely than designed

… as a result of a misperception of the presence of a foreign invader, even although there is no real threat

Os componentes efetores da Resposta Imune normalmente participam da imunidade protetora contra infecções.

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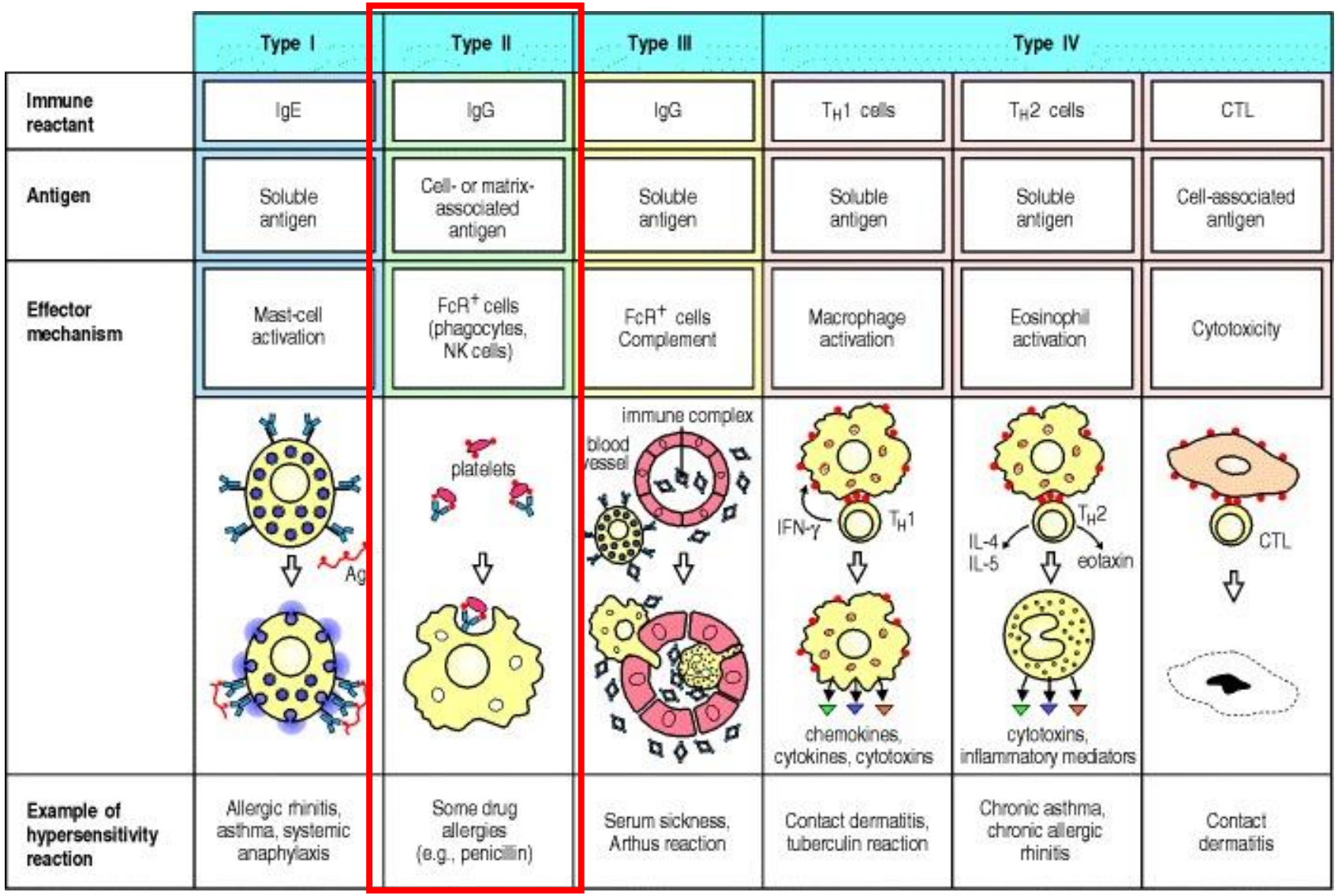
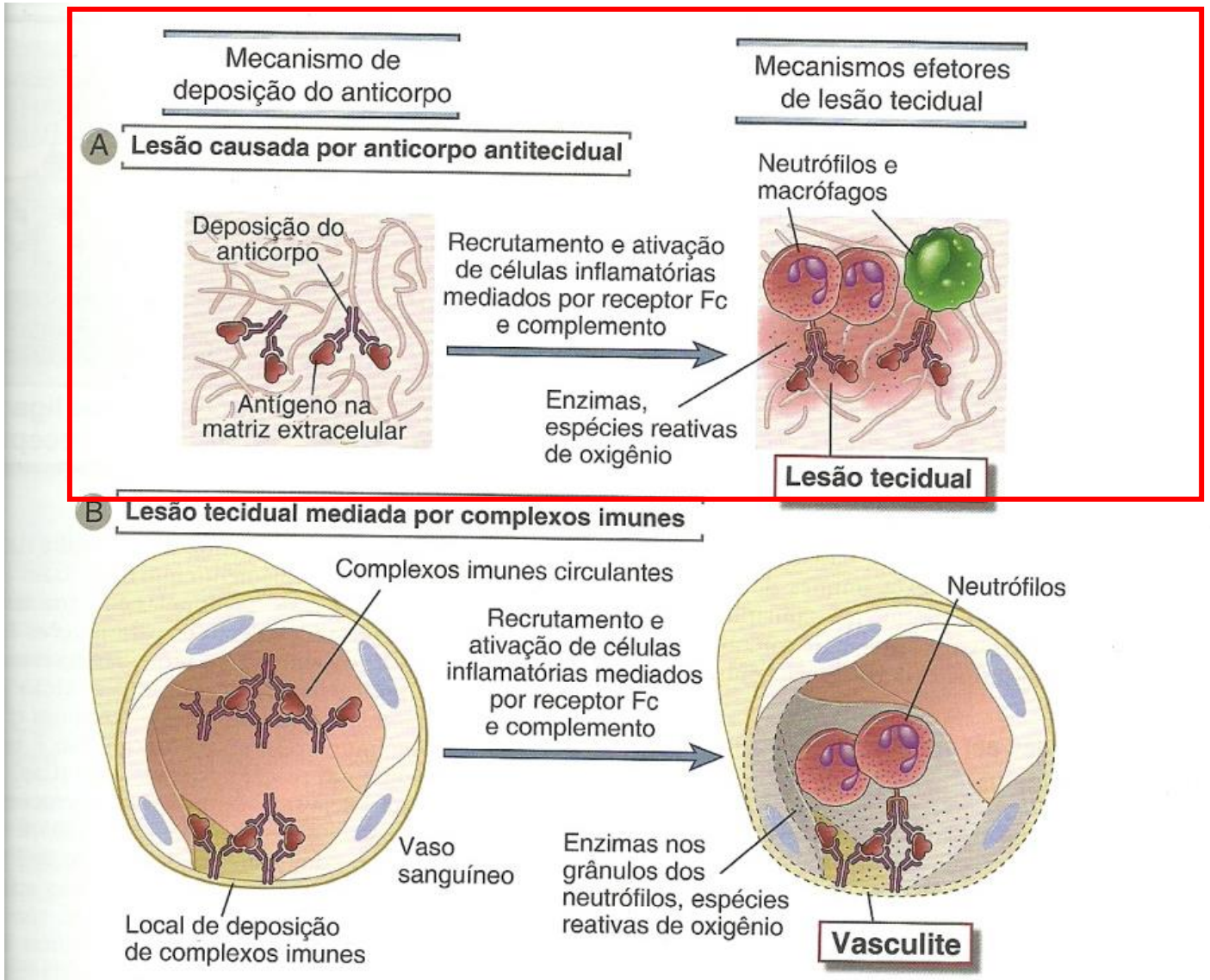


Hipersensibilidades tipo II e III



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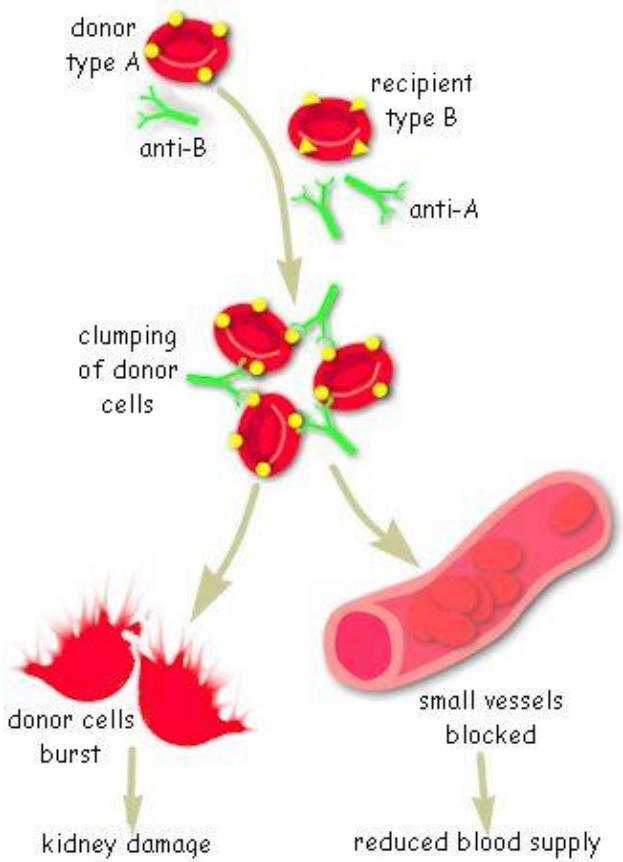
Type IIa Hypersensitivity: Antibody-mediated cytotoxicity

