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This book discussed about very interesting immunological disorder which affects millions of people in the worlds at different age groups and in different seasons of the year. The etiology of that immunological disorder vary from person to another it may be induced by chemical, drug, infection and even by food. Up to date there is no efficient therapeutic method that cure it completely. It comes even after treatment when the patient exposed to the cause. This immunological disorder is called allergy, which is a reaction by your immune system to something that does not bother most other people. People who have allergies often are sensitive to more than one thing.

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Allergy overview

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Contents:

Dedication:

To my great mother

Acknowledgement:

To my colleagues at Elrazi University, Soba University Hospital and Elsheikh Abdallah Elbadri university for their support and kindness.

Introduction

An allergy is a reaction by your immune system to something that does not bother most other people. People who have allergies often are sensitive to more than one thing. Substances that often cause reactions are

•Pollen

•Dust mites

•Mold spores

•Pet dander

•Food

•Insect stings

•Medicines

Normally, your immune system fights germs. It is your body's defense system. In most allergic reactions, however, it is responding to a false alarm. Genes and the environment probably both play a role.

Allergies can cause a variety of symptoms such as a runny nose, sneezing, itching, rashes, swelling, or asthma. Allergies can range from minor to severe. [1]

History:

Perhaps the earliest report of allergic disease is that of King Menses of Egypt, who was killed by the sting of a wasp at some time between 3640 and 3300 BC. Another report from ancient history is that of Britannicus, the son of the Roman Emperor Claudius. He was allergic to horses and "would develop a rash and his eyes swelled to the extent that he could not see where he was going". Accordingly, the honour of riding at the head of the young patricians fell to Nero who was Claudius adopted son. Nero allegedly threw Christians to the lions and killed Britannicus. Sir Thomas More gives the next authoritative account of allergy: King Richard III used his allergy to strawberries to good effect in arranging the judicial murder of Lord William Hastings. The King surreptitiously ate some strawberries just prior to giving an audience to Hastings and promptly developed acute urticaria. He then accused Hastings of putting a curse on him, an action that demanded the head of Hastings on a plate.

The Roman philosopher, Lucretius observing exaggerated responses to commonly occurring substances said "what is food for some may be fierce poisons for others". However, the modern era of allergy started in the 1800s with the description of hay fever:

1819 – Dr. John Bostock first accurately described hay fever as a disease that affected the upper respiratory tract. Although of unknown origin, oddly enough it had nothing to do with either hay or having a fever. Hay fever, or in medical terms, seasonal allergic rhinitis, is the most

widespread form of allergy, affecting more than 15 million Americans. Common symptoms include sneezing, a runny or stuffed nose, red, itchy, swollen or watery eyes and itching in the nose and throat.

1869 – To investigate his own hay fever, Charles Blakely performed the first skin test by applying pollen through a small break in his skin. His experiment introduced the concept that pollen sensitivity caused hay fever. Today's skin testing methods vary in the way in which the allergen extract is introduced into the skin; however, the principle remains the same. As Blakely found, a positive reaction to a specific allergen becomes evident in about twenty minutes by the appearance of a hive like response at the tested skin site.

1902 – Charles Richet and Paul Portier invented the word 'anaphylaxis' when in the course of other immunization research they discovered this life threatening response to medications and protein substances. Anaphylactic shock occurs within minutes after allergen exposure, causing symptoms from swelling of body tissues, to vomiting, to cramps, to a sudden drop in blood pressure or even a loss of consciousness. It often occurs in people who are particularly sensitive to penicillin, stinging insects, shellfish, peanuts or tree nuts and it must be treated as a medical emergency.

1906 – Austrian Pediatrician Clemens von Pirquet first used the word 'allergy' to describe the strange, non-disease related symptoms that some diphtheria patients developed when treated with a horse serum antitoxin. The word comes from the Greek word 'alol', meaning, 'change in the original state.' Indeed an allergic reaction is the result of the body's change when it adversely responds to a harmless substance.

1911-1914 – The work of Leonard Noon and John Freeman helped established the basis for immunotherapy or allergy shots. Immunotherapy involves injecting the allergy sufferer with small, gradually increasing amounts of the substance that is causing the reaction. The idea is that over time, the body's immune system will become less sensitive to the substance and the allergy symptoms will be reduced or eliminated.

1937 – Daniel Bovet synthesized the first antihistamine drug. He and his colleagues found antihistamines, in blocking the effects of the chemical histamine also protected against some of the symptoms of anaphylaxis. Today's antihistamine drugs are effective in the treatment of the sneezing and runny nose of hay fever and the itching, swelling and redness of hives and some other allergic rashes.

1948 – Philip Hench and Edward Kendall discovered and introduced corticosteroids into clinical medicine. These drugs were found to be effective in the treatment of asthma and both immediate and delayed allergic reactions. Corticosteroids have significantly improved the lives of today's allergy sufferers.

1953 – Researches James F. Riley and Geoffrey B. West discovered the mast cell granule to be the major source of histamine in the body. In this fundamental contribution to the understanding of inflammatory and allergic reactions, Riley and West depended on a valued partner and

experimental subject named Judy. This ten-year-old cocker spaniel earned a place in canine history thanks to her mast cell tumour, which had the highest histamine content ever recorded.

1967 – Kimishige and Teruko Ishizaka further explained the allergy process by discovering the role of IgE class antibodies as the principal mediator in the allergic reaction. In response to repeated exposure to an allergen such as pollen, the allergic individual produces IgE antibodies, which then attach to mast cells. This is the first step in sensitizing the affected tissue. Upon repeated exposure, allergens cross-link IgE antibodies on the surface of the mast cells. It is this binding process that triggers the release of histamine and other mediators, thus causing allergy symptoms.

1980's – In the early 1980s Professor Bengt I Sameulsson received the Nobel Prize in Medicine/Physiology for identifying leukotrienes as the elusive 'slowing reacting substance of anaphylaxis' which had been implicated in allergic inflammation many years earlier. These are natural chemicals in the body, which contribute asthma attacks. His work greatly expanded the understanding of the important biological role leukotrienes play as mediators in asthma, allergy and inflammation. [(2)]

Mechanism of allergy

Allergic reactions are triggered when allergens cross-link preformed IgE bound to the high-affinity receptor FcεRI on mast cells. Mast cells line the body surfaces and serve to alert the immune system to local infection. Once activated, they induce inflammatory reactions by secreting chemical mediators stored in preformed granules, and by synthesizing leukotrienes and cytokines after activation occurs. In allergy, they provoke very unpleasant reactions to innocuous antigens that are not associated with invading pathogens that need to be expelled.

The consequences of IgE-mediated mast-cell activation depend on the dose of antigen and its route of entry; symptoms range from the irritating sniffles of hay fever when pollen is inhaled, to the life-threatening circulatory collapse that occurs in systemic anaphylaxis. The immediate allergic reaction caused by mast-cell degranulation is followed by a more sustained inflammation, known as the late-phase response. This late response involves the recruitment of other effector cells, notably TH2 lymphocytes, eosinophils, and basophils, which contribute significantly to the immunopathology of an allergic response.

Most IgE is cell-bound and engages effector mechanisms of the immune system by different pathways from other antibody isotypes:

Most antibodies are found in body fluids and engage effector cells, through receptors specific for the Fc constant regions, only after binding specific antigen through the antibody variable regions. IgE, however, is an exception as it is captured by the high-affinity Fcε receptor in the absence of bound antigen. This means that IgE is mostly found fixed in the tissues on mast cells that bear this receptor, as well as on circulating basophils and activated eosinophils. The ligation of cell-bound IgE antibody by specific antigen triggers activation of these cells at the site of antigen entry into the tissues. The release of inflammatory lipid mediators, cytokines, and chemokines at sites of IgE-triggered reactions results in the recruitment of eosinophils and basophils to augment the type I response.

There are two types of IgE-binding Fc receptor. The first, FcεRI, is a high-affinity receptor of the immunoglobulin superfamily that binds IgE on mast cells, basophils, and activated eosinophils. When the cell-bound IgE antibody is cross-linked by a specific antigen, FcεRI transduces an activating signal. High levels of IgE, such as those that exist in subjects with allergic diseases or parasite infections, can result in a marked increase in FcεRI on the surface of mast cells, enhanced sensitivity of such cells to activation by low concentrations of specific antigen, and

The second IgE receptor, FcεRII, usually known as CD23, is a C-type lectin and is structurally unrelated to FcεRI; it binds IgE with low affinity. CD23 is present on many different cell types, including B cells, activated T cells, monocytes, eosinophils, platelets, follicular dendritic cells,

and some thymic epithelial cells. This receptor was thought to be crucial for the regulation of IgE antibody levels; however, knockout mouse strains lacking the CD23 gene show no major abnormality in the development of polyclonal IgE responses. However the CD23 knockout mice have demonstrated a role for CD23 in enhancing the antibody response to a specific antigen in the presence of that same antigen complexed with IgE. This antigen-specific, IgE-mediated enhancement of antibody responses fails to occur in mice lacking the CD23 gene. This demonstrates a role for CD23 on antigen-presenting cells in the capture of antigen by specific IgE. Markedly increased IgE-dependent release of chemical mediators and cytokines.

Mast cells reside in tissues and orchestrate allergic reactions:

Mast cells were described by Ehrlich in the mesentery of rabbits and named Mastzellen (‘fattened cells’). Like basophils, mast cells contain granules rich in acidic proteoglycans that take up basic dyes. However, in spite of this resemblance, and the similar range of mediators stored in these basophilic granules, mast cells are derived from a different myeloid lineage than basophils and eosinophils. Mast cells are highly specialized cells, and are prominent residents of mucosal and epithelial tissues in the vicinity of small blood vessels and postcapillary venules, where they are well placed to guard against invading pathogens. Mast cells are also found in subendothelial connective tissue. They home to tissues as agranular cells; their final differentiation, accompanied by granule formation, occurs after they have arrived in the tissues. The major growth factor for mast cells is stem-cell factor (SCF), which acts on the cell-surface receptor c-Kit. Mice with defective c-Kit lack differentiated mast cells and cannot make IgE-mediated inflammatory responses. This shows that such responses depend almost exclusively on mast cells.

Mast cells express FcεRI constitutively on their surface and are activated when antigens cross-link IgE bound to these receptors. Degranulation occurs within seconds, releasing a variety of preformed inflammatory mediators. Among these are histamine—a short-lived vasoactive amine that causes an immediate increase in local blood flow and vessel permeability—and enzymes such as mast-cell chymase, tryptase, and serine esterases. These enzymes can in turn activate matrix metalloproteinases, which break down tissue matrix proteins, causing tissue destruction. Large amounts of tumor necrosis factor (TNF)-α are also released by mast cells after activation. Some comes from stores in mast-cell granules; some is newly synthesized by the activated mast cells themselves. TNF-α activates endothelial cells, causing increased expression of adhesion molecules, which promotes the influx of inflammatory leukocytes and lymphocytes into tissues.

