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A Modern Understanding of Allergies: From Ancient Records to Today's Challenges

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INTRODUCTION

Allergies are not a new phenomenon; our immune systems have overreacted to innocuous substances for centuries, resulting in symptoms like swelling, rashes, red eyes, runny noses, and shortness of breath. Historical records describe asthma symptoms in ancient civilizations such as China, Rome, Egypt, and Greece, where the term "asthma" originated, meaning "panting." Despite the long history, our scientific understanding of allergies has only evolved significantly in recent centuries (1,2).

In 1859, Charles Harrison Blackley, a doctor in Manchester, England, suffered from what was then called "summer colds," characterized by sneezing, watery eyes, and a runny nose. The term "hay fever" already existed, but Blackley was determined to uncover its cause. While heat and ozone were popular theories at the time, he identified pollen as the trigger—proving his hypothesis largely through self-experimentation. (3).

Scientific progress in the 19th century brought many breakthroughs, but the study of allergies lagged. In 1819, John Bostock published a detailed description of hay fever (4). Decades later, Blackley confirmed pollen as a cause, but treatments remained ineffective, and most allergic conditions were still unexplained (4). The early 20th century marked a turning point with advances in immunology. In 1905, Austrian pediatrician Clemens von Pirquet noticed that patients vaccinated with smallpox serum often had severe reactions upon subsequent exposure. Pirquet discovered that these symptoms resulted from the immune system producing antibodies in response to antigens in the serum. He coined the term "allergy" in 1906 to describe this immune response (5).

The journey toward understanding and treating allergies progressed gradually. In 1869, the first skin test for allergies was described, where pollen was introduced into a small cut on the skin to observe reactions (6). By 1914, the concept of immunotherapy emerged, aiming to help individuals develop tolerance through controlled allergen exposure. Over the following years, researchers identified hypersensitivity reactions as the root cause of hay fever, asthma, skin diseases, and even anaphylaxis—a severe, potentially fatal allergic reaction linked to histamine production (Fig.1 Ref. 7,8)

Antihistamines became widely available in the 1930s, helping to manage symptoms by moderating the body's allergic response. Post-World War II, the term "allergy" broadened to include reactions to synthetic chemicals, cosmetics, and certain foods (11). While food allergies had been documented since ancient times, they were notoriously inconsistent and challenging to diagnose. However, meticulous studies in the mid-20th century proved food allergies as legitimate medical conditions, leading to a surge in diagnoses (12).

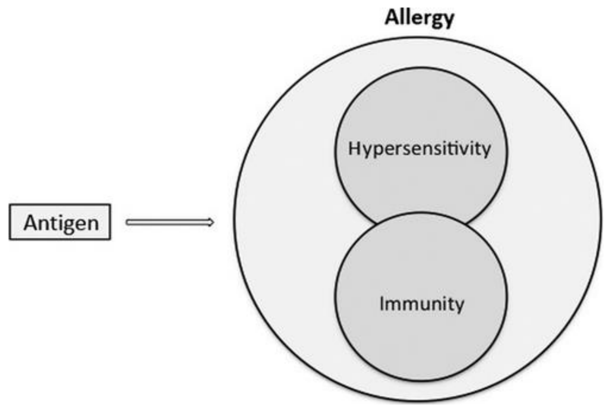

Figure 1: Von Pirquet's original concept of 'allergy'. When an antigen (germs, pollen, food, etc.) comes in contact to our body, a mutation occurs. This change is, according to von Pirquet, an 'allergy'. The first reaction is known as "immunity" and the second is known as "hypersensitivity".

Drug development accelerated, with corticosteroids in 1948 becoming a game-changer for reducing inflammation in asthma attacks and other allergic reactions (13). Specific products, like non-biological washing powders, emerged to address public fears about enzymes in biological detergents (13). Food labeling also became more prevalent, offering allergen warnings to consumers (14).

The 1950s brought significant scientific discoveries, such as the identification of mast cells. These immune cells, located in sensitive areas like the skin, respiratory system, and blood vessels, contain granules packed with histamine and other chemicals. These substances are released during an allergic reaction, causing symptoms (15). By 1963, IgE antibodies were discovered, shedding light on the chain reaction that triggers histamine release. Further research in 1967 revealed that individuals prone to allergies produce excessive IgE, which remains dormant until reactivated by allergens. This discovery provided a clearer picture of allergic mechanisms (16).

Subsequent innovations included blood tests to measure IgE levels, the invention of the EpiPen to treat anaphylactic shock, and research into leukotrienes—chemicals responsible for asthma and inflammation—which earned a Nobel Prize in Medicine in 1982. (17). Today, allergies are the sixth leading cause of chronic illness in the United States, costing the healthcare system around $18 billion annually (18).

Despite advancements in immunotherapy and symptom management, a definitive cure for allergies remains elusive. Allergic diseases, including hay fever, eczema, hives, asthma, and food allergies, continue to affect millions worldwide. People with a family history of allergies are particularly at risk, as genetic predisposition plays a key role. When individuals encounter allergens like pollen, dust, or mold, their immune systems may overreact by producing antibodies to "attack" these harmless substances. This overreaction leads to symptoms such as wheezing, itching, watery eyes, or, in severe cases, life-threatening anaphylaxis (19).