- Results when **IgG or IgM bind to cell surface antigens**
  - Activating **Complement**
  - Binding Fc receptors on Tc cells promoting **ADCC**
- Both processes result in lysis of the Ab-coated cell
- Clinical examples of Type II responses include:
  - Certain autoimmune diseases where Ab's produced vs membrane Ag's
    - Grave's Disease – Ab's produced against thyroid hormone receptor
    - Myasthenia Gravis – Ab's produced against acetylcholine receptors
    - Autoimmune hemolytic anemia – Ab's produced against RBC membrane Ag's
  - Hemolytic Disease of the Newborn
  - Hyperacute graft rejection
    - Blood Transfusion Reactions
    - Graft rejection

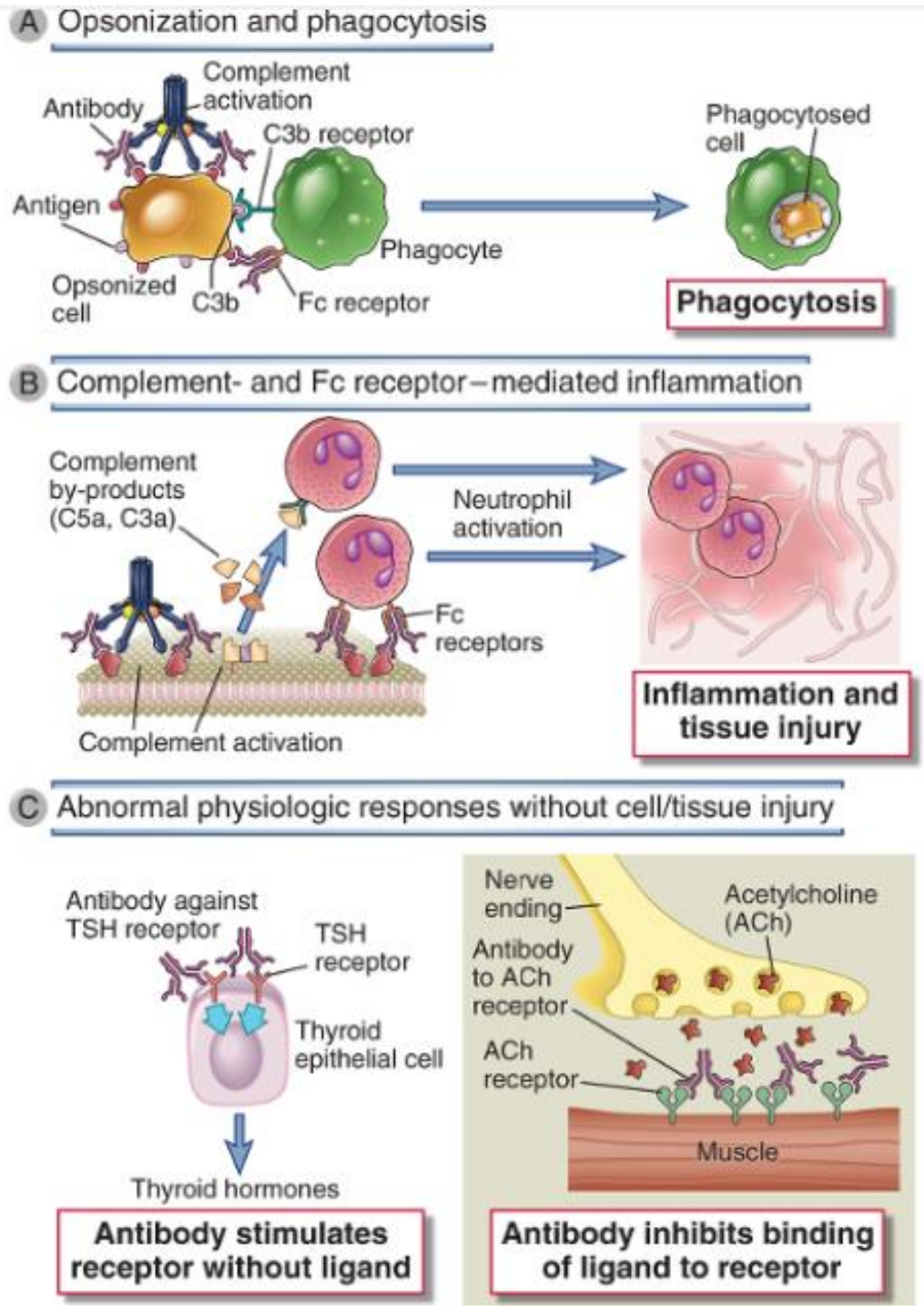
Type II Hypersensitivity: Transfusion reactions



- Produced by mismatched blood types
  - Destroys foreign RBC by complement-mediated lysis triggered by IgG
    - Produces fever, intravascular clots, lower back pain, Hgb in urine
  - Free Hgb produced has 2 fates:
    - passes to the kidneys – hemoglobinuria
    - Breaks down to bilirubin …can be toxic

Type II Hypersensitivity:
Drug-induced hemolytic anemia

- Drugs such as aspirin and antibiotics can bind to the surfaces of RBC's
- These interactions act similar to hapten-carrier conjugate
- Such complexes can trigger Ab-mediated cell lysis by complement activation



Type IIb Hypersensitivity:

Antibody-mediated **stimulation**

Hipersensibilidade tipo II:

mediada por anticorpos contra antígenos teciduais (células e matriz) do paciente

TABELA 18–2 Exemplos de Doenças Causadas por Anticorpos Específicos Celulares ou Teciduais

Doença	Antígeno-alvo	Mecanismos de Doença	Manifestações Clinicopatológicas
Anemia hemolítica autoimune	Proteínas da membrana de eritrócitos (antígenos do grupo sanguineo Rh, antígeno I)	Opsonização e fagocitose de eritrócitos, lise mediada pelo complemento	Hemólise, anemia
Púrpura trombocitopênica autoimune	Proteínas da membrana de plaquetas (integrina gpIIb-IIIa)	Opsonização e fagocitose de plaquetas	Sangramento
Pênfigo vulgar	Proteínas nas junções intercelulares de células epidérmicas (desmogleína)	Ativação de proteases mediada por anticorpos, interrupção de adesões intercelulares	Vesículas cutâneas (bolhas)
Vasculite causada por ANCA	Proteínas granulares de neutrófilos, presumivelmente liberadas por neutrófilos ativados	Degranulação de neutrófilos e inflamação	Vasculite
Síndrome de Goodpasture	Proteína NC1 não colagenosa da membrana basal nos glomérulos e pulmões	Inflamação mediada por receptor Fc e complemento	Nefrite, hemorragia pulmonar
Febre reumática aguda	Antígeno da parede celular de estreptococos; anticorpos com reação cruzada com antígenos miocárdicos	Inflamação, ativação de macrófagos	Miocardite, artrite
Miastenia grave	Receptor de acetilcolina	Anticorpos inibindo a ligação da acetilcolina, receptores submodulados	Fraqueza muscular, paralisia
Doença de Graves (hipertireoidismo)	Receptor de TSH	Estimulação mediada por anticorpos de receptores de TSH	Hipertireoidismo
Diabetes resistente à insulina	Receptor de insulina	Anticorpos inibindo a ligação da insulina	Hiperglicemia, cetoacidose
Anemia perniciosa	Fator intrínseco de células parietais gástricas	Neutralização do fator intrínseco; absorção de vitamina B_{12} diminuída	Eritropoiese anormal, anemia

ANCA, anticorpos citoplasmáticos antineutrófilos; TSH, hormônio estimulante da tireoide.

TYPE III HYPERSENSITIVITY REACTIONS

Gell-Coombs:
Type III hypersensitivity reactions occur when antibody reactions occur …, resulting in the formation of antigen–antibody complexes…

T.V. Rajan (infectocentric view):
Strategy used to handle circulating viral particles.

In nature, the antigen–antibody reactions occurring in the bloodstream during the viremic phase would prevent the virus from reaching potential target cells and causing further damage.

Type III hypersensitivity reactions become deleterious when the demands exceed the capacity of the system

Os componentes efetores da Resposta Imune normalmente participam da imunidade protetora contra infecções.