On activation, mast cells synthesize and release chemokines, lipid mediators such as leukotrienes and platelet-activating factor (PAF), and additional cytokines such as IL-4 and IL-13 which perpetuate the TH2 response. These mediators contribute to both the acute and the chronic inflammatory responses. The lipid mediators, in particular, act rapidly to cause smooth muscle contraction, increased vascular permeability, and mucus secretion, and also induce the influx and activation of leukocytes, which contribute to the late-phase response. The lipid mediators derive from membrane phospholipids, which are cleaved to release the precursor molecule arachidonic acid. This molecule can be modified by two pathways to give rise to prostaglandins, thromboxanes, and leukotrienes. The leukotrienes, especially C4, D4, and E4, are important in

sustaining inflammatory responses in the tissues. Many anti-inflammatory drugs are inhibitors of arachidonic acid metabolism. Aspirin, for example, is an inhibitor of the enzyme cyclooxygenase and blocks the production of prostaglandins.

IgE-mediated activation of mast cells thus orchestrates an important inflammatory cascade that is amplified by the recruitment of eosinophils, basophils, and TH2 lymphocytes. The physiological importance of this reaction is as a defense mechanism against certain types of infection. In allergy, however, the acute and chronic inflammatory reactions triggered by mast-cell activation have important pathophysiological consequences, as seen in the diseases associated with allergic responses to environmental antigens.

Eosinophils are normally under tight control to prevent inappropriate toxic responses:

Eosinophils are granulocytic leukocytes that originate in bone marrow. They are so called because their granules, which contain arginine-rich basic proteins, are colored bright orange by the acidic stain eosin. Only very small numbers of these cells are normally present in the circulation; most eosinophils are found in tissues, especially in the connective tissue immediately underneath respiratory, gut, and urogenital epithelium, implying a likely role for these cells in defense against invading organisms. Eosinophils have two kinds of effector function. First, on activation they release highly toxic granule proteins and free radicals, which can kill microorganisms and parasites but can also cause significant tissue damage in allergic reactions. Second, activation induces the synthesis of chemical mediators such as prostaglandins, leukotrienes, and cytokines, which amplify the inflammatory response by activating epithelial cells, and recruiting and activating more eosinophils and leukocytes.

The activation and degranulation of eosinophils is strictly regulated, as their inappropriate activation would be very harmful to the host. The first level of control acts on the production of eosinophils by the bone marrow. Few eosinophils are produced in the absence of infection or other immune stimulation. But when TH2 cells are activated, cytokines such as IL-5 are released that increase the production of eosinophils in the bone marrow and their release into the circulation. However, transgenic animals overexpressing IL-5 have increased numbers of eosinophils (eosinophilia) in the circulation but not in their tissues, indicating that migration of eosinophils from the circulation into tissues is regulated separately, by a second set of controls. The key molecules in this case are CC chemokines. Most of these cause chemotaxis of several types of leukocyte, but two are specific for eosinophils and have been named eotaxin 1 and eotaxin 2.

The eotaxin receptor on eosinophils, CCR3, is a member of the chemokine family of receptors. This receptor also binds the CC chemokines MCP-3, MCP-4, and RANTES, which also induce eosinophil chemotaxis. The eotaxins and these other CC chemokines also activate eosinophils. Identical or similar chemokines also stimulate mast cells and basophils. For example, eotaxin attracts basophils and causes their degranulation, and MCP-1, which binds to CCR2, similarly activates mast cells in both the presence and absence of antigen. MCP-1 can also promote the differentiation of naive TH0 cells to TH2 cells; TH2 cells also carry CCR3 and migrate toward

eotaxin. These findings show that families of chemokines, as well as cytokines, can coordinate certain kinds of immune response.

A third set of controls regulates the state of eosinophil activation. In their nonactivated state, eosinophils do not express high-affinity IgE receptors and have a high threshold for release of their granule contents. After activation by cytokines and chemokines, this threshold drops, FcεRI is expressed, and the number of Fcγ receptors and complement receptors on the cell surface also increases. The eosinophil is now primed to carry out its effector activity, for example degranulation in response to antigen that cross-links specific IgE bound to FcεRI on the eosinophil surface.

The potential of eosinophils to cause tissue injury is illustrated by rare syndromes due to abnormally large numbers of eosinophils in the blood (hypereosinophilia). These syndromes are sometimes seen in association with T-cell lymphomas, in which unregulated IL-5 secretion drives a marked increase in the numbers of circulating eosinophils. The clinical manifestations of hypereosinophilia are damage to the endocardium and to nerves, leading to heart failure and neuropathy, both thought to be caused by the toxic effects of eosinophil granule proteins.

Eosinophils and basophils cause inflammation and tissue damage in allergic reactions:

In a local allergic reaction, mast-cell degranulation and TH2 activation cause eosinophils to accumulate in large numbers and to become activated. Their continued presence is characteristic of chronic allergic inflammation and they are thought to be major contributors to tissue damage.

Basophils are also present at the site of an inflammatory reaction. Basophils share a common stem-cell precursor with eosinophils; growth factors for basophils are very similar to those for eosinophils and include IL-3, IL-5, and GM-CSF. There is evidence for reciprocal control of the maturation of the stem-cell population into basophils or eosinophils. For example, transforming growth factor (TGF)-β in the presence of IL-3 suppresses eosinophil differentiation and enhances that of basophils. Basophils are normally present in very low numbers in the circulation and seem to have a similar role to eosinophils in defense against pathogens. Like eosinophils, they are recruited to the sites of allergic reactions. Basophils express FcεRI on the cell surface and, on activation by cytokines or antigen, they release histamine and IL-4 from the basophilic granules after which they are named.

Eosinophils, mast cells, and basophils can interact with each other. Eosinophil degranulation releases major basic protein, which in turn causes degranulation of mast cells and basophils. This effect is augmented by any of the cytokines that affect eosinophil and basophil growth, differentiation, and activation, such as IL-3, IL-5, and GM-CSF.

An allergic reaction is divided into an immediate response and a late-phase response:

The inflammatory response after IgE-mediated mast-cell activation occurs as an immediate reaction, starting within seconds, and a late reaction, which takes up to 8–12 hours to develop. These reactions can be distinguished clinically. The immediate reaction is due to the activity of histamine, prostaglandins, and other preformed or rapidly synthesized mediators that cause a rapid increase in vascular permeability and the contraction of smooth muscle. The late-phase

reaction is caused by the induced synthesis and release of mediators including leukotrienes, chemokines, and cytokines from the activated mast cells. These recruit other leukocytes, including eosinophils and TH2 lymphocytes, to the site of inflammation. Although the late-phase reaction is clinically less marked than the immediate response, it is associated with a second phase of smooth muscle contraction, sustained edema, and the development of one of the cardinal features of allergic asthma: airway hyper-reactivity to nonspecific bronchoconstrictor stimuli such as histamine and methacholine.

The late-phase reaction is an important cause of much serious long-term illness, as for example in chronic asthma. This is because the late reaction induces the recruitment of inflammatory leukocytes, especially eosinophils and TH2 lymphocytes, to the site of the allergen-triggered mast-cell response. This late response can easily convert into a chronic inflammatory response if antigen persists and stimulates allergen-specific TH2 cells, which in turn promote eosinophilia and further IgE production.

The clinical effects of allergic reactions vary according to the site of mast-cell activation:

When re-exposure to allergen triggers an allergic reaction, the effects are focused on the site at which mast-cell degranulation occurs. In the immediate response, the preformed mediators released are short-lived, and their potent effects on blood vessels and smooth muscles are therefore confined to the vicinity of the activated mast cell. The more sustained effects of the late-phase response are also focused on the site of initial allergen-triggered activation, and the particular anatomy of this site may determine how readily the inflammation can be resolved. Thus, the clinical syndrome produced by an allergic reaction depends critically on three variables: the amount of allergen-specific IgE present; the route by which the allergen is introduced; and the dose of allergen.

If an allergen is introduced directly into the bloodstream or is rapidly absorbed from the gut, the connective tissue mast cells associated with all blood vessels can become activated. This activation causes a very dangerous syndrome called systemic anaphylaxis.

Disseminated mast-cell activation has a variety of potentially fatal effects: the widespread increase in vascular permeability leads to a catastrophic loss of blood pressure; airways constrict, causing difficulty in breathing; and swelling of the epiglottis can cause suffocation. This potentially fatal syndrome is called anaphylactic shock. It can occur if drugs are administered to people who have IgE specific for that drug, or after an insect bite in individuals allergic to insect venom. Some foods, for example peanuts or brazil nuts, can cause systemic anaphylaxis in susceptible individuals. This syndrome can be rapidly fatal but can usually be controlled by the immediate injection of epinephrine, which relaxes the smooth muscle and inhibits the cardiovascular effects of anaphylaxis.

The most frequent allergic reactions to drugs occur with penicillin and its relatives. In people with IgE antibodies against penicillin, administration of the drug by injection can cause anaphylaxis and even death. Great care should be taken to avoid giving a drug to patients with a past history of allergy to that drug or one that is closely related structurally. Penicillin acts as a hapten; it is a small molecule with a highly reactive β-lactam ring that is crucial for its

antibacterial activity. This ring reacts with amino groups on host proteins to form covalent conjugates. When penicillin is ingested or injected, it forms conjugates with self-proteins, and the penicillin-modified self-peptides can provoke a TH2 response in some individuals. These TH2 cells then activate penicillin-binding B cells to produce IgE antibody to the penicillin hapten. Thus, penicillin acts both as the B-cell antigen and, by modifying self-peptides, as the T-cell antigen. When penicillin is injected intravenously into an allergic individual, the penicillin-modified proteins can cross-link IgE molecules on the mast cells and cause anaphylaxis.

Allergen inhalation is associated with the development of rhinitis and asthma:

Inhalation is the most common route of allergen entry. Many people have mild allergies to inhaled antigens, manifesting as sneezing and a runny nose. This is called allergic rhinitis, and results from the activation of mucosal mast cells beneath the nasal epithelium by allergens such as pollens that release their protein contents, which can then diffuse across the mucus membranes of the nasal passages. Allergic rhinitis is characterized by intense itching and sneezing, local edema leading to blocked nasal passages, a nasal discharge, which is typically rich in eosinophils, and irritation of the nose as a result of histamine release. A similar reaction to airborne allergens deposited on the conjunctiva of the eye is called allergic conjunctivitis. Allergic rhinitis and conjunctivitis are commonly caused by environmental allergens that are only present during certain seasons of the year. For example, hay fever is caused by a variety of allergens, including certain grass and tree pollens. Autumnal symptoms may be caused by weed pollen, such as that of ragweed. These reactions are annoying but cause little lasting damage.