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As research continues, our understanding of allergies deepens, offering hope for more effective treatments and perhaps, one day, a cure.

Understanding Allergies: Causes, Symptoms, and Reactions

Allergies, also referred to as allergic diseases, are conditions where the immune system reacts hypersensitively to otherwise harmless substances in the environment. These include hay fever (allergic rhinitis), food allergies, atopic dermatitis, allergic asthma, and even severe reactions like anaphylaxis. Symptoms often manifest as red eyes, itchy rashes, sneezing, coughing, runny noses, or difficulty breathing. It is essential to distinguish between allergies and other conditions such as food intolerances or food poisoning, which are unrelated to immune hypersensitivity (19-22).

Common Triggers and Mechanisms of Allergies

Pollen, certain foods, metals, insect stings, and medications are among the most frequent allergens. Genetic predisposition and environmental factors both play significant roles in the development of allergies. At the molecular level, the allergic response involves immunoglobulin E (IgE) antibodies, which bind allergens and activate mast cells or basophils. These cells release inflammatory chemicals like histamine, resulting in the symptoms associated with allergic reactions (17, 19-21).

Symptoms Across Different Organs

The impact of allergens can vary depending on the site of exposure (Fig.1, Ref. 23-30):

- **Nose and Sinuses**: Allergens like pollen can cause swelling in the nasal passages, sneezing, and a runny nose, symptoms typically seen in allergic rhinitis.
- **Eyes**: Redness, itching, and watery discharge, collectively known as allergic conjunctivitis, often accompany airborne allergens.
- **Airways**: Exposure may lead to coughing, wheezing, bronchoconstriction, or even severe asthma attacks. In extreme cases, airway swelling (laryngeal edema) can obstruct breathing.
- **Skin**: Contact with certain allergens, such as latex, can result in rashes, hives, or angioedema. Substances that penetrate the skin trigger localized reactions with redness and swelling.
- **Digestive System**: Food allergies may cause symptoms like abdominal pain, bloating, vomiting, or diarrhea.

Anaphylaxis, the most severe form of allergic reaction, can affect multiple organ systems simultaneously, causing swelling, low blood pressure, and potentially fatal outcomes.

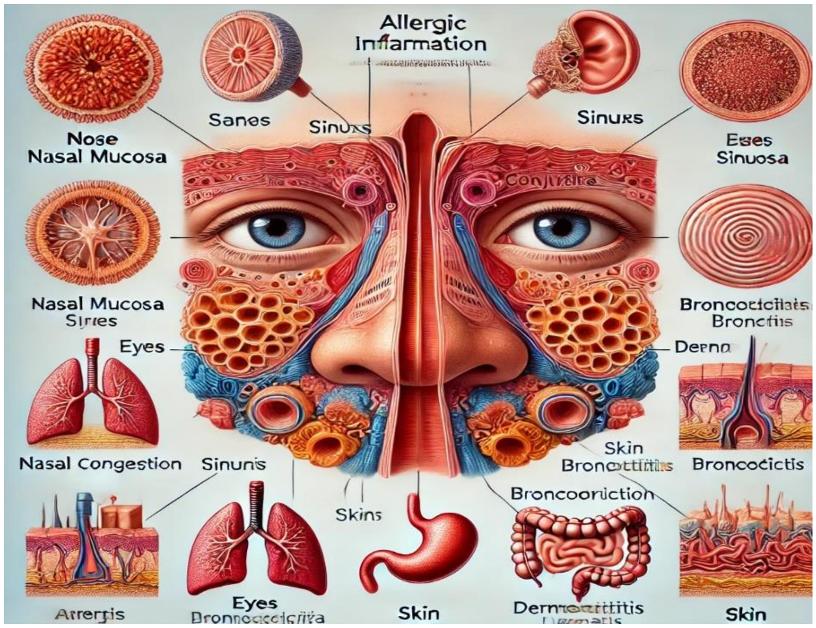

Figure 2: Symptoms across different organs.. The diagram illustrates the tissues affected in allergic inflammation, highlighting key areas such as the nose, sinuses, eyes, airways, skin, and gastrointestinal tract, along with their respective responses.

The Body's Response and Testing for Allergies

When an allergen enters the body, mast cells release histamine, leading to immediate symptoms like swelling and redness. In cases of skin exposure, a "wheal-and-flare" reaction may occur, marked by raised, itchy areas surrounded by redness. Ingested allergens may cause widespread hives (urticaria) when they reach the bloodstream (14, 31-35) Secondary responses often follow the initial allergic reaction. These occur hours later and involve other immune cells like neutrophils and eosinophils migrating to the site, extending the inflammatory process. This delayed reaction underscores the importance of accurate allergy testing (32-34). Allergists utilize skin prick tests and small allergen injections to determine sensitivities. These tests, though effective, carry a slight risk of triggering systemic reactions, including anaphylaxis (34).

Addressing the Rise in Allergies

Modern lifestyles, with increased exposure to pollutants and changes in diet, may have contributed to the growing prevalence of allergies. About 20% of people in developed countries experience allergic rhinitis, 6% have food allergies, and asthma affects a significant portion of the population. Understanding the underlying mechanisms and triggers has paved the way for treatments like antihistamines, corticosteroids, and epinephrine, which help manage symptoms. However, addressing the root causes of allergies remains an ongoing challenge for medical science (36).

