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Martin Roecken
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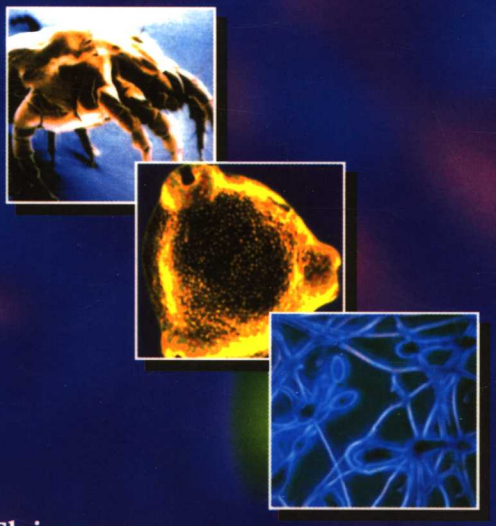
Color Atlas of Allergic Diseases

过敏性疾病彩色图谱



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Color Atlas of Allergic Diseases

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Preface

Allergies are among the most common and economically important diseases in both Europe and the United States. They have a special impact because they so frequently affect children, adolescents, and young adults actively involved in school or work. Thus it is essential that a broad spectrum of medical care providers be familiar with the principles of allergic disease.

The term *allergy* was first coined by the pediatrician Clemens von Pirquet at the beginning of the twentieth century. It has won an established place in the medical literature. The branch of medicine that deals with allergic diseases is known as allergology in Europe, and less accurately, as allergy in United States. In simplest terms, this field deals with the diagnosis and treatment of undesirable, usually excessive, immune reactions to environmental products. Some of the important immunological concepts that have helped form our current concept of allergic disease include the description of immediate and delayed hypersensitivity, the role of immunoglobulin (Ig) E in immediate reactions, the concept of atopy and atopic disease, the production of immunoglobulins by B cells, the interaction of antigen-presenting cells and T cells to produce several different immune responses, and the complex regulatory loops driven by lymphokines, chemokines, and other mediators.

Many of these advances are already familiar to every reader, as their originators have been rewarded with Nobel prizes. Today the thrust of most clinical and laboratory research is for better understanding of the complex regulatory processes that control immune reactions and that can be misdirected to produce allergic diseases.

There is no shortage of literature on allergic diseases. There are superb introductory and advanced textbooks of immunology; some emphasize basic science findings, others concentrate on clinical aspects. In addition, there are innumerable clinical and basic journals documenting the explosion of knowledge in this area over the past few decades.

Our goal has been to produce something slightly different—a simple, clear, very current view of clinical allergy and immunology that will be useful not only to medical students and practicing physicians but also to motivated 'lay' readers. We have attempted to provide a brief but solid theoretical background while at the same offering precise direct advice on clinical issues.

The responsibility for treating patients with allergic diseases is distributed differently in Europe and the United States. In many European countries, including Germany, most allergists are either dermatologists or otorhinolaryngologists, reflecting the backgrounds of the two German authors (M.R., G.G.). In the United States, most allergists are either internists or pediatricians. Independently of the specialty of the practitioner, extensive additional training in both allergy and immunology is required before one can become an allergy specialist.

The Pocket Atlas format developed so successfully by Thieme Verlag is an ideal method for transferring this information. The combination of a very brief text with the clever and didactically proven graphics seemed irresistible to us, and we hope our readers will be similarly pleased. All of the crucial information in the book is presented twice—once in text format and again in a more compact, easier to remember graphic form. Drawings and pictures, especially ones so skillfully created, convey complex interactions, such as those dominating immunology and allergy today, much more effectively than do lengthy descriptions. In addition, the requirements of the graphic artist forced us to simplify and, we hope, make more understandable a number of complex areas.