A more serious syndrome is allergic asthma, which is triggered by allergen-induced activation of sub mucosal mast cells in the lower airways. This leads within seconds to bronchial constriction and increased secretion of fluid and mucus, making breathing more difficult by trapping inhaled air in the lungs. Patients with allergic asthma often need treatment, and asthmatic attacks can be life-threatening. An important feature of asthma is chronic inflammation of the airways, which is characterized by the continued presence of increased numbers of TH2 lymphocytes, eosinophils, neutrophils, and other leukocytes.

Although allergic asthma is initially driven by a response to a specific allergen, the subsequent chronic inflammation seems to be perpetuated even in the apparent absence of further exposure to allergen. The airways become characteristically hyper-reactive and factors other than re-exposure to antigen can trigger asthma attacks. For example, the airways of asthmatics characteristically show hyper-responsiveness to environmental chemical irritants such as cigarette smoke and sulfur dioxide; viral or, to a lesser extent, bacterial respiratory tract infections can exacerbate the disease by inducing a TH2-dominated local response.

Skin allergy is manifest as urticaria or chronic eczema:

The same dichotomy between immediate and delayed responses is seen in cutaneous allergic responses. The skin forms an effective barrier to the entry of most allergens but it can be breached by local injection of small amounts of allergen, for example by a stinging insect. The entry of allergen into the epidermis or dermis causes a localized allergic reaction. Local mast-cell activation in the skin leads immediately to a local increase in vascular permeability, which

causes extravasation of fluid and swelling. Mast-cell activation also stimulates the release of chemicals from local nerve endings by a nerve axon reflex, causing the vasodilation of surrounding cutaneous blood vessels, which causes redness of the surrounding skin. The resulting skin lesion is called a wheal-and-flare reaction. About 8 hours later, a more widespread and sustained edematous response appears in some individuals as a consequence of the late-phase response. A disseminated form of the wheal-and-flare reaction, known as urticaria or hives, sometimes appears when ingested allergens enter the bloodstream and reach the skin. Histamine released by mast cells activated by allergen in the skin causes large, itchy, red swellings of the skin.

Allergists take advantage of the immediate response to test for allergy by injecting minute amounts of potential allergens into the epidermal layer of the skin. Although the reaction after the administration of antigen by intraepidermal injection is usually much localized, there is a small risk of inducing systemic anaphylaxis. Another standard test for allergy is to measure levels of IgE antibody specific for a particular allergen in a sandwich ELISA.

Although acute urticaria is commonly caused by allergens, the causes of chronic urticaria, in which the urticarial rash can recur over long periods, are less well understood. In up to a third of cases, it seems likely that chronic urticaria is an autoimmune disease caused by autoantibodies against the α chain of FcεRI. This is an example of a type II hypersensitivity reaction in which an autoantibody against a cellular receptor triggers cellular activation, in this case causing mast-cell degranulation with resulting urticaria.

A more prolonged inflammatory response is sometimes seen in the skin, most often in atopic children. They develop a persistent skin rash called eczema or atopic dermatitis, due to a chronic inflammatory response similar to that seen in the bronchial walls of patients with asthma. The etiology of eczema is not well understood. TH2 cells and IgE are involved, and it usually clears in adolescence, unlike rhinitis and asthma, which can persist throughout life.

Allergy to foods causes symptoms limited to the gut and systemic reactions:

When an allergen is eaten, two types of allergic response are seen. Activation of mucosal mast cells associated with the gastrointestinal tract leads to trans-epithelial fluid loss and smooth muscle contraction, causing diarrhea and vomiting. For reasons that are not understood, connective tissue mast cells in the dermis and subcutaneous tissues can also be activated after ingestion of allergen, presumably by allergen that has been absorbed into the bloodstream, and this results in urticaria. Urticaria is a common reaction when penicillin is given orally to a patient who already has penicillin-specific IgE antibodies. Ingestion of food allergens can also lead to the development of generalized anaphylaxis, accompanied by cardiovascular collapse and acute asthmatic symptoms. Certain foods, most importantly peanuts, tree nuts, and shellfish, are particularly associated with this type of life-threatening response.

Allergy can be treated by inhibiting either IgE production or the effector pathways activated by cross-linking of cell-surface IgE:

Two treatments are commonly used in clinical practice—one is desensitization and the other is blockade of the effector pathways. There are also several approaches still in the experimental stage. In desensitization the aim is to shift the antibody response away from one dominated by IgE toward one dominated by IgG; the latter can bind to the allergen and thus prevent it from activating IgE-mediated effector pathways. Patients are injected with escalating doses of allergen, starting with tiny amounts. This injection schedule gradually diverts the IgE-dominated response, driven by TH2 cells, to one driven by TH1 cells, with the consequent downregulation of IgE production. Recent evidence shows that desensitization is also associated with a reduction in the numbers of late-phase inflammatory cells at the site of the allergic reaction. A potential complication of the desensitization approach is the risk of inducing IgE-mediated allergic responses.

An alternative, and still experimental, approach to desensitization is vaccination with peptides derived from common allergens. This procedure induces T-cell anergy, which is associated with multiple changes in the T-cell phenotype, including downregulation of cytokine production and reduced expression of the CD3:T-cell receptor complex. IgE-mediated responses are not induced by the peptides because IgE, in contrast to T cells, can only recognize the intact antigen. A major difficulty with this approach is that an individual's responses to peptides are restricted by their MHC class II alleles; therefore, patients with different MHC class II molecules respond to different allergen-derived peptides. As the human population is outbred and expresses a wide variety of MHC class II alleles, the number of peptides required to treat all allergic individuals might be very large.

Another vaccination strategy that shows promise in experimental models of allergy is the use of oligodeoxynucleotides rich in unmethylated cytosine guanine dinucleotides (CpG) as adjuvants for desensitization regimes. These oligonucleotides mimic bacterial DNA sequences known as CpG motifs and strongly promote TH1 responses.

The signaling pathways that enhance the IgE response in allergic disease are also potential targets for therapy. Inhibitors of IL-4, IL-5, and IL-13 would be predicted to reduce IgE responses, but redundancy between some of the activities of these cytokines might make this approach difficult to implement in practice. A second approach to manipulating the response is to give cytokines that promote TH1-type responses. IFN-γ, IFN-α, IL-10, IL-12, and TGF-β have each been shown to reduce IL-4-stimulated IgE synthesis in vitro, and IFN-γ and IFN-α have been shown to reduce IgE synthesis in vivo.

Another target for therapeutic intervention might be the high-affinity IgE receptor. An effective competitor for IgE at this receptor could prevent the binding of IgE to the surfaces of mast cells, basophils, and eosinophils. Candidate competitors include humanized anti-IgE monoclonal antibodies, which bind to IgE and block its binding to the receptor, and modified IgE Fc constructs that bind to the receptor but lack variable regions and thus cannot bind antigen. Yet another approach would be to block the recruitment of eosinophils to sites of allergic

inflammation. The eotaxin receptor CCR3 is a potential target for this type of therapy. The production of eosinophils in bone marrow and their exit into the circulation might also be reduced by a blockade of IL-5 action.

The mainstays of therapy at present, however, are drugs that treat the symptoms of allergic disease and limit the inflammatory response. Anaphylactic reactions are treated with epinephrine, which stimulates the reformation of endothelial tight junctions, promotes the relaxation of constricted bronchial smooth muscle, and also stimulates the heart. Inhaled bronchodilators that act on β-adrenergic receptors to relax constricted muscle are also used to relieve acute asthma attacks. Antihistamines that block the histamine H1 receptor reduce the urticaria that follows histamine release from mast cells and eosinophils. Relevant H1 receptors include those on blood vessels that cause increased permeability of the vessel wall, and those on unmyelinated nerve fibers that are thought to mediate the itching sensation. In chronic allergic disease it is extremely important to treat and prevent the chronic inflammatory tissue injury. Topical or systemic corticosteroids are used to suppress the chronic inflammatory changes seen in asthma, rhinitis, and eczema.

In summary the allergic response to innocuous antigens reflects the pathophysiological aspects of a defensive immune response whose physiological role is to protect against helminthic parasites. It is triggered by antigen binding to IgE antibodies bound to the high-affinity IgE receptor FcεRI on mast cells. Mast cells are strategically distributed beneath the mucosal surfaces of the body and in connective tissue. Antigen cross-linking the IgE on their surface causes them to release large amounts of inflammatory mediators. The resulting inflammation can be divided into early events, characterized by short-lived mediators such as histamine, and later events that involve leukotrienes, cytokines, and chemokines, which recruit and activate eosinophils and basophils. The late phase of this response can evolve into chronic inflammation, characterized by the presence of effector T cells and eosinophils, which is most clearly seen in chronic allergic asthma. [3]

Types of hypersensitivity reactions

Hypersensitivity (also called hypersensitivity reaction or intolerance) is a set of undesirable reactions produced by the normal immune system, including allergies and autoimmunity. They are usually referred to as an over- reaction of the immune system and these reactions may be damaging, uncomfortable, or occasionally fatal. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. They are classified in four groups after the proposal of P. G. H. Gell and Robin Coombs in 1963. [(4)]

Type I hypersensitivity: immediate (atopic or anaphylactic):

Type I hypersensitivity is an allergic reaction. Exposure to the allergen may be by ingestion, inhalation, injection or direct contact. The difference between a normal immune response and a type I hypersensitivity response is that plasma cells secrete IgE antibodies that bind to mast cells and basophils that then release histamines, a vasodilator, and heparin, a blood thinner. These cause inflammation at the site as blood flow to the affected tissues is increased. The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from anaphylactic shock. This is why allergies are manifested as red and watery eyes, runny nose and hives. Asthma is a form of anaphylaxis, as a combination of oedema and airway constriction prevents tissues from getting sufficient oxygen.

Examples of type I hypersensitivity include:

- allergic asthma
- allergic conjunctivitis
- allergic rhinitis (‘hay fever’)
- anaphylaxis
- angio-oedema
- atopic dermatitis (eczema)
- eosinophilia
- urticaria (hives)

Chinese medicine treats asthma attacks essentially by breaking the connection between an antigen and IgE.

Type I hypersensitivities occur in individuals who synthesize IgE antibodies to foreign antigens. IgE binds to specialized Fc receptors on mast cells and eosinophils. Subsequent exposure to the same antigen cross-links cell-bound IgE resulting in mast cell degranulation and rapid release of several pharmacologically active mediators including histamine, prostaglandins, and leukotrienes as well as cytokines, chemokines, and enzymes. These mediators induce vasodilation and smooth muscle contraction leading to increased vascular permeability, bronchial constriction, increased mucus production, vomiting and diarrhea, and, sometimes, death.