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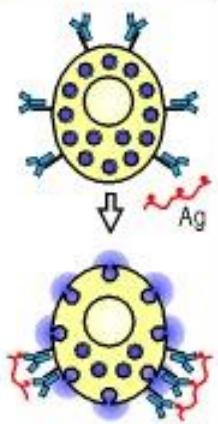
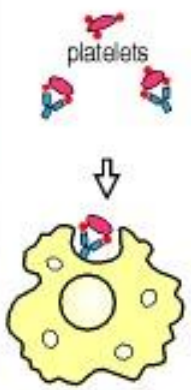
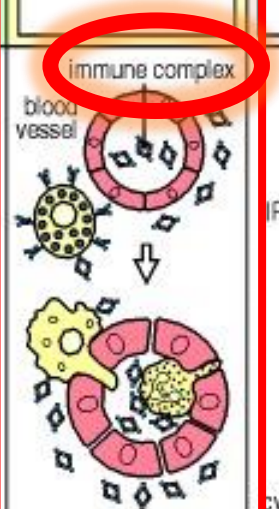
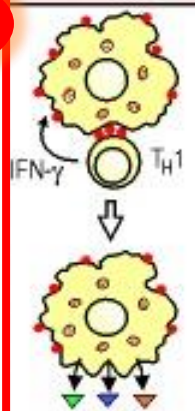
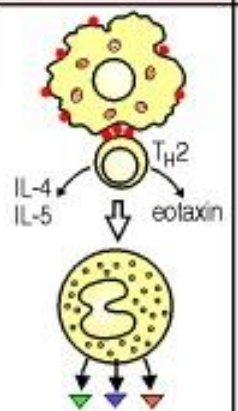
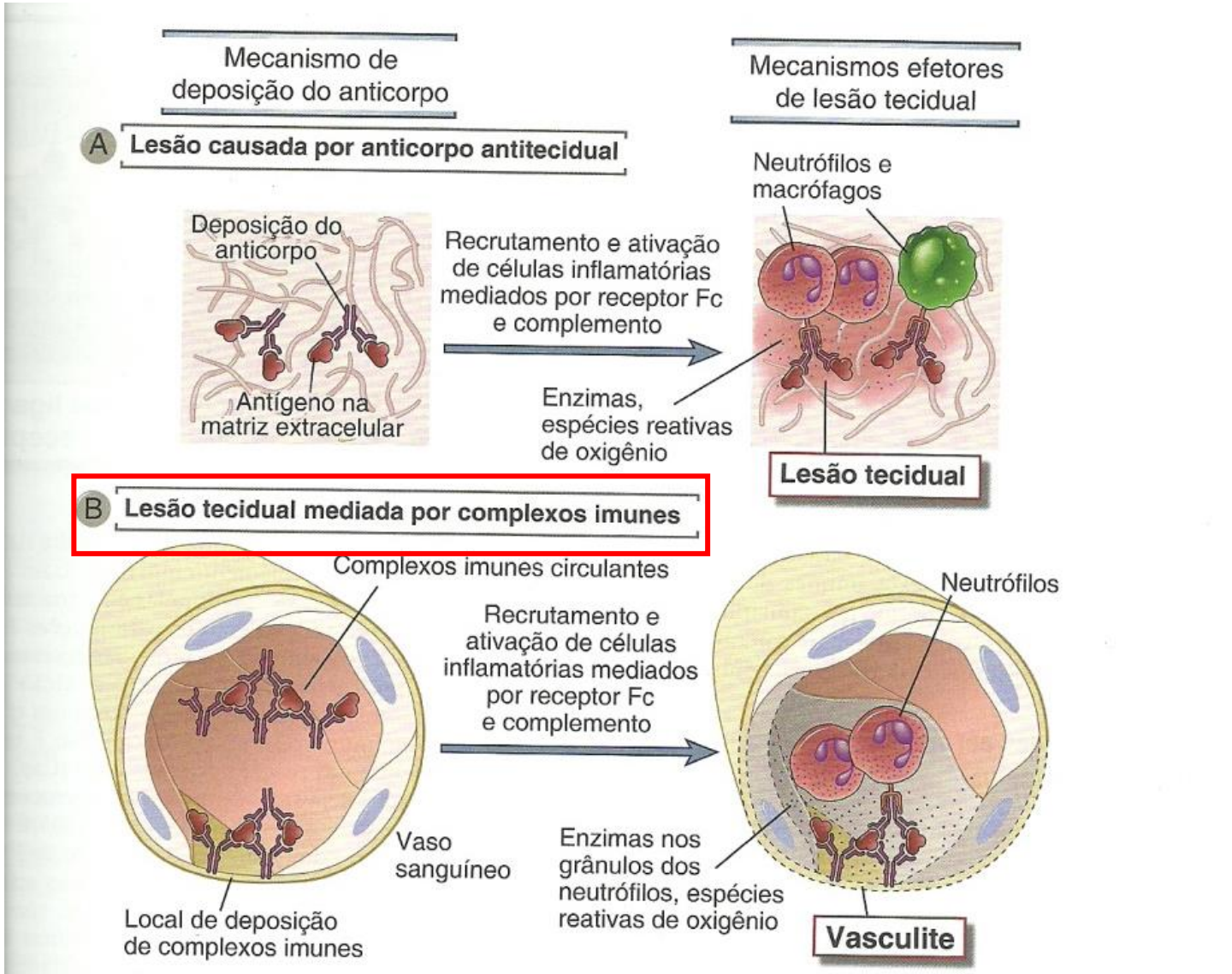
	Type I	Type II	Type III	Type IV		
Immune reactant	IgE	IgG	IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	FcR^+ cells (phagocytes, NK cells)	FcR^+ cells Complement	Macrophage activation	Eosinophil activation	Cytotoxicity
						
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g., penicillin)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

Hipersensibilidades tipo II e III



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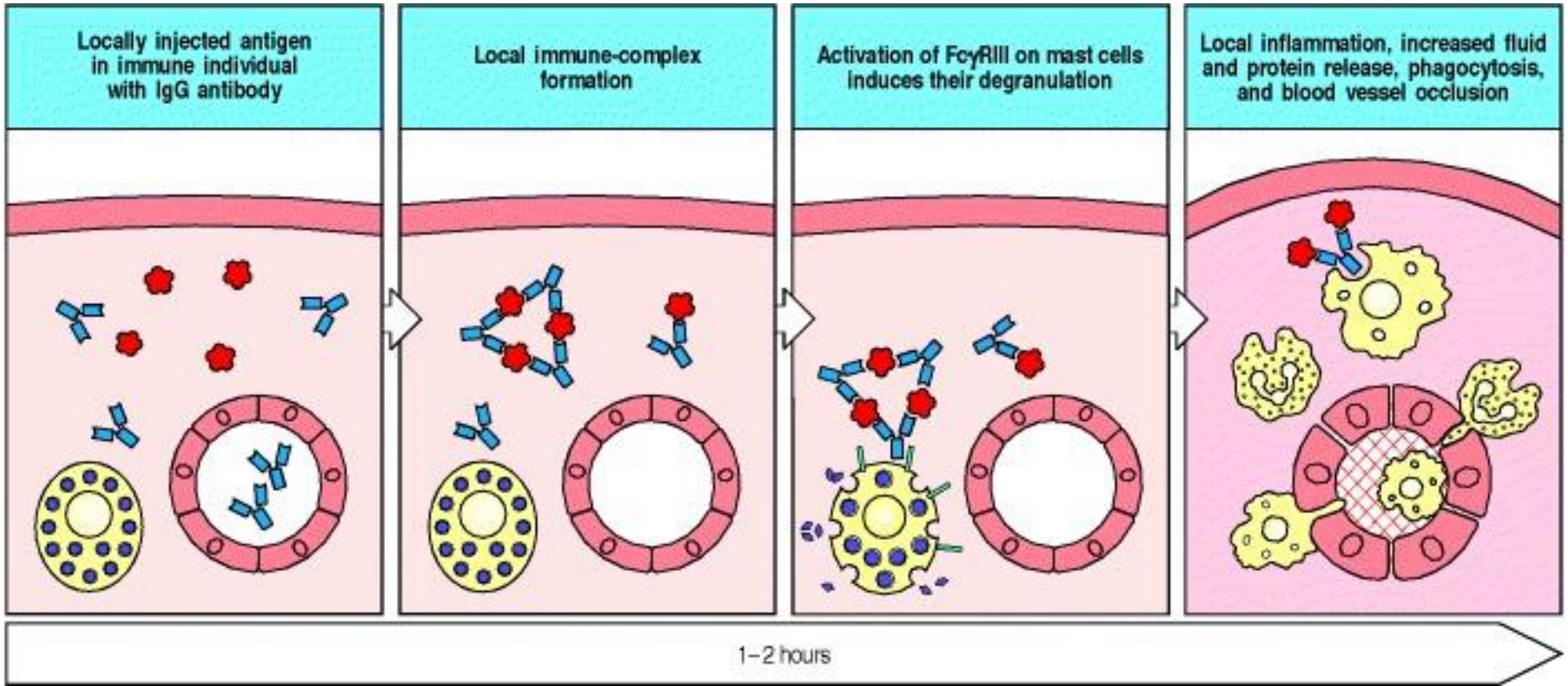
Hipersensibilidade tipo III