Causes of Allergies: Host and Environmental Factors

The risk of developing allergies is influenced by both host factors and environmental triggers. **Host factors**, such as heredity, sex, race, and age, play a pivotal role, with genetics being the most significant. However, the growing prevalence of allergies in recent decades cannot be explained by genetics alone. **Environmental factors**, including reduced exposure to

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infectious diseases during early childhood, increasing pollution levels, dietary changes, and heightened exposure to allergens, have been identified as significant contributors to the rise in allergic disorders.

Dust Mites and Allergies:

Dust mite allergies, often referred to as house dust allergies, occur due to sensitivity to the droppings and exoskeletons of dust mites. These mites release digestive enzymes, such as peptidase 1, that trigger allergic responses like asthma, eczema, and itching (37). Unlike other mites, house dust mites are not parasitic and do not burrow into the skin. However, their presence in household environments is a major source of allergy-related discomfort (38).

Food Allergies:

A variety of foods can cause allergic reactions, but the majority of cases (about 90%) are linked to common allergens like **cow's milk, soy, eggs, wheat, peanuts, tree nuts, fish, and shellfish**. While peanut allergies are infamous for their severity, crustacean allergies are the most common food allergy in the United States (39- 42).

Age-Related Trends:

- Children may outgrow certain allergies, such as those to peanuts or eggs, by the age of five.
- In contrast, milk-protein allergies often persist in children, with symptoms ranging from gastrointestinal discomfort to immune-mediated inflammation.

Lactose intolerance, which is caused by an enzyme deficiency, is often mistaken for a milk allergy but is not related to the immune system. Additionally, allergies to tree nuts, seeds, and genetically modified foods highlight the complex interplay of dietary habits and genetic predisposition (40).

Latex Allergies:

Latex allergies, though rare, can cause reactions ranging from **contact dermatitis** to life-threatening anaphylaxis. These reactions are particularly prevalent among healthcare workers exposed to latex-rich environments, such as operating rooms. Individuals with latex allergies often experience cross-reactivity with fruits like bananas, avocados, and kiwifruit due to structural similarities in their proteins. Symptoms include perioral itching and urticaria, with occasional systemic responses (42).

Medication and Insect Allergies:

About **10% of individuals report penicillin allergies**, though the vast majority are later found to lack a true allergy. Serious reactions to medications occur in only a small fraction of cases. Similarly, **insect allergies**, caused by bites, stings, or inhalation, are common triggers for localized swelling or systemic anaphylaxis (43).

Toxins and Contact Allergies:

Urushiol, a compound found in plants like poison ivy, poison oak, and poison sumac, triggers contact dermatitis through a T-cell-mediated immune response. The reaction, marked by redness, swelling, and blistering, varies in severity among individuals. About 80–90% of adults develop rashes upon contact with urushiol, even in trace amounts (44-46).

The Role of Genetics:

Allergic diseases are strongly familial, with identical twins having a 70% likelihood of sharing the same allergies. However, the specific allergen sensitivity can vary even within families. Genetics influence susceptibility by regulating immune responses, but environmental factors remain crucial. For example, IgE levels, which are highest in childhood, decrease with age, correlating with the prevalence of certain allergic conditions like hay fever (47-50).

Molecular Insights into Allergies:

Advancements in genetics have identified numerous genes linked to allergic disease severity and progression. These include genes regulating inflammatory responses (e.g., **IL-13, IL-4**), maintaining mucosal barriers, and mediating immune cell function. The discovery of **IL-13's role** in allergen-induced asthma highlights the complex interplay between genetic predisposition and environmental triggers. Such insights pave the way for targeted therapies in managing allergic diseases. (51) Allergy research continues to unravel the intricate relationship between genetic and environmental factors, offering hope for better prevention and treatment strategies (52).

Hygiene Hypothesis: Understanding Allergic Diseases

The **hygiene hypothesis** posits that allergic diseases arise due to inappropriate immune responses to harmless antigens, driven by a **TH2-mediated immune response**. In contrast, many bacteria and viruses elicit a **TH1-mediated immune response**, which suppresses TH2 activity. The hypothesis suggests that insufficient exposure to pathogens and microbes during childhood prevents the immune system's TH1 arm from developing properly, leaving the TH2 arm to overreact to benign substances like pollen or dust. Essentially, individuals in overly sterile environments are not exposed to enough microorganisms to keep their immune systems balanced, leading to allergic conditions. (59,60)

Origins of the Hygiene Hypothesis:

This hypothesis was first proposed to explain observations that **hay fever** and **eczema** were less prevalent in children from larger families. Larger families, presumably, exposed children to more infectious agents through their siblings. In contrast, children in smaller families, or in more industrialized, "cleaner" environments, were found to have higher rates of allergic diseases (61,62). The hygiene hypothesis has since been expanded to include the role of **symbiotic bacteria** and **parasites** as important factors in immune system development, alongside exposure to infectious agents (63,64).