Initial documented descriptions of type I hypersensitivities appeared during the 1890s. Emil von Behring in 1894 observed that the initial exposure of an animal to antibody specific for diphtheria toxin produced in horses induced no clinical symptoms. Animals repeatedly injected

with antibody, however, developed cardiovascular and/or pulmonary distress; he termed this reaction hypersensitivity. Contemporaneously several other investigators reported similar findings in experimental animals repeatedly injected with other foreign substances. The reaction, induced by extremely small doses of the foreign substance, occasionally resulted in death of the animal. Originally investigators attributed these reactions, erroneously, to an increased susceptibility to an intrinsic toxic property of the injected substance. At that time, investigators failed to recognize the possible connection with the immune system. Two French scientists identified the immunologic mechanism responsible for this phenomenon in 1902.

Prince Albert I of Monaco had an interest in science, particularly oceanography. He outfitted a number of yachts for scientific study and staffed them with scientists, scientific equipment, and experimental animals. These yachts sailed the Mediterranean Sea every summer with scientists working on questions of interest to the Prince. In 1901, Prince Albert invited Paul Portier (1866–1962) and Charles Richet (1850–1935) to sail on one of these yachts. Prince Albert's scientific director, Jules Richard, suggested that Portier and Richet study the reaction of fish and humans to the Portuguese man-of-war, an invertebrate found in the Mediterranean Sea.

The Portuguese man-of-war (Physilia) captures its prey by brushing against them with its tentacles and immobilizes them. The effect on humans who inadvertently come in contact with these same tentacles includes stinging, burning, redness, extreme pain, and lymphadenopathy.

In previously exposed individuals who develop hypersensitivities, a subsequent exposure may result in difficulty breathing and cardiac arrest.

Portier and Richet initially postulated that the tentacles released a poison that produced the reaction. They prepared extracts of the tentacles, which they injected into various experimental animals, and observed respiratory distress and other reactions suggestive of a powerful toxin with profound effects on the central nervous system. Portier and Richet proposed producing an antibody to the toxin to neutralize it. Theirs was a reasonable approach in the early 1900s and was based on the model of treatment of diphtheria with an antibody directed to diphtheria toxin that produced seemingly miraculous cures. The summer ended and Portier and Richet returned to their laboratory in Paris to continue this work. Since they no longer had access to Portuguese man-of-war for these studies, they switched to a related toxin from a sea anemone, Actinia sulcata.

Portier and Richet injected dogs with a dose of the sea anemone toxin and rested them for several weeks to allow the dogs to develop an expected protective antibody (antitoxin) response. None of the injected dogs demonstrated any adverse reaction. They then reinjected the dogs with a second dose of the toxin to assess the level of protection. Instead of being protected, the dogs developed sudden onset of diarrhea and vomiting, and many of them succumbed to this second injection.

Portier and Richet referred to this unexpected result by the term aphylaxis (shortly changed to anaphylaxis) to distinguish it from phylaxis, a term defined as protection against infection (Portier and Richet, 1902). Richet, awarded the Nobel Prize in Physiology or Medicine in 1913

"in recognition of his work on anaphylaxis," recounted in an address delivered to the International Congress of Physiology in 1910:

Anaphylaxis is the opposite of protection (phylaxis). If one injects an albuminoid substance—for example, a toxin—into the circulatory system of an animal, instead of being protected by this first injection against a further injection of the same toxin, it has become more sensitive to its action. Let us suppose that the fatal dose is 1 cg. The injection of a tenth part of that dose, that is to say 1 mg—will not make it at all ill or scarcely so. But a month later-for almost a month is required for the anaphylactic state to be produced-it has become so sensitive that a dose of 1 mg is enough to kill it by the immediate production of formidable symptoms. Therefore the first injection has caused a condition which is the opposite of protection-namely anaphylaxis.

The Immune System in Anaphylaxis:

Because the mechanism of anaphylaxis was not immediately obvious researchers suggested two possibilities:

- a humoral theory that hypothesized the formation of an enzymatic cleavage product released from the toxin more rapidly on second injection of the toxin (Vaughan and Wheeler, 1907); or
- A cellular theory that proposed that antibody was synthesized in response to the original sensitization and that this antibody was taken up by cells within the target organs (e.g., in the cardiovascular and respiratory systems) prior to the second challenge (Besredka, 1907).

  Attempts to detect specific antibody in serum from injected animals met with failure although some investigators demonstrated that the reaction could be transferred to naïve animals using serum. John Anderson and W.H. Frost working in the Hygiene Laboratory of the U.S. Public Health and Marine Hospital Service, Washington, D.C., demonstrated in 1910 that serum from a hypersensitive animal could transfer anaphylaxis to naive animals. Anderson and Frost injected guinea pigs with horse serum to induce hypersensitivity. They then injected naïve guinea pigs with serum from these hypersensitive guinea pigs. Subsequent injection of the recipient guinea pigs with horse serum induced an anaphylactic reaction. The time required between injection of the serum and demonstration of a hypersensitivity reaction was less than 24 h. Anderson and Ford incubated the original guinea pig serum with horse serum to absorb out any antibody. The treated guinea pig serum failed to transfer the hypersensitivity thus suggesting that antibody was involved in this transfer.

  In 1910, Werner Schultz (1878–1947) also working at the Hygiene Laboratory of the U.S. Public Health and Marine Hospital Service in Washington, D.C., developed an in vitro technique that led to an explanation to the mechanism by which anaphylaxis caused tissue damage. Schultz injected guinea pigs with horse serum. He dissected muscle strips from the ileum of these animals and suspended them in isotonic saline. He then added

either horse serum or serum from other species as control to the preparations. Horse serum induced muscle contraction in preparations from hypersensitive animals while addition of serum from other species failed to produce contraction.
In 1911, Henry Hallett Dale (1875–1968) and Patrick Laidlaw (1881–1940) working at the Wellcome Physiological Research Laboratories in London demonstrated the role of histamine in this reaction. They suspended uterine muscle from nonsensitized guinea pigs in saline, added histamine (β-iminapolyethylamine), and observed muscle contraction identical to that seen when antigen was added to muscle from a sensitized animal. Despite the fact that Werner Schultz and Henry Dale never collaborated, the phenomenon they studied is called the Schultz–Dale reaction, and investigators used this model for almost 50 years to dissect, diagnose, and explain antibody-mediated type I hypersensitivity.

Dale received his MD from Cambridge and pursued physiological and pharmacological investigations while at University College and the National Institute of Medical Research, both in London. Dale pursued other studies including ones on the transmission of nerve impulses and shared the Nobel Prize for Physiology or Medicine in 1936 with Otto Loewi "for their discoveries relating to chemical transmission of nerve impulses."

Type I hypersensitivity reactions in humans were not immediately recognized despite anecdotal evidence that humans developed anaphylaxis. In 1896, Gottstein reported human fatalities following administration of horse antibodies specific for diphtheria toxin. Other investigators observed fatal consequences of bee stings.

In 1921, Otto Prausnitz (1876–1963) and Heinz Küstner (1897–1963) working at the Hygiene Institute of the University of Breslau in Germany, reported the transfer of skin hypersensitivity from an allergic to a healthy individual. They collected serum from Küstner, who was exquisitely sensitive to fish, and injected it subcutaneously into Prausnitz. Twenty-four hours later they applied a fish extract locally to Prausnitz' skin and observed an immediate skin reaction characterized by the appearance of a wheal and flare. This Prausnitz–Küstner (P-K) reaction proved useful to demonstrate the pathophysiology of hypersensitivity in humans. In fact Ishizaka and his coworkers employed the P-K reaction in the mid-1960s to identify the antibody isotype responsible for allergy to ragweed pollen.

While these early studies showed that antibody transferred one of the models of type I hypersensitivity, the identity of the specific antibody isotype responsible was described 45 years later. Kimishige Ishizaka working with his wife Teruka and colleagues at the University of Colorado Medical School (1966) and S. Gunnar O. Johansson and Hans Bennich (1967) working at University Hospital, Uppsala, Sweden, described a novel isotype of antibody, IgE, involved in type I hypersensitivities.

Humans synthesize IgE antibodies to provide protective immunity against protozoal parasites. However, a group of genetically susceptible individuals produce IgE to foreign antigens that subsequently activate an immediate hypersensitivity upon re-exposure to the antigen. The most common antigens to which IgE is synthesized are foods (e.g., peanuts, seafood), drugs (e.g., penicillin, codeine), and insect venom (e.g., wasps, bees). IgE antibodies induced by these antigens bind to effector cells (mast cells) throughout the body. Reintroduction of the sensitizing antigen cross-links two IgE molecules causing release of vasoactive mediators (e.g., histamine) leading to the signs and symptoms associated with hypersensitivity including shortness of breath, asthma, allergic rhinitis, hypotension, irregular heartbeat, eczema, urticaria, and gastrointestinal disorders. [5]

Type II Hypersensitivity

Type II hypersensitivity is an antibody-dependent process in which specific antibodies bind to antigens, resulting in tissue damage or destruction. If the antigen is present on cell surfaces, antibody binding can result in cell lysis through the in situ fixation of complement. IgM antibodies (multimeric) are often more effective in fixing complement than are than IgG antibodies (monomeric). Type II hypersensitivity is typified by a transfusion reaction in which mismatched red blood cells are rapidly destroyed by specific preformed antibodies (anti-ABO or -Rh) and complement. Although fixation of complement can result in direct cell lysis, opsonization and recruitment of inflammatory cells is often a more important cause of cell injury.

Type II hypersensitivity is mediated by IgM or IgG targeting membrane-associated antigens. A sensitization phase leads to production of antibodies that recognize substances or metabolites that accumulate in cellular membrane structures. In the effector phase, target cells become coated with antibodies, a process termed opsonization, which leads to cellular destruction by three mechanisms: (i) phagocytosis, (ii) complement-dependent cytotoxicity (CDC), and (iii) ADCC. First, IgG or IgM antibodies coating target cells can bind to Fc receptors present on cells such as macrophages and neutrophils and mediate phagocytosis. IgG or IgM antibodies can also activate complement via the classical pathway. This leads to deposition of C3b, which can mediate phagocytosis. Complement activation also leads to production of the MAC, which forms pores in the cellular membrane resulting in cytolysis (CDC). Finally, IgG antibodies can bind FcγRIII on NK cells and macrophages, thus mediating release of granzymes and perforin and resulting in cell death by apoptosis (ADCC).

The most common causes of type II reactions are medications including penicillins, cephalosporins, hydrochlorothiazide, and methyldopa, which become associated with red blood cells or platelets leading to anemia and thrombocytopenia. The mechanisms involved in type II hypersensitivity also play a role in cellular destruction by autoantibodies.