O depósito de complexos imunes em tecidos causam reação inflamatória local – Reação de Arthus



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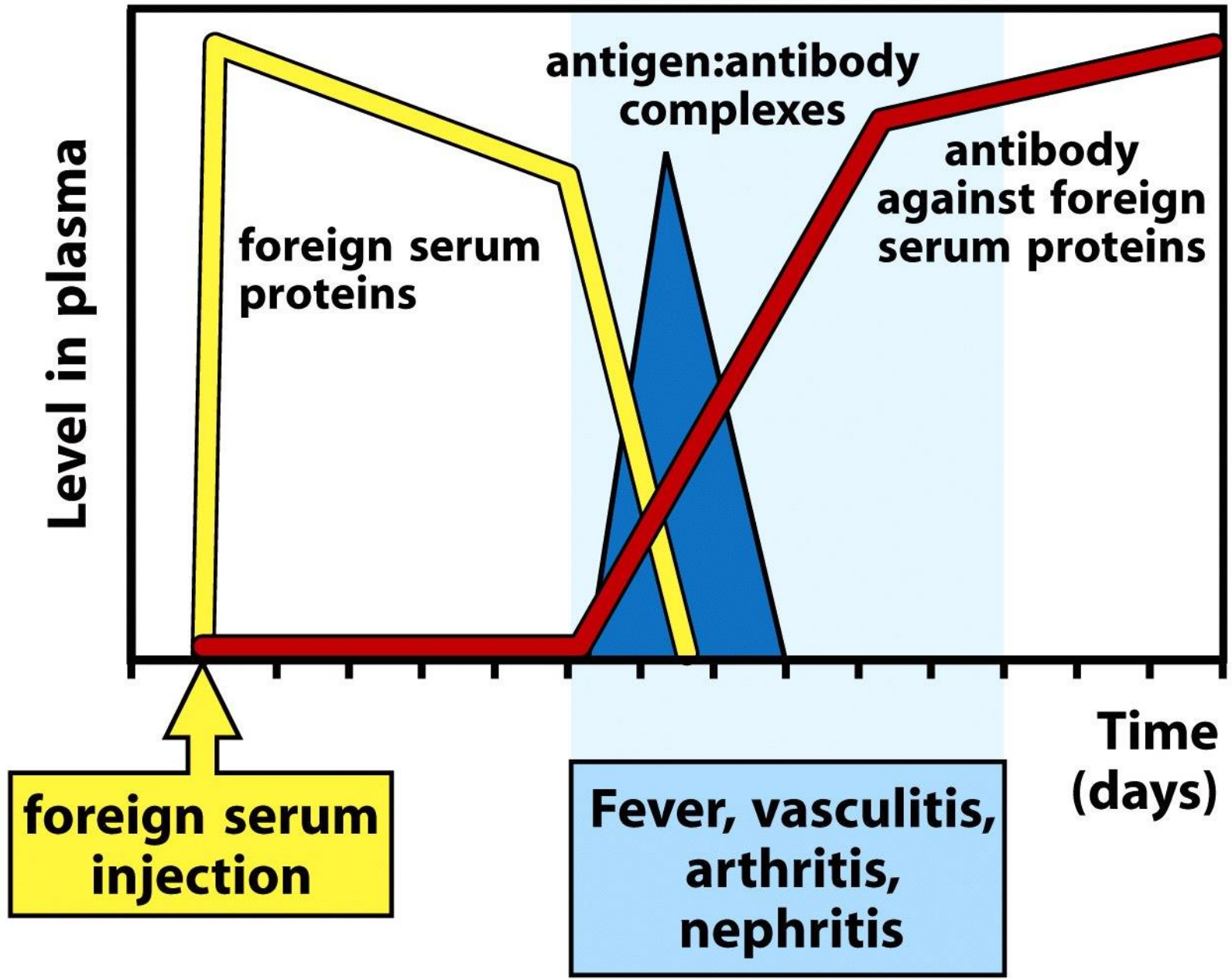
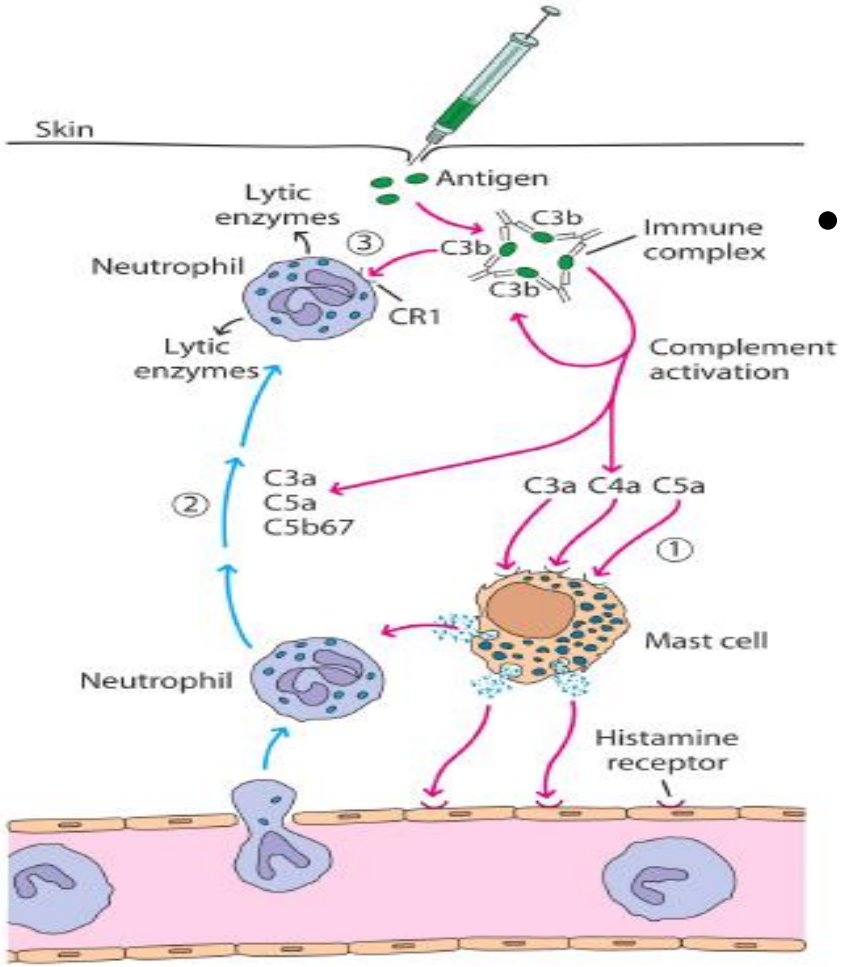


Figure 13-27 Immunobiology, 7ed. (© Garland Science 2008)