The biggest thank you for this English version goes of course to the creative illustrator, Professor Jürgen Wirth, whose illustrations serve as the backbone of this effort. We would also like to thank our German colleagues listed on the next page who helped with various sections of the German book. Their work has for the most part been incorporated into this English text, although many areas have been updated and reworked. Stephanie Engelhardt was the professional editor of the German version and without her contributions this English book would also not have been as instructive and well-structured. The clinical pictures of skin disorders are from the Department of Dermatology, Ludwig Maximilian University, Munich, Germany, where two of us (M.R., W.B.) worked together. We thank the chairman, Gerd Plewig MD, and the chief photographer, Peter Bilek, for their generous assistance.

We would also like to thank Dr. Clifford Bergman and Thieme Verlag for enthusiastically backing this new English edition. We hope we have lived up to their expectations and, most importantly, produced a book that you, the reader, will both enjoy and find useful.

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Spring 2003

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Introduction

The *Pocket Atlas of Allergy* has the goal of presenting the pathophysiology, clinical features, and therapy of allergic diseases in a compact and understandable fashion. The book should be useful not only for medical students and practicing physicians but also for colleagues in the basic sciences and even lay persons. The Pocket Atlas format of Thieme Verlag is ideal for this purpose, as the modern techniques of graphic design employed in this series are ideal for conveying complex interactions in simplified manner. The book has been carefully updated to reflect current knowledge in immunology and allergology. Many aspects of the pathogenesis, clinical features, and therapy of allergic diseases are controversial. It is impossible to discuss these complex issues completely in an introductory book of limited length. Thus, established ideas have been presented with a centrist viewpoint, hoping to provide readers with such a solid background that they can then tackle and assess complex or speculative topics on their own in an informed manner. The book is divided into five sections.

Section I provides an introduction to the immunological basis of allergic diseases. The most important terms are defined for use throughout the book and the epidemiology of allergic diseases, reflecting the alarming increase in recent years, is outlined. The molecular and cellular bases of immune protection are explored in some detail. Both intrinsic mechanisms and the better-known acquired mechanisms featuring the production of antibodies and the many aspects of a cell-mediated immune response are discussed.

Section II provides a multidisciplinary approach to the diagnosis of allergic diseases, incorporating the expertise of dermatologists, otorhinolaryngologists, ophthalmologists, internists, pediatricians, and occupational medicine specialists. The relevant history and physical examination for each of these organ systems are outlined. In addition, the various methods of in vivo and in vitro allergy diagnosis are summarized.

Section III presents an overview of the treatment of allergic diseases. Specific immunotherapy including hyposensitization is covered, as well as medical treatment with antihistamines, corticosteroids, and other agents. Prophylaxis or allergen avoidance is also outlined, as are dietary measures, climate therapy, and skin care.

Section IV covers the various allergic diseases, once again from a multidisciplinary perspective. The pathophysiology, diagnosis, clinical findings, and therapy are concisely presented. The first part of the section concerns itself with allergic emergencies and their management, after which allergies affecting the skin, ears, nose, throat, lungs, eyes, and gastrointestinal tract are covered. In addition, pediatric aspects are explored, along with psychosomatic disease, environmental issues, and immunizations.

Section V is the appendix, containing more detailed information on a variety of topics that are simply too long for the format of the text. Extensive information is included on emergency management, patch testing, and medications.