Type II hypersensitivity results from antibodies of either the IgG or IgM class binding to specific antigens on a cell surface or extracellular matrix, with subsequent activation of the classical complement cascade. This leads either to direct lytic damage of the target cells or facilitates opsonization by attracting polymorphs and macrophages/monocytes bearing C3bR. C3 components can also bind C3bR on mast cells and basophils and trigger the production of molecules which attract and activate other effector cells. In addition, IgG is able to directly cross-link effector cells. In this case, the antibody acts as a bridge between the target cells and the effector cells through the engagement of Fc receptors on effector cells (Figure 3). It is known that only antigen bound IgG (but not free IgG) can bind FcγR with high avidity. Fcγ receptors are present on a variety of effector cells: phagocytic (macrophages, neutrophils), non-phagocytic (platelets, eosinophils), and large granular lymphocytes (killer (K) and natural killer (NK) cells). Different IgG subclasses vary in their ability to bind FcγR-bearing effector cells, human IgG1 and IgG3 being able to bind more efficiently than IgG2 or IgG4. The destruction of antibody-

coated cells by NK cells is referred to as antibody-dependent cellular cytotoxicity (ADCC) and represents a mechanism by which an antibody can direct an antigen-specific attack by an effector cell lacking specificity for the antigen. Thus, target specificity of NK cells is broader than that of cytotoxic T cells, but it does not occur at random.

Type II reactions can involve the activation of a membrane oxidase complex responsible for the secretion of oxygen radicals. Cytotoxicity also follows the activation of phospholipase A2, which produces arachidonic acid secretion and consequently leukotriene/prostaglandin release. These vasoactive amines contribute to the target cell damage.

Reactions to red cells represent the clearest examples of type II hypersensitivity. The observation made by Landsteiner, at the beginning of the twentieth century, that the serum of some human blood donors agglutinates the red cells of other normal blood donors, underlies the basis of the present understanding of two life-threatening reactions: hemolytic anemia of the newborn (erythroblastosis fetalis) and blood transfusion reactions. In both cases, the blood group of the 'donor' does not match with that of the 'recipient'.

Erythroblastosis fetalis

In this condition it is the rhesus (Rh) antigen system on the red cell surface which is responsible for the reaction causing fetal–maternal incompatibility. The name has derived from a similar antigen recognized by the serum of rabbits immunized with rhesus monkey red cells. The human Rh (D) antigen is encoded by a dominant gene which is present in approximately 80% of the population. There are therefore Rh+ and Rh− individuals. The disease follows the gradual sensitization of a Rh− mother to the blood group Rh+ antigen of fetal red cells bearing the paternal Rh+ antigen. This happens at the time of first delivery when the mixing of maternal newborn blood occurs. As a consequence, Rh+-specific IgG is made in the postpartum period. With subsequent pregnancies, these antibodies cross the placenta into the fetal circulation and react with fetal red cells, destroying them. Therefore the disease mainly occurs with the second or subsequent Rh+-incompatible children. The symptoms are hepatosplenomegaly, elevated bilirubin with jaundice, hemorrhage and kidney failure.

Transfusion reactions:

Among the 19 different human blood group systems, the group ABO is the most important. Nearly all individuals make IgM antibodies to the antigens of the ABO system that they lack. These antibodies do not cross the placenta; they occur naturally, without prior immunization, possibly through cross-reactions of similar antigens on a variety of environmental agents. If an individual is blood group A, he or she will be tolerant to A and agglutinate B red cells, and vice versa for a blood group B individual. Conversely, a blood group O person will make anti-A and anti-B as natural antibodies and will only tolerate blood transfusions from group O individuals. Thus, if mismatched blood is transfused, it will cause blood agglutination, complement activation and intravascular hemolysis in the recipient. The hemolytic damage is characterized by jaundice, fever, kidney failure and rapid death of the patient.

A less common example of type II hypersensitivity is the autoimmune hemolytic anemia (AHA), in which patients react to their own red blood cells. The diagnosis is generally made by a positive Coombs test in which the autoimmune reaction is detected by an agglutination obtained with the addition of human-specific immunoglobulin which agglutinates the autoantibody-coated cells.

Finally, in certain autoimmune diseases, type II reactions can cause immunopathologic damage as the autoantibodies are directed to cell surface or to cytoplasmic antigens. Good pastures syndrome, pemphigus and myasthenia gravis are all caused by autoantibodies directed to cell surfaces antigens. In Good pastures syndrome the autoantibodies are directed to the glomerular basement membrane, causing glomerulonephritis, and sometimes also to the alveolar basal membrane, causing lung hemorrhage. In pemphigus the Pathogenetic antibodies are directed to desmosome antigens and cause the breakdown of the epidermis. In myasthenia gravis the autoimmune destruction is directed against acetylcholine receptors and is responsible for extreme muscular weakness. Conversely, in other organ-specific autoimmune diseases, such as insulin-dependent diabetes mellitus (IDDM) and Hashimotos thyroiditis, the autoantibodies are mainly directed against cytoplasmic antigens (islet cells and thyroid peroxidase, respectively). Their pathogenic relevance is still uncertain. There are indications that IDDM and Hashimotos disease might be caused by a T rather than B cell mediated mechanism. [6]

Type III hypersensitivity

Type III hypersensitivity reactions are also termed immune complex reactions. Complexes of antigen and antibody form in the circulation and are then deposited in susceptible tissues; they may also form directly in the tissue. The latter mechanism is termed the Arthus reaction, and is typically seen with repeated insect stings, where a red swollen lesion develops after a sting. The tissue damaging mechanisms are similar to those described for the antigen-antibody complexes that form in type II responses. The response times of types II and III hypersensitivity reactions are slower than that of type I reactions; they typically develop 3–6 h after exposure to antigen. The response can also become chronic, particularly in autoimmune reactions, where antigen persists.

The clinical manifestations of type III hypersensitivity reactions relate to the tissue deposition, for example vasculitic (skin), serum sickness (systemic), nephritis (kidneys) and extrinsic allergic alveolitis (lungs).

Type III hypersensitivity results from soluble antigen-antibody immunocomplexes that activate complement. The antigens may be self or foreign (i.e., microbial). Such complexes are deposited on membrane surfaces of various organs (e.g., kidney, lung, synovium). The by-products of complement activation (C3a, C5a) are chemotaxins for acute inflammatory cells, resulting in infiltration by polymorphonuclear (PMN) cells. Lysosomal enzymes are released that result in tissue injury. Platelet aggregation occurs, resulting in microthrombus formation in the vasculature. This type of hypersensitivity was classically characterized as the Arthus reaction, identified by a high degree of PMN infiltrate, vasoactive amine release, and erythema and edema in response to intradermal injection of antigen. Type III reactions and accompanying inflammatory injury are seen in diseases such as rheumatoid arthritis, systemic lupus erythematosus, and post infectious arthritis.

Serum sickness is a systemic type III hypersensitivity reaction, historically described in patients injected with therapeutic horse antiserum for the treatment of bacterial infections. In general, serum sickness occurs after the injection of large quantities of a soluble antigen. Clinical features include chills, fever, rash, urticaria, arthritis, and glomerulonephritis. Disease manifestations become evident 7 to 10 days after exposure to the antigen, when antibodies are generated against the foreign protein and form immune complexes with these circulating antigens. Immune complexes are deposited in blood vessels, where they activate phagocytes and complement, producing widespread tissue injury and clinical symptoms. The effects are transient, however, and resolve after the antigen is cleared.

A syndrome similar to serum sickness occurs in chronic infections in which pathogens persist in the face of continued immune response. In subacute bacterial endocarditis, antibody production continues but fails to eliminate the infecting microbes. As the pathogens multiply, generating new antigens, immune complexes form in the circulation and are deposited in small blood

vessels, where they lead to inflammatory damage of skin, kidney, and nerve. Hepatitis B virus infection may be associated with immune complex deposition early in its course, during a period of antigen excess, because antibody production in response to hepatitis B surface antigen is as yet relatively insufficient; some anicteric patients may present with acute arthritis. Mixed essential cryoglobulinemia, which may be associated with hepatitis C viral infection, is an immune complex–mediated vasculitis in which deposition of complexes containing IgG, IgM, and hepatitis C antigens causes inflammation in peripheral nerves, kidneys, and skin. Serum sickness also can develop in transplant recipients who are treated with mouse monoclonal antibodies specific for human T cells to prevent rejection, and in patients with myocardial infarction who are treated with the bacterial enzyme streptokinase to effect thrombolysis.

Systemic lupus erythematosus, the prototypical immune complex–mediated autoimmune disease, is characterized by circulating IgG directed against common cellular constituents, typically DNA and DNA-binding proteins. Small immune complexes are deposited in skin, joints, and glomeruli and initiate local tissue damage. [7]

Delayed Hypersensitivity Reactions

Delayed hypersensitivity reactions are inflammatory reactions initiated by mononuclear leukocytes. The term delayed is used to differentiate a secondary cellular response, which appears 48-72 hours after antigen exposure, from an immediate hypersensitivity response, which generally appears within 12 minutes of an antigen challenge. These reactions are mediated by T cells and monocytes/macrophages rather than by antibodies. They are also termed type IV hypersensitivity reactions.

Delayed hypersensitivity is a major mechanism of defense against various intracellular pathogens, including mycobacteria, fungi, and certain parasites, and it occurs in transplant rejection and tumor immunity. The central role of CD4+ T cells in delayed hypersensitivity is illustrated in patients with AIDS. Because of the loss of CD4+ cells, the host response against intracellular pathogens such as Mycobacterium tuberculosis is markedly impaired. The bacteria are engulfed by macrophages but are not killed.

If T-cell function is abnormal, the patient presents with opportunistic infections, including infection with mycobacteria, fungi, parasites, and, often, mucocutaneous candidiasis. [1] Undesirable consequences of delayed-type hypersensitivity (DTH) reactions include illness such as contact dermatitis and allograft rejection. Examples of DTH reactions are contact dermatitis (e.g., poison ivy rash), tuberculin skin test reactions, granulomatous inflammation (e.g., sarcoidosis, Crohn disease), allograft rejection, graft versus host disease, and autoimmune hypersensitivity reactions. Of note, the Rhus genus of plants, which includes poison ivy, poison oak, and poison sumac, all cause identical rashes.

The cellular events that result in delayed hypersensitivity reactions primarily involve T cells and macrophages. First, local immune and inflammatory responses at the site of foreign antigen up-regulate endothelial cell adhesion molecule expression, promoting the accumulation of leukocytes at the tissue site. The antigen is engulfed by macrophages and monocytes and is processed and presented to a T cell that has a specific receptor for that processed antigen. Macrophages secrete interleukin (IL)–1, IL-2, IL-6, and other lymphokines. Cytotoxic T cells can also be activated. The recruited macrophages can form giant cells. The characteristic histologic appearance of the macrophage–T-cell infiltrate is a granuloma. This type of infiltrate in the tissue is called granulomatous inflammation.

Several variants of DTH exist, and their precise pathophysiologic mechanisms are slightly different. For example, in contact hypersensitivity reactions, the epidermis is involved; in pulmonary tuberculosis (TB), lung tissue is involved.

DTH reactions are extremely common. Persons of any age can be affected, but infants may not have the fully-developed immune capability to elicit a reaction.