Supporting Evidence from Epidemiology:

Epidemiological studies provide strong evidence for the hygiene hypothesis (65-68):

1. **Developing vs. Industrialized Nations**: Immunological and autoimmune diseases are far less common in developing nations than in industrialized countries. Immigrants moving from the developing to the developed world often experience a rise in allergic and immune disorders over time, correlating with their length of stay in industrialized regions (65)
2. **Antibiotics and Allergies**: The use of antibiotics in the first year of life has been linked to increased risks of developing asthma and allergic diseases. (66).
3. **Antibacterial Products**: Overuse of antibacterial cleaning products has been associated with a higher incidence of asthma (67).

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4. **Mode of Birth**: Babies delivered via **caesarean section**, which bypasses exposure to maternal microbiota during vaginal delivery, are more likely to develop allergic conditions (67).

Role of Parasites and Gut Flora:

Parasites, particularly **intestinal worms** like hookworms, have long coexisted with humans, shaping the immune system's function. Research suggests that some parasites secrete chemicals that suppress the immune system, preventing it from overreacting to allergens. With the advent of modern sanitation, the absence of these parasites has contributed to immune system imbalances, making individuals more prone to allergies (68,69).

- **Delayed Gut Flora Development**: In infants, delayed establishment of gut microbiota has been linked to allergies. Gut flora plays a crucial role in regulating the immune system, and disruptions in its development can increase susceptibility to allergic diseases. (70)
- **Conflicting Research**: While some studies show reduced allergies in populations exposed to parasites, others, such as studies in China and Ethiopia, have found increased allergy rates in individuals with intestinal worm infections. Clinical trials are currently exploring the potential of using certain parasites for allergy treatments (71).

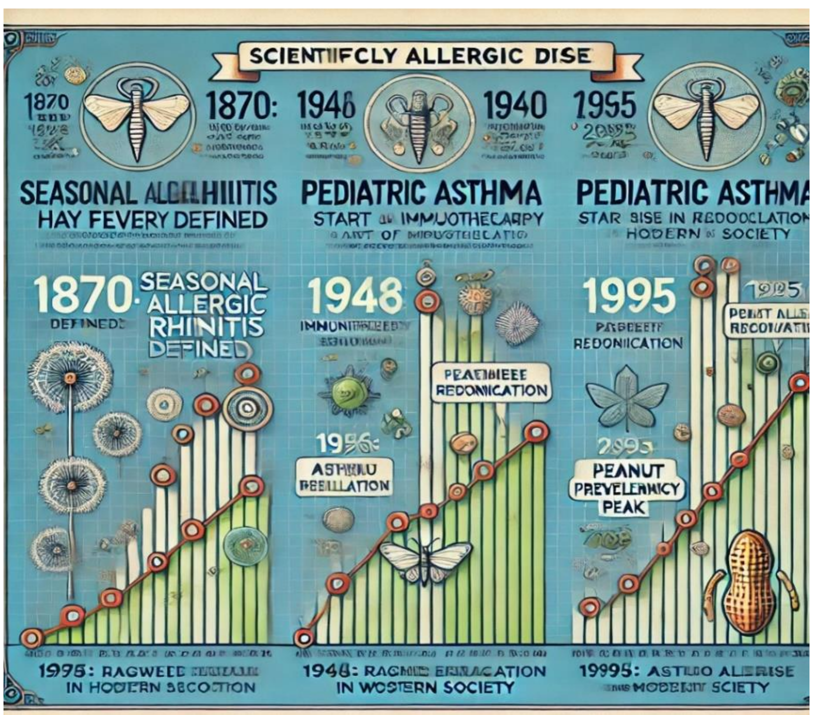

Figure 3: It leads to a gradual increase in allergic rhinitis, pediatric asthma and peanut allergy with the main phenomena of modern hygiene adoption in Western society.

Environmental and Urban Influences:

Allergic diseases are more prevalent in industrialized and urban settings compared to rural or agricultural areas. However, this disparity is narrowing. In urban environments, **male-dominated tree planting** has inadvertently increased pollen counts, a phenomenon termed **"botanical sexism"** by horticulturist Tom Ogren. Additionally, alterations in exposure to microorganisms, endotoxins, and modern urban lifestyles have contributed to rising allergy rates (72,73).

Chronic Stress and Allergies:

Chronic stress has been identified as another factor aggravating allergic conditions. Stress influences the immune system by suppressing interleukin-12 production, favoring a TH2-dominant immune response. Managing stress can alleviate allergic symptoms in highly susceptible individuals (74).