Abbreviations

ABPA	allergic bronchopulmonary aspergillosis
ADCC	antibody-dependent cellular cytotoxicity
ACE	angiotensin converting enzyme
AMA	antimitochondrial antibody
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
APC	antigen-presenting cell
BALT	bronchus-associated lymphoid tissue
BDT	basophil degranulation test
C	complement factor
C3a	complement factor 3a, an anaphylotoxin
C5a	complement factor 5a, an anaphylotoxin
cANCA	cytoplasmic ANCA (directed against proteinase 3)
CAST	cellular antigen stimulation test
CBC	complete blood count
CCR	CC chemokine receptor
CD	cluster of differentiation
CD40L	CD40 ligand
CFU	colony forming unit
CIE	cross immune electrophoresis
CLA	cutaneous lymphocyte-associated antigen
cm	centimeter
CNS	central nervous system
COLAP	colonoscopic allergen provocation
COPD	chronic obstructive pulmonary disease
CRIE	cross radioimmune electrophoresis
CSF	colony stimulating factor
CTL	cytotoxic T lymphocyte
d	day
DC	dendritic cell
DTHR	delayed-type hypersensitivity reaction
EAA	exogenous allergic alveolitis
ECP	eosinophilic cationic protein
e.g.	for example
ELISA	enzyme-linked immunosorbent assay
EM	erythema multiforme
ENT	ear, nose and throat (otorhinolaryngology)
EPO	eosinophilic peroxidase
EPX	eosinophil-derived neurotoxin
FEV_1	forced expiratory volume (1 second)
GALT	gut-associated lymphoid tissue
GM-CSF	granulocyte monocyte colony stimulating factor
h	hour
HES	hydroxy ethyl starch
HLA	human leukocyte antigen
HML-1	human mucosal lymphocyte antigen-1
i.c.	intracutaneous
ICAM	intercellular adhesion molecule
IFN	interferon
IL	interleukin
i.m.	intramuscular
IU	international units
i.v.	intravenous
JAK	Janus kinase
kg	kilogram
LC	Langerhans cell
LGL	large granular lymphocyte
LTC_4	leukotriene C_4
LTD_4	leukotriene D_4
LTE_4	leukotriene E_4
m	meter
M-CSF	monocyte colony stimulating factor
MALT	mucosa-associated lymphoid tissue
MBP	major basic protein
MCH	metacholine
MCP	monocyte chemoattractant protein
mg	milligram
MHC	major histocompatibility complex
MIF	migration inhibition factor
min	minute
mm	millimeter
NALT	nose-associated lymphoid tissue
NARES	non-allergic rhinitis eosinophilia syndrome
ng	nanogram
NGF	nerve growth factor
NK	natural killer
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug

OAS	oral allergy syndrome
ODTS	organic dust toxic syndrome
pANCA	perinuclear ANCA (directed against myeloperoxidase)
PAF	platelet activating factor
PCR	polymerase chain reaction
PEG	polyethylene glycol
PG	prostaglandin
PGD	prostaglandin D
PGE	prostaglandin E
PL	phospholipase
PLA	phospholipase A
p.o.	per os (orally)
PPD (S)	purified protein derivative (standard)
PRIST	paper radioimmuno sorbent test
RANTES	regulated upon activation, normal T cell expressed and secreted
RAST	radio allergo sorbent test
RF	rheumatoid factor
RhD	Rhesus antigen D
ROS	reactive oxygen singlet
RSV	respiratory syncytial virus
s	second
SALT	skin-associated lymphoid tissue
SIgA	secretory IgA
SLE	systemic lupus erythematosus
SRaw	specific airway resistance
T_C	cytotoxic T cell
T_H	helper T cell
TCR	T-cell receptor
TEN	toxic epidermal necrolysis
TGF	transforming growth factor
TNF	tumor necrosis factor
TU	tuberculin unit
VCAM	vascular cell adhesion molecule

At a Glance

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Introduction

The Immune System and Protection

One of the many tasks of the immune system is to protect against infectious agents and exogenous toxins. Thus it must be able to distinguish between harmless and dangerous exposures. This task is accomplished by two closely interconnected systems (p. 8)—the innate (nonadaptive) and the acquired (adaptive) immune systems. Before potentially harmful material can penetrate into the body and activate the immune system, it must overcome a cascade of external barriers that repel the vast majority of toxins and organisms.

Epithelial cells. The most important barrier is the outer layer of cells, either of the skin or of the mucosal surface of the gastrointestinal tract. The epithelial cells of the skin (known as keratinocytes) have a completely different task from those cells lining the oral or intestinal mucosa and, not surprisingly, have different structures and mechanisms for both holding themselves together and anchoring to the underlying connective tissue.

Mucus. The mucosal epithelium is somewhat less stable than that of the skin; it lacks keratin and lipid barriers in most areas, but compensates to an extent by the production of protective fluids. The saliva not only facilitates the passage of food but is rich in protective materials such as immunoglobulin (Ig) A and various complement factors that serve to capture and neutralize toxins and bacteria. The thicker slimy coating of various mucosal surfaces is known as mucus; it serves as both a chemical and a mechanical barrier. In the lungs, the ciliated epithelium transports the mucus and particles toward the mouth for elimination. In the stomach the acid milieu has disinfectant properties.