Delayed hypersensitivity reactions are normal physiological events. Anything that alters these normal events can lead to multiple opportunistic infections. DTH reactions may include, but are not limited to, contact dermatitis (e.g., poison ivy rash), tuberculin skin test reactions, granulomatous inflammation (e.g., sarcoidosis, Crohn disease), allograft rejection, graft versus

host disease, and autoimmune hypersensitivity reactions. Morbidity and mortality vary (e.g., ranging from a rash to chronic debilitating diseases) based on the active disease present. [8]

Delayed-type hypersensitivity reactions are a prominent feature of several chronic diseases in humans, which for the most part are due to infectious agents, such as mycobacteria, protozoa and fungi. Important diseases include tuberculosis, leprosy, listeriosis, leishmaniasis, deep fungal infections (e.g. blastomycosis) and helminthic infections (e.g. schistosomiasis). These diseases are caused by pathogens which represent a persistent, chronic, antigenic stimulus. In such cases, protective immunity and delayed hypersensitivity often occur but are not always coincidental. [9]

Hypersensitivity: Stimulatory (Type V)

Type V hypersensitivity is the final type of hypersensitivity in which antibodies are produced with the property of stimulating specific cell targets. The clearest example is Graves's disease caused by antibodies that stimulate the thyroid-stimulating hormone receptor, leading to over activity of the thyroid gland. [10]

These reactions occur when IgG class antibodies directed towards cell surface antigens have a stimulating effect on their target.

It is thought that such a reaction may occur in the pathogenesis of neonatal hyperthyroidism, where maternal stimulating anti-thyroid IgG antibodies are able to cross the placenta. [11]

Type V hypersensitivity reactions were additionally added to the scheme originally described by Coombs and Gell. Contrary to type IV and in agreement with types I, II, and III, respectively, they are mediated by antibodies too. The type V reactions are sometimes considered as a subtype of the type II hypersensitivity. As its mechanisms do not destroy target cells, they are responsible for induction of organ/tissue dysfunctions only most of authors prefer it to be and independent, the 5th type of hypersensitivity reactions.

Cells receive information from their microenvironment in which they live; they sense signals that process and transduce into the cell nucleus by means of second signals. The specificity of binding between the signal and its receptor is mediated by complementarities of structures. For instance, thyroid-stimulating hormone (TSH) released from the adenohypophysis, by binding to its receptors in membranes of the thyroid gland stimulates adenylate-cyclase system what results in production of hormones.

Morbus Graves is characterised by production of antibodies directed against the TSH binding receptor that subsequently stimulate the thyroid gland, resulting in production of hormones (thyroxine and triiodothyronine). Contrary to physiological situation, there is no feedback mechanism – the increased levels of the thyroid gland hormones do not stop its hormones production as at the physiological condition when elevated amounts of thyroxines switch off the production of TSH and subsequent synthesis of hormones. The result is the hormone overproduction and appearance of clinical symptoms of hyperthyroidism. As antibodies increase the function of a target organ, this type of hypersensitivity is called stimulatory.

Autoantibodies cannot only stimulate cells of a target organ/tissue, however, on the contrary, also to inhibit it (hence the designation - inhibitory hypersensitivity reactions). A prototype of such a situation is myastenia gravis. It is an autoimmune disease characterised by production of autoantibodies directed against the acetylcholine receptors (AchR) present in neuro-muscular plates. By occupying the receptors, they inhibit a physiological binding of acetylcholine to, resulting in precluding signal transmission and muscle activation. The result of the events is a paralysis of striated muscles. In some cases the anti-acetylcholine receptors antibodies activate the complement system; a destruction of cell present in neuro-muscular plates follows; the condition is more severe than in the previous situation and is incurable.

Pernicious anemia (PA) is a disease is characterised by vitamin B12 deficiency caused by the absence of intrinsic factor. Vitamin B12 cannot be produced by the human body and must be obtained from the diet. When foods containing B12 are eaten, the vitamin is usually bound to protein and is released by stomach acid. Following its release, most B12 is absorbed by the body in the ileum after binding to a protein known as intrinsic factor. It is produced by parietal cells of the gastric mucosa and the intrinsic factor-B12 complex is absorbed by receptors on the ileum epithelial cells. In patients suffering from PA, antibodies to parietal cells cause the destruction of the gastric mucosa, in which the parietal cells are located, leading to the subsequent loss of intrinsic factor synthesis. In other subgroup of PA patients, antibodies to intrinsic factor are directly induced. Without intrinsic factor, the ileum can no longer absorb the B12 and the disease develops. [12]

Food allergies

More than 50 million Americans have an allergy of some kind. Food allergies are estimated to affect 4 to 6 percent of children and 4 percent of adults, according to the Centers for Disease Control and Prevention.

Food allergy symptoms are most common in babies and children, but they can appear at any age. You can even develop an allergy to foods you have eaten for years with no problems. Learn more about the types of food allergies. [13]

Food allergy is an abnormal response to a food triggered by your body's immune system.

In adults, the foods that most often trigger allergic reactions include fish, shellfish, peanuts, and tree nuts, such as walnuts. Problem foods for children can include eggs, milk, peanuts, tree nuts, soy, and wheat.

The allergic reaction may be mild. In rare cases it can cause a severe reaction called anaphylaxis. Symptoms of food allergy include

•Itching or swelling in your mouth

•Vomiting, diarrhea, or abdominal cramps and pain

•Hives or eczema

•Tightening of the throat and trouble breathing

•Drop in blood pressure. [14]

Corn Allergy

Allergic symptoms of a corn allergy develop when a person's immune system becomes sensitized and overreacts after eating corn or foods containing corn-based ingredients, or after being exposed to corn pollen. Corn and corn-derived products are used in many processed foods, as well as in many other everyday items.

A corn allergy can be difficult to diagnose using standard skin or blood tests because it is difficult to differentiate from allergies to grass pollens and to other seeds and grain. A food elimination diet, in which specific items are removed from a person's diet for a period of time to see if symptoms improve, is one way to determine whether a corn allergy is present.

Corn Allergy Symptoms:

- Hives or a skin rash
- Nausea, stomach cramps, indigestion, vomiting or diarrhea
- Stuffy or runny nose
- Sneezing
- Headache

- Asthma
- Anaphylaxis (less common), a potentially life-threatening reaction that impairs breathing and can send the body into shock.

  Corn Allergy Triggers:

  Corn and Most corn-derived products, like cornstarch and high-fructose corn syrup, do not contain corn protein. If you have a corn allergy, you do not need to avoid these products.

  Diagnosis:

  Diagnosing a corn allergy can be complicated. Symptoms can vary from person to person, and a single individual may not always experience the same symptoms during every reaction. If you suspect you are allergic to corn, make an appointment to see an allergist who specializes in food allergies. Start a food diary before the appointment, and keep track of any reactions. If you have a reaction, you should note: What (and how much) you ate when the symptoms started what you did to alleviate the symptoms How long it took before the symptoms were relieved your allergist will ask you about your history of allergy symptoms. You'll also be asked about your overall health and your family medical history, including any relatives with allergies. Because a corn allergy can be difficult to diagnose through skin tests or blood tests, your allergist may put you on a food elimination diet, in which you avoid the suspected food allergen for a specific period of time (normally two to four weeks). If your symptoms improve when the item is removed from your diet, it's likely that you are allergic to it. If the food elimination diet produces inconclusive results, your allergist may recommend an oral food challenge. During this test, you will be fed tiny amounts of corn or corn products in increasing doses over a period of time in an allergist's office or a food challenge center. Emergency medication and emergency equipment will be on hand during this procedure in case you have a severe reaction.

  Corn Allergy Management and Treatment:
- Avoid corn and corn-derived products.
- Administer epinephrine (adrenaline) to counter a severe reaction. [15]

Egg Allergy:

Egg allergy develops when the body's immune system becomes sensitized and overreacts to proteins in egg whites or yolks. When eggs are eaten, the body sees the protein as a foreign invader and sends out chemicals to defend against it. Those chemicals cause the symptoms of an allergic reaction.

Experts estimate that as many as 2 percent of children are allergic to eggs. Fortunately, studies show that about 70 percent of children with an egg allergy will outgrow the condition by age 16.

Still, the stakes are high: Children who are allergic to eggs can have reactions ranging from a mild rash to anaphylaxis, a life-threatening condition that impairs breathing and can send the body into shock.

Egg Allergy Symptoms:

- Skin reactions, such as hives or a rash
- Respiratory problems
- Stomach pain
- Anaphylaxis (less common)

Diagnosis:

Eggs are one of the most common food allergens. People with an allergy to chicken eggs may also be allergic to other types of eggs, such as goose, duck, turkey or quail.

Within a short period of time after eating (or even touching) eggs, you may experience the following symptoms:

- Skin reactions, such as swelling, a rash, hives or eczema
- Wheezing or difficulty breathing
- Runny nose and sneezing red or watery eyes
- Stomach pain, nausea, vomiting or diarrhea
- Anaphylaxis.

In the skin-prick test, a small amount of a liquid containing egg protein is placed on the back or forearm, which is then pricked with a small, sterile probe to allow the liquid to seep into the skin. If a raised, reddish spot forms within 15 to 20 minutes that can indicate an allergy. Depending on the protein in the liquid, skin-prick tests can determine whether your allergy is to egg white proteins or egg yolk proteins. Allergy to egg white proteins is most common.

In the blood test, a blood sample is sent to a laboratory to test for the presence of immunoglobulin E antibodies to egg protein.

If these tests aren't definitive, your allergist may order an oral food challenge. Under medical supervision, you'll eat small amounts of egg to see if a reaction develops. Because of the possibility that a reaction could be severe, this test is conducted in your allergist's office or at a food challenge center with emergency equipment and medication on hand.

A food elimination diet also may be used to determine if an allergy is present. If symptoms disappear when eggs are removed from the diet and reappear when eggs are again eaten, an egg allergy is likely.

Management and Treatment:

The best way to manage an egg allergy is to avoid eating eggs.

Unfortunately, eggs are a hidden ingredient in many foods, including canned soups, salad dressings, ice cream and many meat-based dishes, such as meatballs and meatloaf. Even some commercial egg substitutes contain egg protein. As a result, people with an egg allergy must be vigilant about reading labels and asking about the ingredients of foods prepared by others.

Egg is one of eight allergens with specific labeling requirements under the Food Allergen Labeling and Consumer Protection Act of 2004. That law requires manufacturers of packaged food products sold in the U.S. and containing egg as an ingredient to include the presence of egg or egg products, in clear language, on the ingredient label.

Anyone diagnosed with an allergy to either egg whites or egg yolks should avoid eggs altogether; it is not possible to completely separate the white from the yolk.

People with an egg allergy can sometimes tolerate baked goods and other foods containing eggs that have been heated for a prolonged period at a high temperature. Still, there is no way to predict when, or whether, an egg-allergic individual can safely tolerate any product containing eggs. If you're allergic to eggs, or your child is, ask an allergist which foods must be avoided.