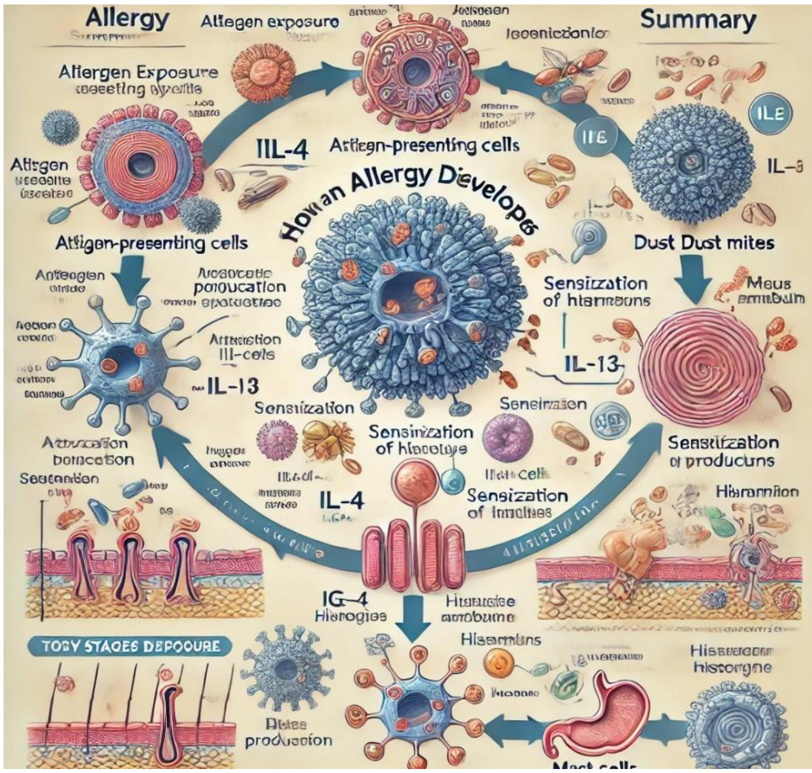

Figure 4: Pathophysiology of Allergy development. The diagram illustrates the pathophysiology of allergy development, showcasing the sequential stages in a visually organized and educational manner

The Role of Hygiene in Modern Allergies:

The hygiene hypothesis highlights how shifts in lifestyle, urbanization, and sanitation practices have unintentionally altered the immune system's development. While advancements in cleanliness and healthcare have reduced infectious diseases, they may have left the immune system vulnerable to overreacting to harmless substances, contributing to the global rise in allergic diseases. Further research into parasitic co-evolution, gut flora, and environmental exposures may offer new insights into managing and preventing allergies (75,76)

Initial Stages of an Allergic Reaction

Type I Hypersensitivity Reaction:

The initial stage of an allergy involves a **Type I hypersensitivity reaction** against an allergen that the immune system encounters for the first time. This process begins when a professional antigen-presenting cell (such as a dendritic cell) presents the allergen to a type of immune cell known as **TH2 lymphocytes**, a subset of T cells. These cells produce **interleukin-4 (IL-4)**, a cytokine that plays a critical role in allergy development (77).

Role of B Cells and IgE Production:

TH2 lymphocytes interact with **B cells**, immune cells responsible for antibody production. Stimulated by IL-4, B cells produce large quantities of a specific antibody called **immunoglobulin E (IgE)**. The secreted IgE circulates in the bloodstream and binds to **IgE-specific receptors (FcεRI)** on the surface of mast cells and basophils, which are involved in acute inflammatory responses. At this stage, these immune cells are **sensitized** to the allergen (78,79).

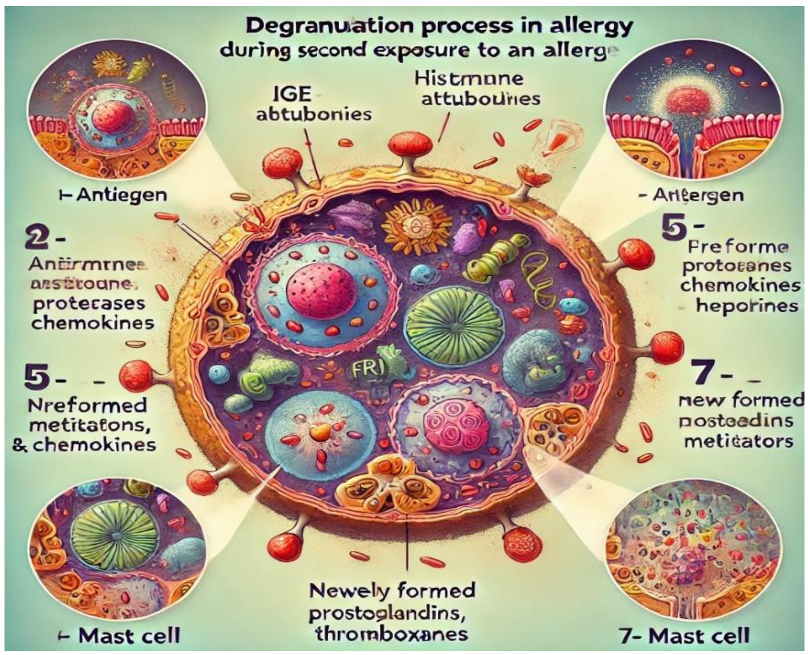

Figure 5: Degranulation process in allergy. Second exposure to allergens. 1 – antigen; 2 – IgE antibody; 3 – FcεRI receptor; 4 – preformed mediators (histamine, proteases, chemokines, heparin); 5 – granules; 6 – mast cell; 7 – newly formed mediators (prostaglandins, leukotrienes, thromboxane's PAF).

Subsequent Allergen Exposure:

Upon subsequent exposure to the same allergen (Fig 5):

1. The allergen binds to the IgE molecules on the surface of the mast cells or basophils.
2. **Cross-linking of IgE and FcεRI receptors** occurs when multiple receptor complexes interact with the allergen.
3. This cross-linking activates the sensitized cells, causing them to undergo **degranulation**.