Defensins. The defensins comprise a third, phylogentically very old, level of defense, which protects before the immune system is activated. They are a group of molecules produced by various epithelia and are very effective in lysing many forms of bacteria and fungi. They are abundant in the mouth and the perianal region and may explain why infections are so uncommon in these two sites although they have such high concentrations of bacteria.

Nonspecific immune response. If these three barriers—epithelia, mucus and defensins—are broken through or overwhelmed, initially nonspecific inflammation occurs. A variety of intrinsic mechanisms serve to attract phagocytes and provide initial damage control. These mechanisms allow the organism to respond rapidly to danger before it has time to develop a specific immune response. At the same time, the early reaction stimulates the later specific reaction. All of the body's cells are capable of participating in the innate response.

Specific immune response. The specific immune response is stimulated by the initial contact with a foreign antigen occurring within a lymphoid organ. More time is required for a complete specific response than for a nonspecific response. Once a specific immune response has been developed, it remains available for a far more rapid and effective defense whenever the organism is reexposed to the same foreign antigen. Thus the immune system must have a mechanism for remembering these antigens. Special T and B cells known as memory cells accomplish this task. The T cells are responsible for the cellular specific immune response, while B cells manufacture the antibodies that are the major component of the humoral specific immune response.

The Immune System and Allergy

Allergy is defined as a undesirable specific immune response against exogenous substances that have breached the defensive barriers of the body though they are harmless as a rule. This aberrant immune response can lead to a variety of clinical responses that are harmful to the affected individual. Allergic responses are often directed against antigens that cannot be avoided.

A. Various Types of Intolerance Reactions

An intolerance reaction can be defined as the inability of the organism to cope appropriately with a specific exogenous substance or stimulus. Such a reaction can be allergic, pseudoallergic, idiosyncratic, or toxic. Many people assume that all such reactions are allergic, but this is often not the case.

1. Allergy and delayed-type hypersensitivity. The term "allergy" was first introduced by Clemens von Pirquet in 1906 to distinguish between helpful and harmful immune reactions. Today one defines allergy as an excessive, illness-producing specific immune reaction (= *hypergy*) directed against exogenous substances (= *allergens*). So-called autoimmune diseases in which the suspected antigen is a normal but modified self-protein are excluded from this definition. The principal actor in an allergic reaction to a given allergen is the acquired, specific immune response (p. 8f). The initial contact with a potential allergen may lead to sensitization of the exposed organism without producing any clinical symptoms. Antigen-specific lymphocytes and antibodies are produced. When the individual is exposed to the antigen again, an allergic reaction with clinical signs or symptoms can appear. Coombs and Gell in 1963 proposed the still standard classification of allergic reactions into Types I through IV (p. 24f). Severe Type I allergic reactions are known as anaphylaxis, while Type IV reactions are known as delayed-type hypersensitivity. Richet and Portier first employed the term anaphylaxis in 1902 to describe an acute reaction to rabbit serum.

The term "atopy" was introduced by Coca and Cooke in 1923. It describes an inherited tendency to develop eczema and Type I allergies against inhalation allergens. Atopy thus includes atopic dermatitis, allergic rhinitis, and extrinsic or allergic asthma.

2. Pseudoallergy. Pseudoallergic reactions are often clinically identical to allergic reactions but they have different, often poorly understood, pathogenic mechanisms. Pseudoallergic reactions atypically involve medications and foods. In general the affected individuals have an allergic-like reaction but it is impossible to demonstrate the presence of sensitizing antibodies. The reaction is dose-related, and can be triggered on first exposure to the substance, in contrast to allergic reactions. Among the best-known pseudoallergic reactions are those caused by nonsteroidal anti-inflammatory drugs, especially aspirin. Other frequent causes are ACE (angiotensin-converting enzyme) inhibitors, contrast materials, plasma expanders, morphine, muscle relaxants, and various antibiotics (p. 50f).