Antihistamines may help to relieve mild symptoms of egg allergy, such as itching.

In addition, your allergist may prescribe epinephrine (adrenaline) in an auto-injector, to be taken in the event you develop symptoms of anaphylaxis a potentially fatal reaction that includes shortness of breath, swelling of the throat, and dizziness from a sudden drop in blood pressure. Your allergist will teach you how to use the auto-injector, which should be kept with you at all times and used as soon as symptoms start to appear. You or someone near you should also call for an ambulance, even if epinephrine provides relief, as the symptoms may recur.

Eggs in vaccines:

Several types of the seasonal flu (influenza) vaccine contain small amounts of egg protein.

According to the Centers for Disease Control and Prevention (CDC), no one with an egg allergy should receive the nasal spray version of the flu vaccine.

A flu vaccine administered by injection is safe for most egg-allergic people as long as it is given in a medical office equipped to deal with potential adverse effects, including anaphylaxis. If you're allergic to eggs, you shouldn't get your flu shot at a drugstore or a supermarket pharmacy or as part of a vaccination program at your workplace.

One type of injected flu vaccine (the recombinant vaccine) does not contain any egg protein; it is approved for use in people ages 18 to 49.

The yellow fever vaccine also contains egg protein. Both the World Health Organization and CDC state that a severe egg allergy is a contraindication for that vaccine. Yellow fever is most commonly found in parts of Africa and South America; the vaccine may be required for travel to countries where the disease is found. If needed, your doctor can provide a waiver letter for the vaccine requirement. [(16)]

Milk & Dairy Allergy:

Between 2 and 3 percent of children younger than 3 are allergic to milk. Although experts once believed that the vast majority of them would outgrow this allergy by the time they turned 3, recent studies contradict this theory. In one study, fewer than 20 percent of children had

outgrown their allergy by age 4. Still, about 80 percent of children are likely to outgrow their milk allergy before they are 16.

Milk Allergy Symptoms:

- Hives
- Stomach upset
- Vomiting
- Bloody stools, especially in infants
- Anaphylaxis, a rare, potentially life-threatening reaction that impairs breathing and can send the body into shock.

  Diagnosis:

  At your appointment, your allergist will take a detailed history, including asking what you ate, what symptoms you experienced, how long the symptoms lasted and what you did to alleviate them. The most common allergy tests are a skin-prick test or a blood test; both look for the presence of immunoglobulin E (IgE) antibodies, which develop when your body is exposed to a substance to which it is sensitive. These antibodies trigger the release of chemicals that cause allergic symptoms.

  In the skin-prick test, a liquid containing milk or a milk protein extract is placed on your forearm or back. Your skin is pricked with a small, sterile probe, allowing the liquid to seep into your skin. If you develop a raised, reddish welt, typically within 15 to 20 minutes that can indicate an allergy. In a blood test, a blood sample is tested for the presence of IgE antibodies. The results are reported as a numerical value.

  Research suggests that some types of milk proteins (casein and two proteins found in whey, alpha-lactalbumin and beta-lactalbumin) are more likely to cause serious reactions. A newer type of blood test, known as a component test, can help the allergist determine your risk for a serious reaction by looking for allergies to those specific proteins.

  Another test your allergist may order is an oral food challenge. Under medical supervision, you'll eat small amounts of a substance containing milk or a milk powder to see if a reaction develops. Because of the possibility that a reaction could be severe, this test is conducted in your allergist's office or at a food challenge center with emergency equipment and medication on hand.

  Management and Treatment:

  Avoidance of milk or items containing milk products is the only way to manage a milk allergy. People who are allergic to milk and the parents of children who have this allergy must read ingredient labels very carefully.

  Milk is one of eight allergens with specific labeling requirements under the Food Allergen Labeling and Consumer Protection Act of 2004. That law requires manufacturers of packaged food products sold in the U.S. and containing milk as an ingredient to include the presence of milk or milk products, in clear language, on the ingredient label.

There are two main types of milk protein — casein and whey. Casein, the "solid" part of milk, comprises about 80 percent of milk protein. Whey proteins, found in the liquid part of milk, make up the other 20 percent. Milk proteins are found in many foods, including all dairy products, and in many places where they might not be expected. For example, some canned tuna, sausage, meats and other nondairy products may contain casein. Beverage mixes and body-building and energy drinks commonly contain whey. Milk protein has also been found in some chewing gum.

Some companies may voluntarily include information that their food products "may contain traces of milk" or that they are manufactured in a facility that also processes milk, though such advisory statements are not required by law.
Allergies to food (including milk) are the most common causes of anaphylaxis, a potentially life-threatening allergic reaction. Symptoms include swelling of the airways, impairing the ability to breathe, and a sudden drop in blood pressure, causing dizziness and fainting. An allergist will advise patients with a food allergy to carry an auto-injector containing epinephrine (adrenaline), which is the only treatment for anaphylactic shock, and will teach the patient how to use it. If a child has the allergy, teachers and caregivers should be made aware of his or her condition as well.

Some people with this allergy can tolerate foods containing milk that has been extensively heated, such as a baked muffin. Still, people with an allergy to milk protein should consult an allergist before determining whether they should completely avoid milk and other dairy products.

Milk is a fairly easy ingredient to substitute in recipes. Most recipes calling for milk can be just as successful by substituting the equivalent in water, juice, or soy or rice milk. If your infant is allergic to milk, talk to your pediatrician about which formula to use. Often, an extensively hydrolyzed elemental formula or a casein-hydrolysate formula is recommended for milk allergy in infants, as the proteins in these formulas have been extensively broken down.

<u>Milk or dairy allergies and lactose intolerance are not related.</u>

People with a milk or dairy allergy experience symptoms because their immune system reacts as though milk and other dairy products are a dangerous invader. This reaction can cause hives, an upset stomach, vomiting, bloody stools and even anaphylactic shock — a life-threatening allergic response.
Milk allergy and lactose intolerance:

Individuals who are lactose intolerant cannot digest the sugar in milk (lactose) because they have a deficiency of lactase, an enzyme produced by cells in the lining of the small intestine. Lactase is required to metabolize lactose. The lack of this enzyme — which

sometimes can just be temporary, due to infection — causes symptoms such as abdominal gas, diarrhea or abdominal cramps.

If you suffer digestive problems after eating or drinking dairy products, try tracking your diet and noting how your body reacts to the items you consume. You may also try temporarily cutting dairy products — milk, cheese and yogurt, for example — from your diet and see if your symptoms improve. [17]

Peanut Allergy:

An allergy to peanuts is among the most common food allergies found in children in the United States. Many schools have declared that they are "nut-free," meaning that the onetime staple of kids' lunchboxes - a peanut butter and jelly sandwich - is nowhere to be found on school grounds these days.

Many schools have declared that they are "nut-free," meaning that the onetime staple of kids' lunchboxes — a peanut butter and jelly sandwich — is nowhere to be found on school grounds these days. That's because peanuts can cause a life-threatening reaction in some people. Peanuts are one of the food allergens most commonly associated with anaphylaxis, a sudden and potentially deadly condition that requires immediate attention and treatment.

Peanut Allergy Symptoms:

- Itchy skin or hives, which can appear as small spots or large welts
- An itching or tingling sensation in or around the mouth or throat
- Nausea
- A runny or congested nose
- Anaphylaxis (less common), a potentially life-threatening reaction that impairs breathing and can send the body into shock.

Diagnosis:

Diagnosing a peanut allergy can be complicated. Symptoms can vary from person to person, and a single individual may not always experience the same symptoms during every reaction.

Because a peanut allergy can be difficult to diagnose through skin tests or blood tests, your allergist may put you on a food elimination diet, in which you avoid the suspected food allergen for a specific period of time (normally two to four weeks). If your symptoms improve when the item is removed from your diet, it's likely that you are allergic to it.

If the food elimination diet produces inconclusive results, your allergist may recommend an oral food challenge. During this test, you will be fed tiny amounts of peanut or peanut-based products in increasing doses over a period of time in an allergist's office or a food challenge center. Emergency medication and emergency equipment will be on hand during this procedure in case you have a severe reaction.

Management and Treatment:

Peanut is one of eight allergens with specific labeling requirements under the Food Allergen Labeling and Consumer Protection Act of 2004. Under that law, manufacturers of packaged food products sold in the U.S. and containing peanuts as an ingredient must include the presence of peanuts, in clear language, on the ingredient label.

To avoid the risk of anaphylactic shock, people with a peanut allergy must be very careful about what they eat. Peanuts and peanut products are commonly found in candies, cereals and baked goods, such as cookies, cakes and pies. If you're eating out, ask the restaurant staff about ingredients - for example, peanut butter may be an ingredient in a sauce or marinade. Be extra careful when eating Asian and Mexican food and other cuisines in which peanuts are commonly used. Even ice cream parlors may not be safe for people with a peanut allergy, since peanuts are a common topping.

Foods that don't contain peanuts as an ingredient can be contaminated by peanuts in the manufacturing process or during food preparation. As a result, people with a peanut allergy should avoid products that bear precautionary statements on the label, such as "may contain peanuts" or "made in a factory that uses nut ingredients." Note that the use of those advisory labels is voluntary, and not all manufacturers do so.

If you're cooking from scratch, it's easy to modify recipes to remove peanut ingredients and substitute ingredients that aren't allergens, such as toasted oats, raisins or seeds. Some people who can't tolerate peanuts or eat peanut butter can consume other nut or seed butters. Keep in mind that these products may be manufactured in a facility that also processes peanuts - so check the label carefully and contact the manufacturer with any questions.

Many individuals with an allergy to peanuts can safely consume foods made with highly refined peanut oil, which has been purified, refined, bleached and deodorized to remove the peanut protein from the oil. Unrefined peanut oil - often characterized as extruded, cold-pressed, aromatic, gourmet, expelled or expeller-pressed - still contains peanut protein and should be avoided. Some products may use the phrase "arachis oil" on their ingredient lists; that's another term for peanut oil. If you have a peanut allergy, ask an allergist whether you should avoid all types of peanut oil. [18]

Wheat Allergy:

If you notice certain symptoms after eating cereal, bread or pasta — for instance, if you develop hives or a rash or get a stomachache, or your nose gets stuffy or runs — you may have a wheat allergy, a condition that affects millions of Americans.

Wheat allergies, like hay fever and other allergies, develop when the body's immune system becomes sensitized and overreacts to something in the environment — in this case, wheat — that typically causes no problem in most people.

Generally, you are at greater risk for developing an allergy to any food, including wheat, if you come from a family in which allergies or allergic diseases, such as asthma or eczema, are

common. If both of your parents have allergies, you're more likely to develop a food allergy than someone with only one parent who has allergies.