Type III Hypersensitivity: Localized type III reactions



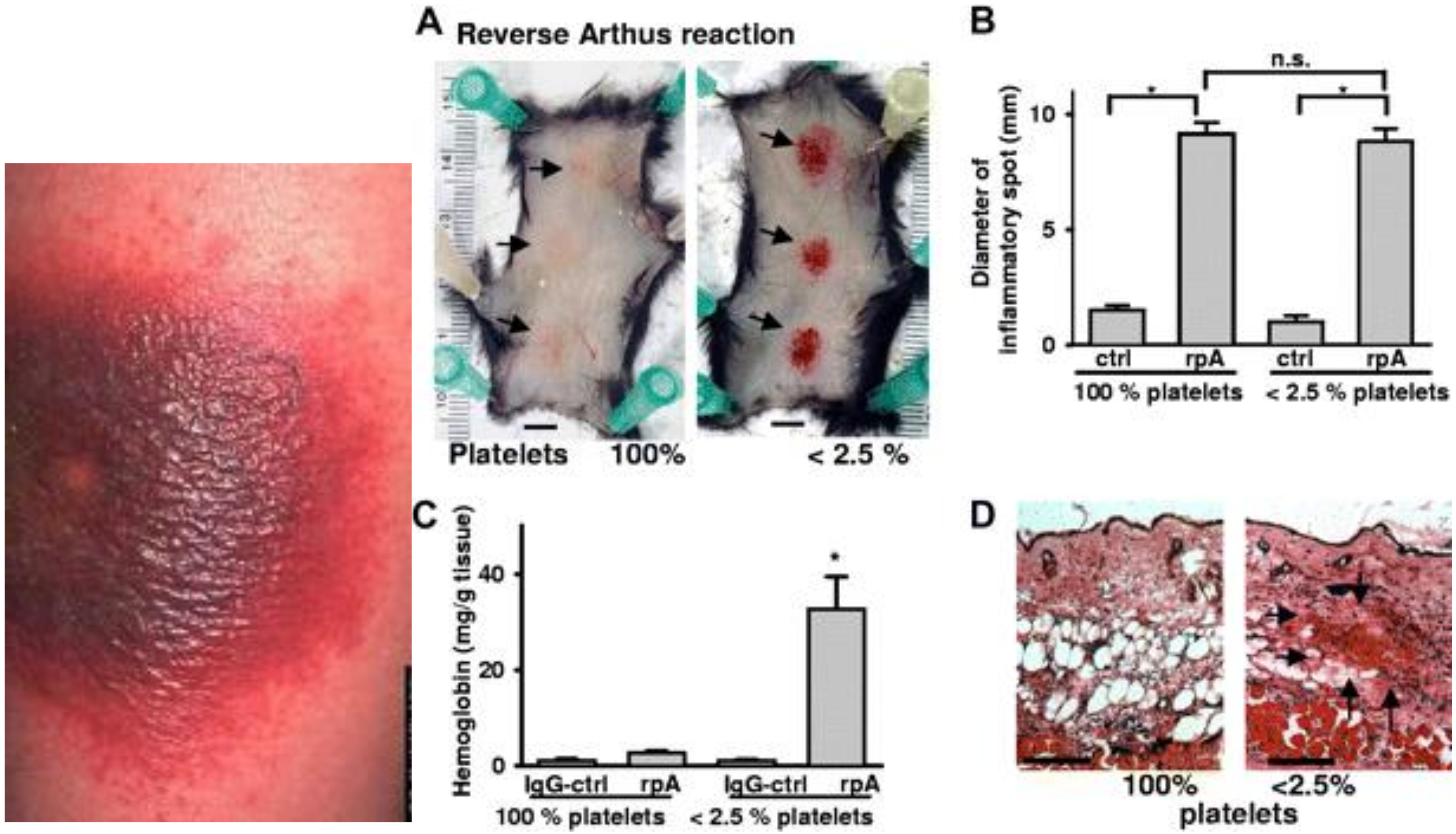
- Arthus reactions:
  - Exposure to an Ag for which there already is a high concentration of Ab
  - Produces edema/erythema from damage to blood vessels and tissues
    - Insect bites
    - Inhalation of bacteria, fungi, dried fecal matter
      - Farmer's lung
      - Pigeon breeder's lung

Arthus reactions have been infrequently reported after vaccinations containing diphtheria and tetanus toxoid. The CDC's description:

Arthus reactions (type III hypersensitivity reactions) are rarely reported after vaccination and can occur after tetanus toxoid–containing or diphtheria toxoid–containing vaccines. An Arthus reaction is a local vasculitis associated with deposition of immune complexes and activation of complement. Immune complexes form in the setting of high local concentration of vaccine antigens and high circulating antibody concentration. Arthus reactions are characterized by severe pain, swelling, induration, edema, hemorrhage, and occasionally by necrosis. These symptoms and signs usually occur 4–12 hours after vaccination.

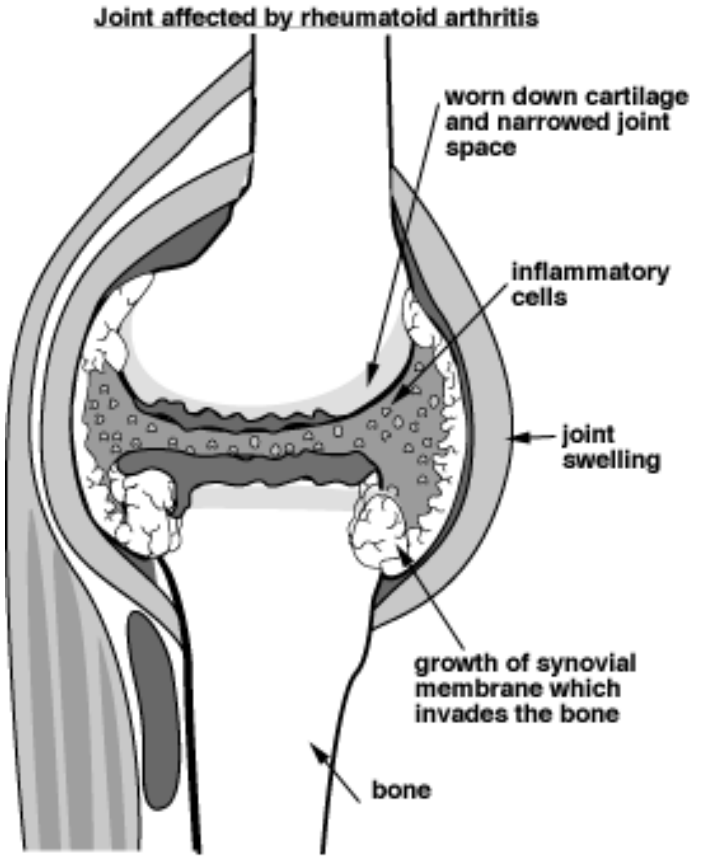
ACIP has recommended that persons who experienced an Arthus reaction after a dose of tetanus toxoid–containing vaccine **should not receive Td more frequently than every 10 years**, even for tetanus prophylaxis as part of wound management.

Advisory Committee on Immunization Practices do CDC

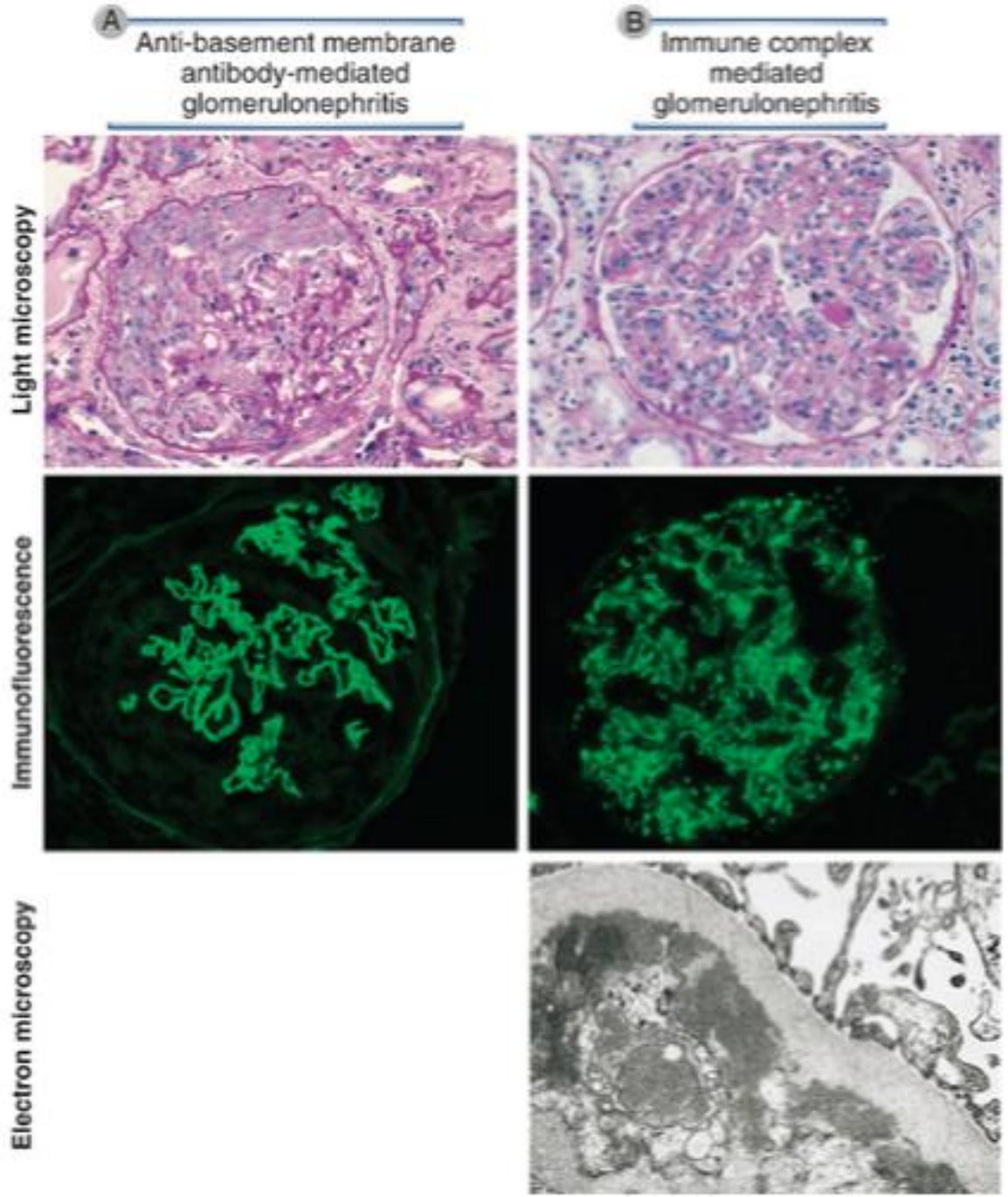


Participação de plaquetas para conter hemorragia na reação de Arthus
Reação tipo III localizada (e.g., picadas de insetos)