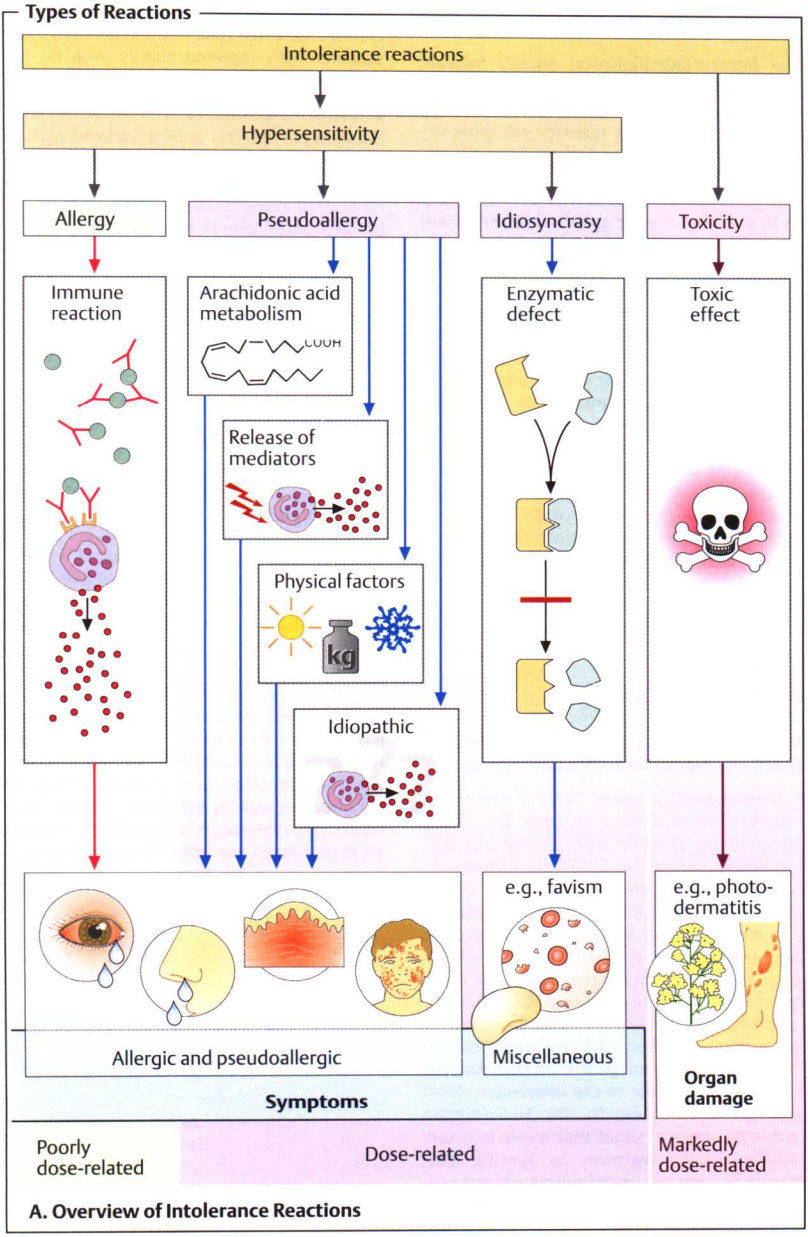
A variety of foods also tend to cause pseudoallergic reactions, especially when they are rich in biogenic amines (histamine, serotonin, tyramine). Potential sources of these substances include ripe cheeses, red wine, and nuts. Other triggers include certain food additives such as preservatives and taste enhancers (p. 48; Appendix).

Pseudoallergic reactions can be enhanced and can even be induced by physical stimuli or through stress.

3. Idiosyncrasy. An idiosyncratic reaction is an inborn, nonimmunological reaction to a foreign substance. An enzyme defect is most commonly the explanation. The symptoms are dose-related and appear with first exposure to the substance. Clinically the picture often resembles an allergic reaction. Two common examples are lactase deficiency (extremely common among Orientals) and favism (lack of glucose-6-phosphate dehydrogenase).