During degranulation, the mast cells and basophils release inflammatory mediators such as **histamine, cytokines, interleukins, leukotrienes, and prostaglandins** (80**)**. These chemicals trigger systemic effects, including:

- **Vasodilation**
- **Mucous secretion**

- **Nerve stimulation**
- **Smooth muscle contraction**

Resulting Symptoms:
The release of these mediators results in common allergic symptoms such as:
- **Rhinorrhea** (runny nose)
- **Itchiness**
- **Shortness of breath (dyspnea)**
- **Anaphylaxis**, a severe, potentially life-threatening reaction.

Symptoms may be localized to specific areas (e.g., **asthma** in the respiratory system or **eczema** on the skin) or systemic, affecting the entire body (81).

Late-Phase Response
Delayed Immune Response:
After the acute allergic response subsides, a **late-phase response** may occur, typically **2–24 hours** after the initial reaction. This response is characterized by the migration of additional immune cells, including: **Neutrophils, Lymphocytes, Eosinophils, Macrophages (82).** These cells arrive at the site of the initial reaction and release mediators that sustain inflammation.

Chronic Effects:
In asthma, late-phase responses often lead to persistent airway inflammation and remodeling. Although similar mechanisms are at play in other allergic responses, asthma-specific effects remain largely dependent on the activity of **TH2 cells** and **eosinophils (83).**

Allergic Contact Dermatitis
Type IV Hypersensitivity:
Unlike most allergic reactions, **allergic contact dermatitis** is classified as a **Type IV hypersensitivity reaction**. This condition involves (84)
1. Activation of **CD8+ T cells**, which destroy target cells upon contact.
2. Recruitment of **activated macrophages**, which release hydrolytic enzymes that contribute to tissue damage.

Mechanism:
Allergic contact dermatitis results from **delayed immune activation**, leading to symptoms such as skin redness, swelling, and crusted lesions. Unlike **Type I hypersensitivity**, this reaction is slower to develop and involves cellular immune responses rather than antibody-mediated processes. (85).

Allergy Diagnosis: Methods and Procedures:
Accurate diagnosis is critical for effective management of allergic diseases. Proper testing helps confirm or rule out allergies, guiding counseling, avoidance measures, and treatment plans that improve quality of life while reducing the need for medications. Several diagnostic tools are available to identify allergens and evaluate their impact. (86)

Skin Prick Testing

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Overview:
Skin prick testing, also known as puncture or prick testing, is one of the most commonly used diagnostic methods for allergies (Fig.6). It involves introducing tiny amounts of suspected allergens, such as pollen, grass, or food extracts, into the skin using a small device or needle. Common testing sites include the inside forearm or the back. Positive and negative controls (e.g., saline or histamine) are used to ensure accurate interpretation (87).

Figure 6: Skin testing on arm

Process and Interpretation:
Within 30 minutes of exposure, an allergic reaction may appear as redness, swelling, or a hive-like response called a "wheal and flare." Results are measured based on the size of the wheal. A positive result is typically defined as a wheal at least 3 mm larger than the negative control. However, a positive result does not always indicate a clinically significant allergy, emphasizing the importance of professional interpretation by allergists (88).

Limitations:
Skin prick tests may not be suitable for individuals with widespread skin disease or those who have taken antihistamines recently. In such cases, alternative diagnostic methods like blood testing are preferred.

Patch Testing for Skin Allergies:
Patch testing is used to identify delayed allergic reactions, such as contact dermatitis (Fig. 7). Adhesive patches containing common allergens are applied to the back, and reactions are evaluated 48 to 96 hours later. This method is particularly effective for identifying skin sensitivities to substances like latex or metals (88).

Figure 7

Blood Testing
Advantages:
Blood tests are a quick and simple alternative to skin prick tests, especially for individuals with conditions that preclude skin testing. This method measures specific **IgE antibodies** in the

blood to detect allergic responses. It is suitable for all ages and can be performed irrespective of medication use, skin condition, or pregnancy (89).

Quantitative Analysis:
Results from blood tests provide insights into the severity of an allergy by quantifying IgE levels. Higher IgE values are generally associated with more severe symptoms. However, low IgE levels do not rule out sensitization, making clinical correlation essential. Multiple allergens can be tested with a single blood sample, making this method both comprehensive and convenient.

Techniques:
Laboratory methods for measuring IgE antibodies include:

- Enzyme-linked immunosorbent assay (ELISA)
- Radioallergosorbent test (RAST)
- Fluorescent enzyme immunoassay (FEIA)
- Chemiluminescence immunoassay (CLIA)

Challenge Testing and Elimination Diets

Challenge Testing:
This method involves controlled exposure to small amounts of a suspected allergen, either orally, through inhalation, or via other routes. It is primarily used for food or medication allergies and must be conducted under medical supervision due to the risk of severe reactions.

Elimination Diets:
For food-related allergies, patients are instructed to eliminate suspected allergens from their diet for a set period. If symptoms improve, the allergen may be reintroduced to confirm its role in causing allergic reactions.