Type III Hypersensitivity: Systemic (generalized) reactions



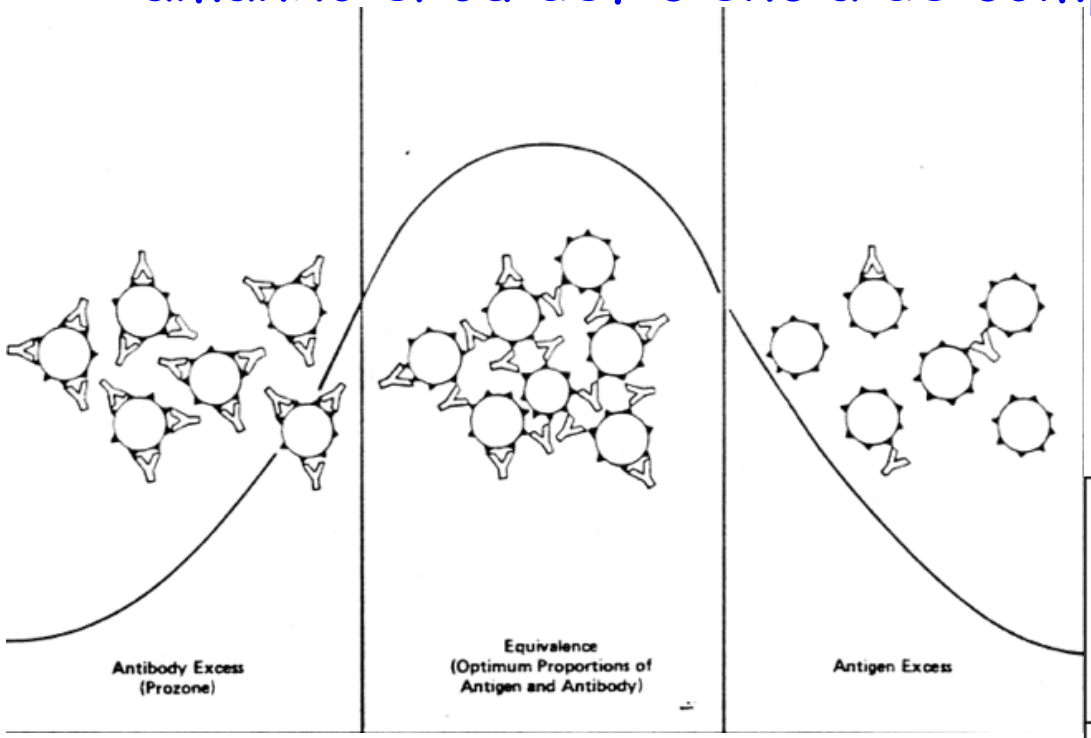
- Produced when large amounts of Ag enter the bloodstream
  - The sites of deposition vary; usually in tissues where plasma is filtered
  - Esp. in kidneys, blood vessels, and joints
- Can cause tissue damaging reactions:
  - Serum sickness
  - Autoimmune diseases
  - Drug reactions
  - Infectious diseases

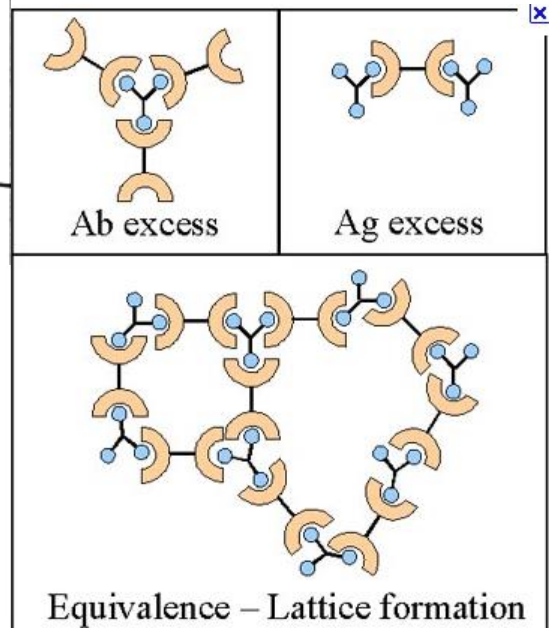


Reações de Hipersensibilidade Tipo II e III

Os Complexos Imunes: quando viram um problema

Tamanho e/ou deficiência de complemento





Excesso
de anticorpo
PROZONA

Equivalência
REDE INSOLÚVEL

Excesso
de antígeno
PÓSZONA

Complexos solúveis

Miller and Nussenzweig:

Binding of complement to antigen–antibody complexes has an unexpected result:
Binding of excess complement (primarily C3) to preformed antigen-antibody complexes results in their disaggregation into smaller entities that no longer bind more complement.

Takahashi:

Further showed that these complexes do not activate the lytic components of complement and do not release anaphylotoxins.
He also showed that these smaller complexes can be ingested by the reticulo-endothelial system, the complex of littoral macrophages in the spleen and liver, and eliminated.

Thus, the formation of antigen–antibody complexes has a **host protective** response and is perhaps the ideal one to eliminate circulating viral particles.

Clinicians have long noted that renal disease in systemic lupus erythematosis (SLE) is inversely related to complement levels

Proc. Nat. Acad. Sci. USA
Vol. 72, No. 2, pp. 418–422, February 1975

A New Complement Function: Solubilization of Antigen–Antibody Aggregates

(immune-complexes/immune-complex diseases)

GARY W. MILLER* AND VICTOR NUSSENZWEIG

The Department of Pathology, New York University School of Medicine, New York, N.Y. 10016

Communicated by Michael Heidelberger, November 11, 1974

Quanto mais complemento, mais solúvel fica o complexo imune

Evita deposição em locais inapropriados

Facila depuração pelo SRE

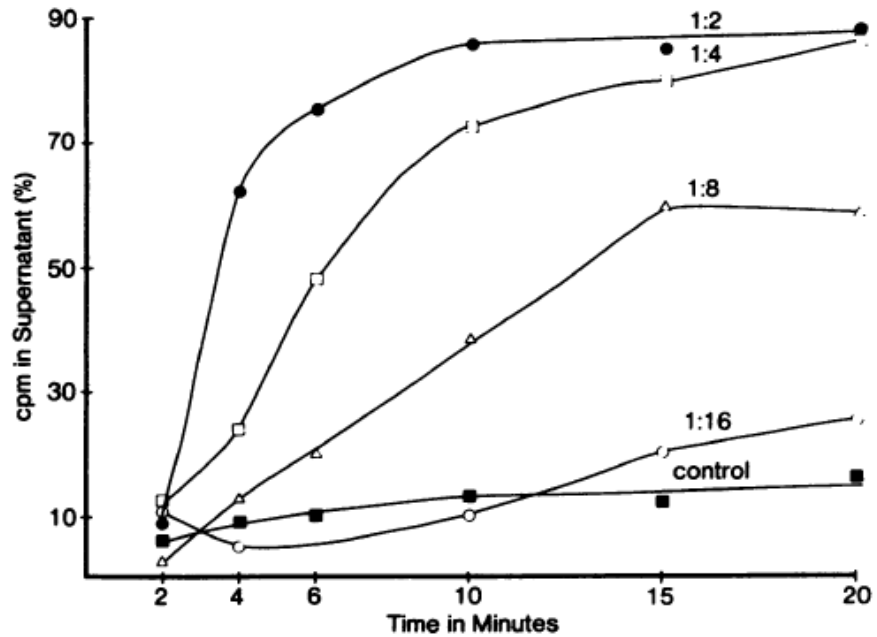


FIG. 1. Solubilization of an immune precipitate by normal serum. An immune precipitate was prepared from ^{125}I-labeled bovine serum albumin and mouse Ab against bovine serum albumin at equivalence, and 25 μl of the suspension was added to 200 μl of 1:2, 1:4, 1:8, and 1:16 dilutions of normal mouse serum, and to 200 μl of 1:2 dilution of heat-treated mouse serum (56°, 30 min). Samples were taken from the mixtures after various times at 37°, diluted, centrifuged, and counted.

TABELA 18–3 Exemplos de Doenças Humanas Mediada por Complexos Imunes

Doença	Antígeno Envolvido	Manifestações Clinicopatológicas
Lúpus eritematoso sistêmico	DNA, nucleoproteínas, outros	Nefrite, artrite, vasculite
Poliarterite nodosa	Antígeno de superfície do vírus da hepatite B	Vasculite
Glomerulonefrite pós-estreptocócica	Antígenos da parede celular de estreptococos; pode ser "plantado" na membrana basal do glomérulo	Nefrite
Doença do soro	Proteínas variadas	Artrite, vasculite, nefrite

EM RESUMO:

A formação de complexos imunes no ambiente dos vasos sanguíneos serve para depurar partículas virais e outros antígenos solúveis.