4. Toxicity. A toxic reaction may be caused by exogenous factors such as ultraviolet or ionizing radiation, or by substances that are applied (strong acids or bases) or ingested. When a substance is toxic in very low doses, it is referred to as a poison. A toxic reaction is always dose-dependent or exposure-dependent. A complex example in the skin is the phototoxic reaction to wild grasses and certain vegetable greens (e.g., celery, parsley) that contain furocoumarins. The combination of the plant-derived chemical and sunlight produces a toxic sunburnlike reaction. The furocoumarins or the sunlight alone in the same dosages would have virtually no effect.

Note: Some use the term intolerance to describe a pseudoallergic reaction, while others equate it with an idiosyncratic reaction. To avoid confusion, we have taken it as an umbrella term.



A. Overview of Intolerance Reactions

A. Frequency of Allergies

The latest epidemiological studies indicate that 25–30% of the population in industrialized countries have allergic problems. The most common allergic diseases are those associated with atopy. The prevalence of allergic rhinitis is estimated at 10–15%; of atopic dermatitis at up to 10%; of allergic urticaria at up to 10%; and of allergic asthma at 5–10%. Food allergies are found in around 2% of the population. The frequency of allergic disorders is age-dependent. In infancy and childhood, food allergies and atopic dermatitis are the most common disorders. In contrast, in adolescents and adults, allergic rhinitis and allergic asthma are more common. In the elderly, all the atopic disorders decrease in prevalence. There are also regional differences. City dwellers have a higher prevalence of atopic disorders than do those living in the country. Those living in industrialized regions have more allergic diseases than do inhabitants of developing regions. In childhood, boys are more often affected; in adulthood, women are more likely to have allergic disease. In recent decades, there has been a definite increase in allergic diseases in industrialized countries.

B. Causes of Allergies

While the etiology of allergies is multifactorial, three factors are the most relevant.

1. Genetic predisposition. There is definite an inherited risk to acquire allergies. The risk of atopy among children with two healthy (i.e., unaffected parents) is 5–15% in Germany. In contrast, if one parent is atopic the risk is about 20–40%, and if both parents are affected it increases to 60–80%. The predisposition toward atopy, the involvement of various organs, and the severity of the disease can all be transferred from the parents to the children.

Linkage analyses have identified a variety of genes that are linked with the predisposition to atopic disease. One gene is on chromosome 11q; another is close to the interleukin (IL)-4 gene on chromosome 5q. The HLA (human leukocyte antigen) genes play a role in determining allergic reactions to specific substances but are not linked with a general predisposition. For example, 95% of the individuals who have IgE antibodies against the major ragweed antigen Amb 5 are HLA DR2/Dw2. In contrast, this HLA type is found in only 22% of patients with ragweed allergy who do not have antibodies against Amb 5.

2. Allergen exposure. Early exposure to potential antigens appears to be associated with an increased incidence of atopic disease. Children who are nursed with cow milk or exposed to other food allergens in the first six months of life are more likely to develop both gastrointestinal allergies and atopic dermatitis during early life. The time of year children are born also appears to play a role in their allergic risk. Those who are born just before the start of a given pollen season are more likely to be sensitized to the pollen than those born as the season ends.

3. Adjuvant exposure. The exact role of various adjuvants in the development of allergies remains a puzzle. A correlation between air pollution (SO_2, NO_2, ozone, diesel soot, cigarette smoke, smog) and increased incidence of pulmonary diseases is highly likely. Less clear is how often air pollution is associated with increased respiratory allergies. Viral and bacterial respiratory tract infections in childhood appear to have a protective effect. Thus children in day care centers or kindergartens (or in developing countries with more limited vaccination programs) tend to have fewer respiratory allergies. Children who grow up in an allergen-rich environment, such as on a farm, tend to have fewer allergies. The explanation is probably the suppression of IgE production by lymphocytes making interferon γ. On the other hand, gastrointestinal infections in children seem to increase the risk of a cow milk allergy.