Unreliable Testing Methods:
Certain tests, such as applied kinesiology, cytotoxicity testing, or urine autoinjection, lack scientific validation and are not recommended for allergy diagnosis. Patients should rely on proven diagnostic methods to ensure accurate results (90).

Differential Diagnosis:
Before confirming an allergy diagnosis, healthcare providers must rule out other conditions with similar symptoms. For example, **vasomotor rhinitis** can mimic allergic rhinitis but is not caused by allergens. A thorough medical history and appropriate testing help identify the true cause of symptoms and guide effective treatment. By combining these diagnostic approaches, clinicians can tailor management strategies to address individual patient needs effectively (91).

PREVENTION AND MANAGEMENT OF ALLERGIES

Allergy Prevention Strategies

Early Allergen Exposure:
Research suggests that introducing peanut products early in life may reduce the risk of peanut allergies. Similarly, breastfeeding exclusively for the first few months may lower the likelihood of developing dermatitis. Contrary to earlier assumptions, there is no substantial evidence that a mother's diet during pregnancy or breastfeeding influences the risk of allergies in her child.

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Additionally, delaying the introduction of certain foods does not appear to provide any protective benefits. In fact, early exposure to potential allergens can often be protective (92-95).

Dietary Supplements:

Certain supplements during pregnancy and early childhood may help reduce allergy risks. For example:

- **Fish Oil**: Supplementing fish oil during pregnancy has been associated with a lower risk of allergies in children (96,97).
- **Probiotics**: Probiotic supplements during pregnancy or infancy may reduce the likelihood of atopic dermatitis, a common allergic condition. (98,99).

Managing Allergies:

Effective allergy management generally involves avoiding known triggers, using medications to alleviate symptoms, and, in some cases, employing immunotherapy to modify the immune response (100).

Medications for Allergy Relief

Common Treatments:

Several medications are used to manage allergic symptoms by blocking the actions of inflammatory mediators or preventing cell activation (100-103).

- **Antihistamines**: Reduce itching, swelling, and other allergic symptoms.
- **Glucocorticoids**: Alleviate inflammation in severe allergic reactions.
- **Mast Cell Stabilizers**: Prevent degranulation of mast cells, reducing histamine release.
- **Antileukotriene Agents**: Address symptoms such as bronchoconstriction, particularly in asthma.

Emergency Treatment:

In cases of severe allergic reactions like anaphylaxis, epinephrine (adrenaline) is administered to reverse life-threatening symptoms. Where immediate medical attention is unavailable, epinephrine autoinjectors, such as EpiPens, are a critical resource (102-106).

Allergen Immunotherapy

Overview:

Immunotherapy involves gradually exposing an individual to increasing amounts of an allergen to alter the immune response. It has shown significant effectiveness for environmental allergies, insect venom sensitivities, and allergic asthma. However, its benefits for food allergies remain unclear, and it is not generally recommended for these conditions (105,106)

Benefits:

Meta-analyses have demonstrated that subcutaneous injections of allergens are effective for managing allergic rhinitis and asthma. The benefits of immunotherapy often persist for years after the treatment is concluded. Sublingual immunotherapy, where allergens are administered under the tongue, is another option and is often preferred by patients due to its convenience compared to injections. However, its benefits for seasonal allergies are relatively modest. Notably, immunotherapy should not be used as the sole treatment for asthma (106-107)

Alternative Treatments for Allergies

Experimental Treatments:

- **Enzyme Potentiated Desensitization (EPD)**: This experimental therapy uses diluted allergens and beta-glucuronidase to modulate immune responses. However, evidence does not support its effectiveness for allergies or autoimmune diseases (106).

Homeopathy:

Despite anecdotal claims, rigorous clinical trials have not found homeopathic remedies effective for treating allergies. Studies consistently show no difference between homeopathic treatments and placebos. (107-109)

Complementary Approaches:

Some alternative treatments, such as saline nasal irrigation and butterbur, have shown promise in alleviating allergic symptoms. However, many other methods, including honey, acupuncture, omega-3 supplements, and herbal remedies like stinging nettle and quercetin, lack substantial scientific support. The National Center for Complementary and Integrative Health highlights the need for more robust evidence for most alternative treatments 109- 111).

Epidemiology of Allergic Diseases

Rise of Allergic Diseases in the Western World:

Over the past 2–3 decades, allergic diseases such as hay fever and asthma have seen significant increases in Western nations. While the rise in allergic asthma and other atopic disorders began in the 1960s and 1970s, it accelerated during the 1980s and 1990s. Some researchers suggest this trend has been ongoing since the 1920s. In contrast, the number of new atopy cases in developing countries has remained considerably lower, highlighting a disparity likely influenced by environmental and lifestyle factors (112,113)

Statistical Overview of Allergies (114-119)

United States vs. United Kingdom:

- **Allergic Rhinitis**: In the U.S., 35.9 million people (11% of the population) are affected, compared to 3.3 million (5.5%) in the U.K.
- **Asthma**: About 10 million Americans have allergic asthma (3% of the population), with its prevalence increasing by 75% between 1980 and 1994. African Americans have a 39% higher prevalence than Europeans. In the U.K., 5.7 million people (9.4%) are affected, with rates rising among younger children but declining slightly among teenagers.
- **Atopic Eczema**: In the U.S., about 9% of the population is affected, with prevalence rising from 3% to 10% in children between 1960 and 1990. The U.K. sees similar trends, with 5.8 million people affected, though only about 1% have severe eczema.
- **Anaphylaxis**: Annually, the U.S. reports over 40 deaths from insect venom, 400 from penicillin anaphylaxis, and 150 from food allergies. In the U.K., between 1999 and 2006, 48 deaths were recorded across all age groups due to anaphylaxis.
- **Food Allergies**: Around 7.6% of children and 10.8% of adults in the U.S. have food allergies. Peanut and tree nut allergies affect approximately three million Americans. In the U.K., 5–7% of infants and 1–2% of adults are affected, with peanut allergies rising by 117.3% from 2001 to 2005.

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Changing Patterns in Allergic Diseases (120-123)

Environmental and Lifestyle Factors:

While genetic predisposition plays a role in atopy, the rapid rise in allergic diseases cannot be explained by genetics alone. Environmental and lifestyle changes are significant contributors, including:

- **Increased Allergen Exposure**: Changes in housing and extended time spent indoors have increased exposure to perennial allergens.
- **Hygiene and Cleanliness**: The "hygiene hypothesis" suggests that improved hygiene reduces bacterial and viral infections early in life, leading to unrestrained TH2 immune responses and higher rates of allergies.
- **Diet and Exercise**: Changes in diet, increased obesity, and reduced physical activity are additional contributors.

Microbial Environment and Allergy Development:

Emerging evidence highlights the role of the gastrointestinal microbiome in allergy development. Exposure to certain food and fecal-oral pathogens, such as **hepatitis A**, **Toxoplasma gondii**, and **Helicobacter pylori**, has been linked to a more than 60% reduction in atopy risk. Similarly, higher rates of parasitic infections correlate with reduced asthma prevalence. These infections are thought to influence TH1/TH2 immune balance, reducing allergic tendencies (124, 125).

Endotoxins and Farm Exposure:

Exposure to endotoxins, pets, and farm environments has shown protective effects against allergies, further supporting the importance of environmental microbial exposure in immune regulation (126)

CONCLUSION

The 21st century began with efforts to standardize the terminology in the field of allergology. One of the significant milestones was the publication of the first institutional framework for allergy nomenclature in 2001. This initiative was led by the European Academy of Allergy and Clinical Immunology (EAACI), which created a Task Force to define and classify hypersensitivity reactions. Their findings were published as a Position Statement in 2001, later revised in 2004 with support from the World Allergy Organization. According to the report, hypersensitivity was defined as "objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons." It distinguished between two types of hypersensitivity: nonallergic hypersensitivity, where no immunological mechanism is proven, and allergic hypersensitivity, where a specific immunological mechanism, such as antibody- or cell-mediated reactions, is involved. Under this classification, "allergy" was considered a hypersensitivity reaction triggered by specific immunological mechanisms.

Despite these efforts, the practical use of allergy-related terminology in the medical field has remained inconsistent. Physicians often use the term "hypersensitivity" to refer exclusively to undesirable immune system reactions, which deviates from the broader definition outlined in the 2001 EAACI report. Similarly, the word "allergy" is widely equated with immune-mediated adverse reactions, though the nature of these reactions varies across different medical contexts.

For example, in respiratory diseases, clinical guidelines consistently use "allergy" to refer specifically to IgE-mediated conditions such as allergic rhinitis and asthma. In dermatological conditions, however, the use of "allergy" depends on the disease. For urticaria, it almost exclusively denotes IgE-mediated hypersensitivity, while in contact dermatitis, "allergy" includes both delayed and cell-mediated hypersensitivity. In latex reactions, "allergy" is always IgE-mediated, but in adverse drug or food reactions, it can refer to any type of hypersensitivity. These varying criteria demonstrate the contextual flexibility of the term, which complicates its application. Outside of the medical field, the concept of "allergy" has further evolved and expanded in the 21st century. Building on its popularization from the 1930s, the term is now broadly applied to encompass a wide range of conditions and discomforts, even those unrelated to health. In casual usage, "allergy" might refer to any bothersome or upsetting experience, diluting its medical precision. While this ambiguity in everyday language is less concerning than the inconsistencies in medical contexts, it highlights the broader challenges in maintaining clarity around the concept of allergies.

In conclusion, while significant progress has been made in defining and categorizing allergic conditions in the 21st century, challenges remain in ensuring consistent usage of allergy-related terminology. The varied interpretations and applications of "allergy" reflect both the complexity of the field and the evolving understanding of immunological reactions. While strategies like early allergen exposure and dietary supplementation show promise in preventing allergies, management primarily involves a combination of avoidance, medication, and immunotherapy. The epidemiology of allergic diseases reveals a complex interplay of genetic predisposition and environmental factors. Continued research into both conventional and alternative treatments is essential to improve outcomes for individuals affected by allergic diseases. Moreover, the rise in allergies in industrialized nations reflects changes in hygiene, lifestyle, and microbial exposure, pointing to the need for further research into preventive strategies and the role of the microbiome in immune system development.

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