A eficácia da depuração depende da solubilidade do complexo imune e da disponibilidade de receptores Fc em células do SER e de complemento

(neste caso o complemento solubiliza os complexos grandes sem produzir os fragmentos de anafilotoxinas e quimiotáticos e os componentes líticos)

... Excesso de complexos imunes solúveis causa doença

Porque podem exceder a capacidade do SER e/ou do sistema complemento que solubiliza os agregados de complexos imunes insolúveis

... Complexos imunes em grandes agregados causa doença

Porque o tamanho do complexo imune afeta sua hemodinâmica
Mas podem ser depurados no baço

Alergias Alimentares

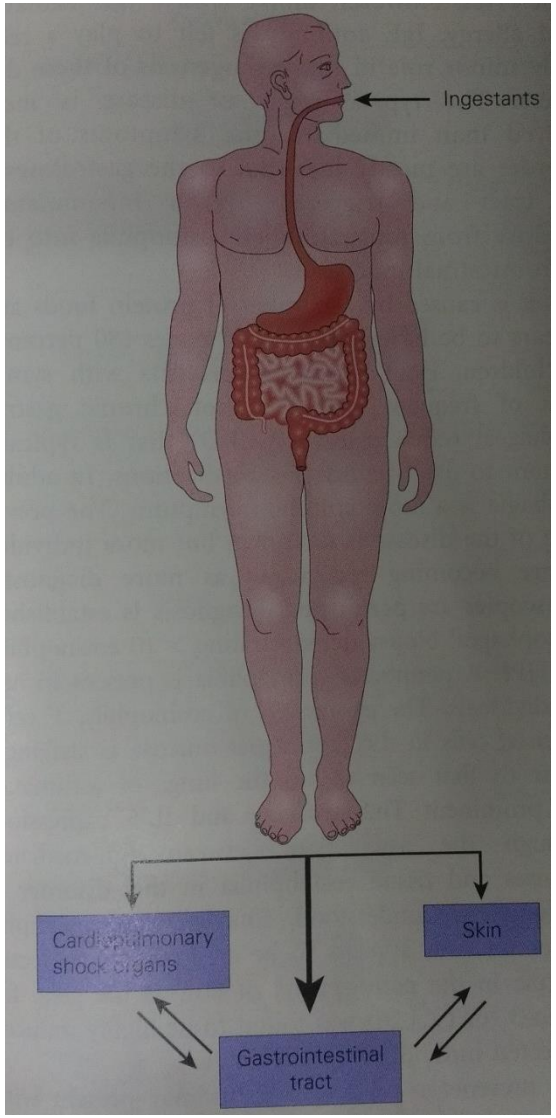
Alergia gastrointestinal: hipersensibilidade manifestada contra certos componentes exógenos, geralmente alimentos, introduzidos no TGI

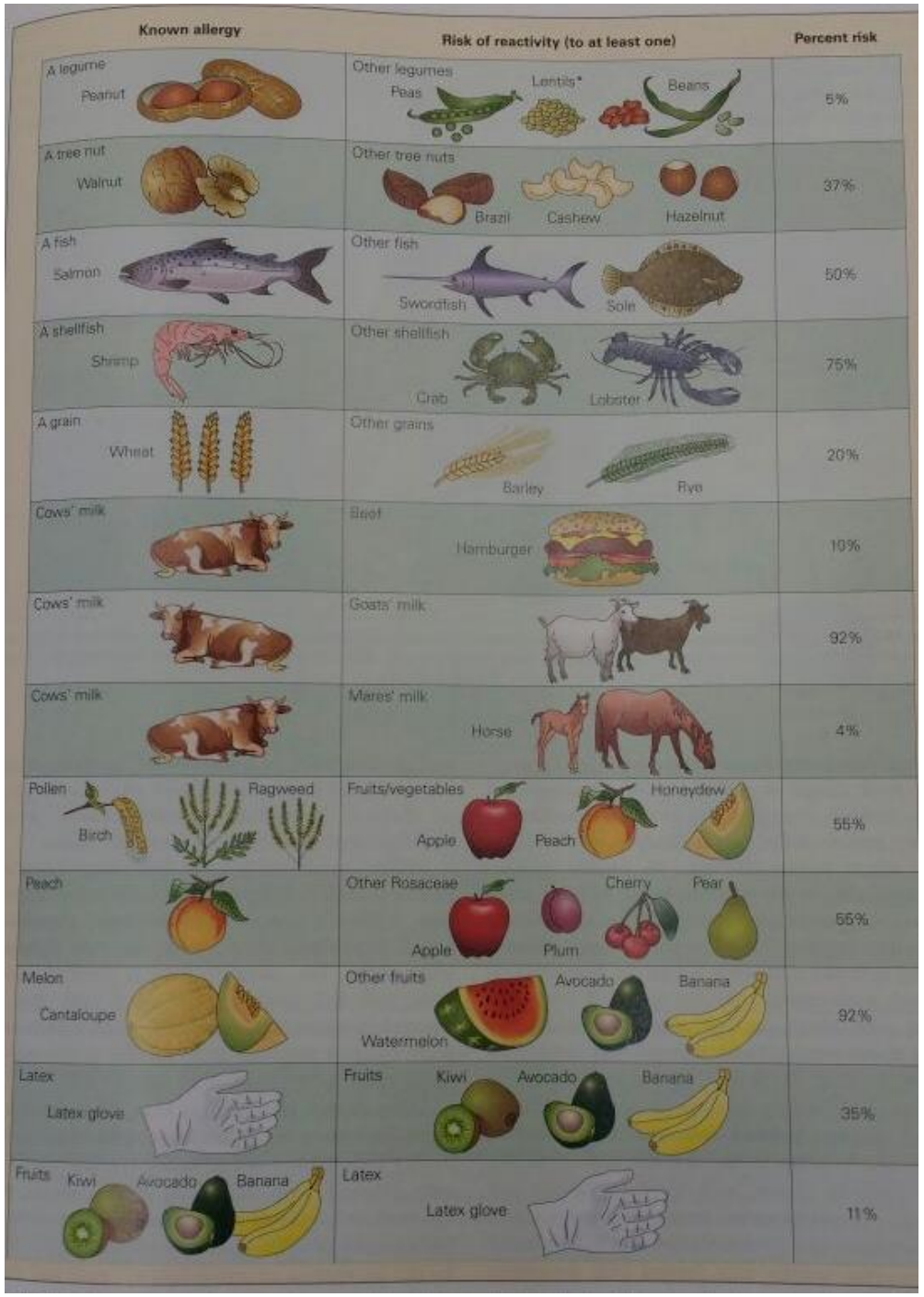
Efeito adverso na saúde causado por resposta immune que ocorre sempre quando há exposição a determinado componente de alimento

Envolve IgE e outros componentes da resposta immune

Afeta o TGI, mas quando envolve IgE pode afetar os três órgãos de choque: pele e trato cardiopulmonar, além de intestino.

Não confundir com intoxicação alimentar (e.g., ação de toxina - superantígeno estafilocócico), intolerância alimentar (lactose)





Por que certos componentes de alimentos são alérgenos?

Controvertido se é causado por menor digestibilidade

Mais comuns:
Ovos, leite, amendoim, nozes, trigo, peixes e moluscos

Frutas (não confundir com fitofotosensibilização)
Aves...

Existe reativdade cruzada entre categorias de alérgenos, com graus diferentes de risco conforme a categoria

Doenças associadas com alergia alimentar de acordo com o MALT específico e órgãos afetados

Mediadas por IgE; respostas mistas; independente de IgE (anticorpos IgG e IgA e linfócitos T)

Immunologic mechanism	Affected MALT system	Target organ	Clinical disorder
IgE	GALT	GI tract	Immediate GI hypersensitivity; OAS
	SALT	Skin	Acute urticaria; angioedema
	BALT	Respiratory tract	Bronchospasm; asthma; anaphylaxis
Non-IgE (including cell-mediated)	GALT	GI tract	Celiac disease; cow's milk enteropathy; dietary protein enterocolitis; breast milk colitis; proctocolitis; proctitis
	SALT	Skin	Dermatitis herpetiformis
	BALT	Respiratory tract	Heiner syndrome
	NALT	CNS	Behavioral disorders *
Mixed IgE and non-IgE	GALT	GI tract	Eosinophilic esophagitis (EOE)
			Eosinophilic gastroenteritis (EG)
	SALT	Skin	Atopic dermatitis
	BALT	Respiratory tract	FA-induced bronchial asthma

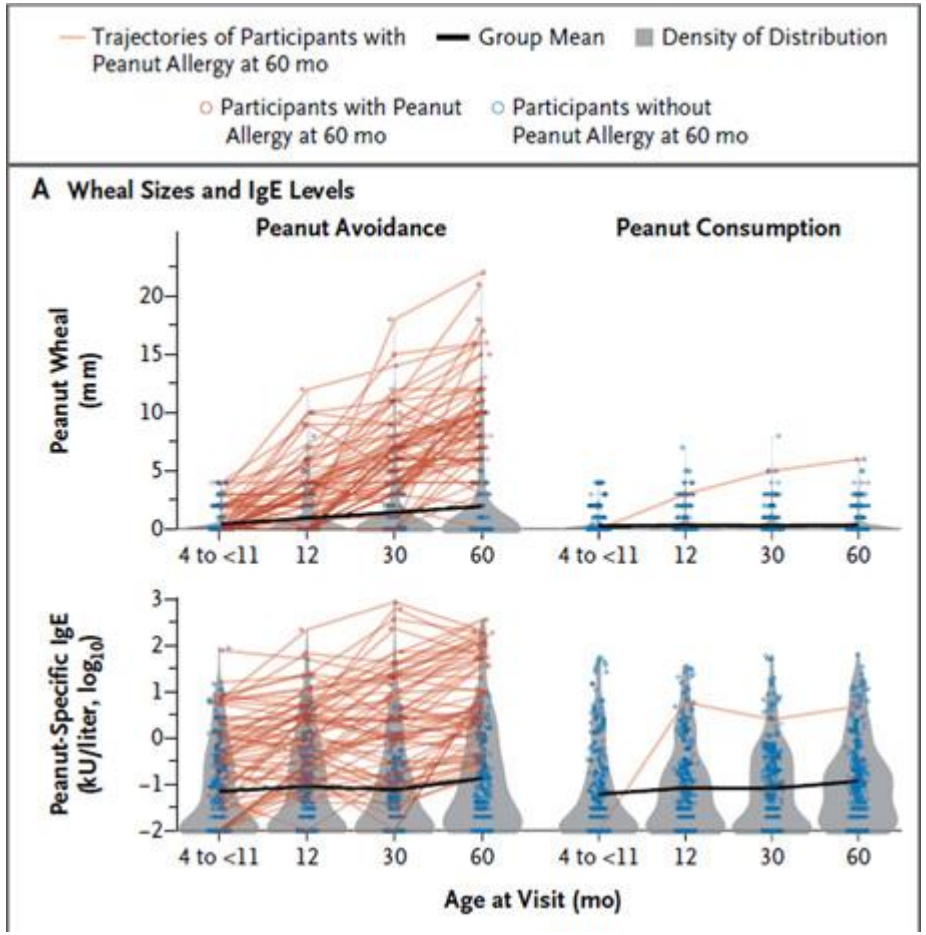
Sabra S. IgE and non-IgE food allergy. Ann Allergy

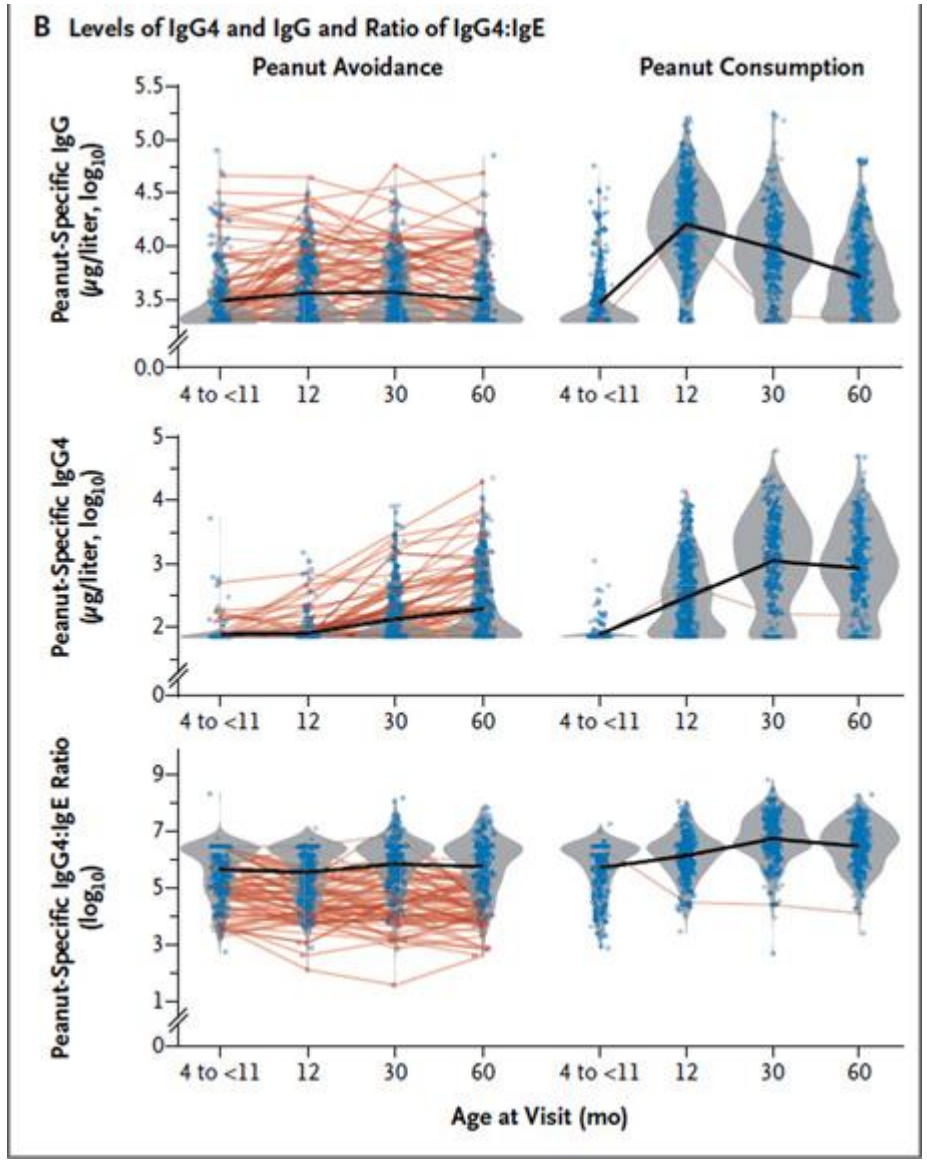
GALT: tecido linfóide associado ao trato gastrointestinal
SALT: tecido linfóide associado à pele
BALT: tecido linfóide associado a brônquios

* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5390324/
low–fermentable oligo-, di-, and monosaccharide and polyol (FODMAP) diet

A distinct subset of patients with pulmonary hemosiderosis has hypersensitivity to cow's milk which result in formation of IgG antibodies against basement membrane. This is called **Heiner syndrome**. Mechanism of haemorrhage is similar to that observed in Goodpasture syndrome.


במבה
חטיף בוטנים


Trajectories of Participants with Peanut Allergy at 60 mo
Group Mean
Density of Distribution
Participants with Peanut Allergy at 60 mo
Participants without Peanut Allergy at 60 mo
A Wheal Sizes and IgE Levels
Peanut Avoidance
Peanut Consumption
Peanut Wheal (mm)
Peanut-Specific IgE (kU/liter, log10)
4 to <11
12
30
60
Age at Visit (mo)


B Levels of IgG4 and IgG and Ratio of IgG4:IgE
Peanut Avoidance
Peanut Consumption
Peanut-Specific IgG (μg/liter, log10)
Peanut-Specific IgG4 (μg/liter, log10)
Peanut-Specific IgG4:IgE Ratio (log10)
4 to <11
12
30
60
Age at Visit (mo)

O amendoim contém ao menos 11 proteínas distintas. Essas proteínas são degradadas por enzimas dos indivíduos quando comem o amendoim e os peptídeos assim gerados podem ser reconhecidos pelo seu sistema imune. Estudos demonstram que a introdução precoce do amendoim na dieta de lactentes diminui muito a chance de desenvolverem alergia a esse alimento, mesmo naqueles lactentes que apresentam o marcador genético de risco aumentado para tal, isto é, o alelo do complexo de histocompatibilidade humano HLA-DQA1*01:02. A resposta imune que controla a alergia depende de uma mudança no padrão de imunidade específica às proteínas do amendoim.

- **A exposição precoce e continuada a alérgenos do amendoim modifica o isotipo empregado pela resposta imune anticórpica do tipo Th2, que deixa de produzir anticorpos IgE mono-específicos e passa a produzir anticorpos IgG4 bi-específicos monovalentes. Esse novo tipo de anticorpo impede que mastócitos sejam armados, desgranulem e liberem histamina quando interagem com um alérgeno do amendoim**

Na imunoterapia oral empregada para tratar alergia a amendoim, o paciente portador ingere quantidades cada vez maiores desse alimento, sendo muitas vezes medicado concomitantemente com o anticorpo monoclonal Omalizumab para prevenir reações de hipersensibilidade graves. Assinale a(s) alternativa(s) que descrevem os componentes dos mecanismos imunológicos envolvidos no tratamento da alergia ao amendoim.

- **O tipo de hipersensibilidade é classificado como tipo I e anticorpo monoclonal é específico para as estruturas Fc de IgEs circulantes solúveis e assim impede que as IgEs se liguem a receptores de Fc do tipo épsilon de mastócitos que assim não podem ser armados e nem disparados para desgranularem e liberarem mediadores vasoativos, histamina e proteases que danificam tecidos e degradam alérgenos.**