Wheat Allergy Symptoms:

- Hives or skin rash
- Nausea, stomach cramps, indigestion, vomiting or diarrhea
- Stuffy or runny nose
- Sneezing
- Headaches
- Asthma
- Anaphylaxis (less common), a potentially life-threatening reaction that can impair breathing and send the body into shock.

Wheat Allergy Triggers:

- Bread, pasta or any other food containing wheat
- Nonfood items with wheat-based ingredients, such as cosmetics or bath products.

Diagnosis:

Some indications of an allergy to wheat — stomach cramps, diarrhea and other gastrointestinal symptoms — overlap with those produced by a sensitivity to gluten or by celiac disease, an autoimmune disorder, so it's crucial to get an accurate diagnosis. An allergist can determine whether an allergy is present.

Your allergist will first take a medical history, asking particularly about other family members with allergies or allergic diseases, such as asthma or eczema. If both of your parents have food allergies, you're more likely to have them as well.

Diagnosis of an allergy can be made through a skin-prick test or a blood test.

In the skin-prick test, a small amount of a liquid containing wheat protein is placed on the back or forearm, which is then pricked with a small, sterile probe to allow the liquid to seep into the skin. If a raised, reddish spot forms within 15 to 20 minutes that can indicate an allergy.

In the blood test, a blood sample is sent to a laboratory to test for the presence of immunoglobulin E antibodies to wheat protein. The results are reported as a numerical value. A blood test that looks for different antibodies can be used to screen for celiac disease.

If these tests aren't definitive, your allergist may order an oral food challenge. Under medical supervision, you'll eat small amounts of wheat to see if a reaction develops. Because of the possibility that a reaction could be severe, this test is conducted in your allergist's office or at a food challenge center with emergency equipment and medication on hand.

Management and Treatment:

A wheat allergy reaction can cause symptoms that range from mild to life-threatening; the severity of each reaction is unpredictable. People who have previously experienced only mild symptoms may suddenly experience a life-threatening reaction known as anaphylaxis. In the U.S., food allergy is the leading cause of anaphylaxis outside the hospital setting.

Epinephrine (adrenaline) is the first-line treatment for anaphylaxis, which can occur within seconds or minutes, can worsen quickly and can be deadly. In this type of allergic reaction, exposure to the allergen causes the whole-body release of a flood of chemicals that can lead to lowered blood pressure and narrowed airways, among other serious symptoms.

Once you're diagnosed with a food allergy, your allergist will likely prescribe an epinephrine auto-injector and teach you how to use it. Check the expiration date of your auto-injector, note the expiration date on your calendar and ask your pharmacy about reminder services for prescription renewals.

Be sure to have two doses available, as the severe reaction may recur. If you have had a history of severe reactions, take epinephrine as soon as you suspect you have eaten an allergy-causing food or if you feel a reaction starting. Epinephrine should be used immediately if you experience severe symptoms such as shortness of breath, repetitive coughing, weak pulse, generalized hives, tightness in the throat, trouble breathing or swallowing, or a combination of symptoms from different body areas such as hives, rashes or swelling coupled with vomiting, diarrhea or abdominal pain. Repeated doses of epinephrine may be necessary.

If you are uncertain whether a reaction warrants epinephrine, use it right away, because the benefits of epinephrine far outweigh the risk that a dose may not have been necessary.

Common side effects of epinephrine may include anxiety, restlessness, dizziness and shakiness. Rarely, the medication can lead to abnormal heart rate or rhythm, heart attack, a sharp increase in blood pressure, and fluid buildup in the lungs. Patients with certain pre-existing conditions, such as diabetes or heart disease, may be at higher risk for adverse effects and should speak to their allergist about using epinephrine.

Your allergist will provide you with a written emergency treatment plan that outlines which medications should be administered and when (note that between 10 and 20 percent of life-threatening severe allergic reactions have no skin symptoms). Be sure that you understand how to properly and promptly use an epinephrine auto-injector.

Other medications, such as antihistamine and corticosteroids, may be prescribed to treat symptoms of a food allergy, but it is important to note that there is no substitute for epinephrine — this is the only medication that can reverse the life-threatening symptoms of anaphylaxis.

Managing food allergies in children:

Because fatal and near-fatal wheat allergy reactions, like other food allergy symptoms, can develop when a child is not with his or her family, parents need to make sure that their child's school, day care or other program has a written emergency action plan with instructions on preventing, recognizing and managing these episodes in class and during activities such as sporting events and field trips. A nonprofit group, Food Allergy Research & Education, has a list of resources for schools, parents and students in managing food allergies.

Gluten "Allergy":

Gluten is a protein found in grains, such as wheat, barley and rye. Some people are allergic to wheat, but that is not the same as a gluten allergy. Gluten allergy is a misleading term commonly confused with wheat allergy, or sometimes celiac disease. There is no such thing as a gluten allergy, but there is a condition called Celiac Disease. Celiac Disease is a digestive condition that is potentially serious if not diagnosed or treated. Symptoms of celiac disease include severe diarrhea after eating gluten-containing products, a rash, severe weight loss or failure to properly gain weight, and abdominal pain. In small children, you may only see poor weight gain and no pain, or other symptoms. Diagnosis of celiac disease can only be made by a board-certified gastroenterologist. It must also be made when the person is eating foods with gluten, as gluten avoidance is the active treatment. A gluten intolerance is not an allergy, and there are currently no tests for accurate diagnosis. People with certain symptoms might need to be tested for celiac disease, but few people with gluten intolerance have celiac disease. Gluten intolerance is not an indication for allergy testing and is not a condition where an allergist could offer help. There are many people who label themselves as "allergic" to gluten, and unfortunately limit their diet without having seen a specialist.

People with gluten intolerance should be seen by their primary care provider or referred to a gastroenterologist if there is concern about celiac disease. [19]

Meat Allergy:

If your nose gets stuffy or begins to run after eating meat, or you become nauseated or develop a rash, you may have a meat allergy.

Meat from any kind of mammal — beef, lamb, pork, goat, and even whale and seal — can cause an allergic reaction. While we do not definitively know the number of people in the U.S. affected by meat allergy, we do know that it is uncommon.

A bite from the Lone Star tick can cause people to develop an allergy to red meat, including beef and pork. The Lone Star tick has been implicated in initiating the red meat allergy in the US and this tick is found predominantly in the Southeast from Texas, to Iowa, into New England.

A meat allergy can develop any time in life. If you are allergic to one type of meat, it is possible you also are allergic to other meats, as well as to poultry, such as chicken, turkey and duck.

Studies have found that a very small percentage of children with milk allergy are also allergic to beef. Talk with your allergist to see if you should remove beef from your milk-allergic child's diet.

Symptoms:

- Hives or skin rash
- Nausea, stomach cramps, indigestion, vomiting, diarrhea
- Stuffy/runny nose
- Sneezing
- Headaches
- Asthma
- Anaphylaxis, a severe potentially deadly allergic reaction that restricts breathing.

Triggers:
Eating meat from mammals and sometimes poultry.
Diagnosis:
Symptoms of meat allergy can vary from person to person, and you may not always experience the same symptoms during every reaction. Allergic reactions to food can affect the skin, respiratory tract, gastrointestinal tract, and cardiovascular system. Meat allergies may also develop at various ages.
To make a diagnosis, allergists ask detailed questions about your medical history and your symptoms. Be prepared to answer questions about:

- What and how much you ate
- How long it took for symptoms to develop
- What symptoms you experienced and how long they lasted.

The allergist will usually order a blood test and/or perform a skin test. These indicate whether food-specific immunoglobulin E (IgE) antibodies are present in your body.

- Skin tests provide results in about 20 minutes. The skin on your arm or back is pricked with a sterile small probe that contains a tiny amount of the food allergen. The tests, which are not painful but can be uncomfortable, are considered positive if a wheal (resembling the bump from a mosquito bite) develops at the site.
- Blood tests measure the amount of IgE antibody to the specific food(s) being tested. Results are typically available in about one to two weeks and are reported as a numerical value.

Your allergist will use the results of these tests in making a diagnosis. While both of these diagnostic tools can signal a food allergy, an allergist may need to consider your medical history and conduct additional tests before confirming your diagnosis.

In some cases, an allergist may wish to conduct a double-blind, placebo-controlled oral food challenge, which is considered to be the gold standard for food allergy diagnosis. It can be costly and time-consuming. In some cases it is potentially dangerous, so it is not routinely performed.

During an oral food challenge, the patient is fed tiny amounts of the suspected trigger food in increasing doses over a period of time under strict supervision by an allergist. Emergency medication and emergency equipment are on hand during this procedure.

Oral food challenges also may be performed to determine if a patient has outgrown a food allergy.

Management and Treatment:

Once a meat allergy is diagnosed, the best treatment is to avoid the trigger. Carefully check ingredient labels of food products, and learn whether what you need to avoid is known by other names.

Be extra careful when you eat out. Waiters (and sometimes the kitchen staff) may not always know the ingredients of every dish on the menu. Depending on your sensitivity, even just walking into a kitchen or another place where food is prepared can cause an allergic reaction.

All patients with food allergies must make some changes in what they eat. Your allergist can direct you to helpful resources, including special cookbooks, patient support groups, and registered dietitians, who can help you plan meals.

Managing a severe food reaction with epinephrine:

A food allergy, including a meat allergy, can cause symptoms that range from mild to life-threatening; the severity of each reaction is unpredictable. People who have previously experienced only mild symptoms may suddenly experience a life-threatening reaction called anaphylaxis. In the U.S., food allergy is the leading cause of anaphylaxis outside the hospital setting.

Epinephrine is the first-line treatment for anaphylaxis, which results when exposure to an allergen triggers a flood of chemicals that can send your body into shock. Anaphylaxis can occur within seconds or minutes, can worsen quickly, and can be deadly.

Once you've been diagnosed with a food allergy, your allergist will likely prescribe an epinephrine auto-injector and teach you how to use it. Check the expiration date of your auto-injector, note the expiration date on your calendar, and ask your pharmacy about reminder services for prescription renewals.

Be sure to have two doses available, as the severe reaction may reoccur. If you've had a history of severe reactions, take epinephrine as soon as you suspect you've eaten an allergy-causing food or if you feel a reaction coming on. Epinephrine should be used immediately if you experience severe symptoms such as shortness of breath, repetitive coughing, weak pulse, hives, and tightness in your throat, trouble breathing or swallowing, or a combination of symptoms from different body areas such as hives, rashes, or swelling on the skin coupled with vomiting, diarrhea, or abdominal pain. Repeated doses of epinephrine may be necessary.

Even if you are uncertain whether a reaction warrants epinephrine, use it right away; the benefits of epinephrine far outweigh the risk.

Common side effects of epinephrine may include anxiety, restlessness, dizziness, and shakiness. Rarely, the medication can lead to abnormal heart rate or rhythm, heart attack, sharp increase in blood pressure, and fluid build-up in the lungs. If you have certain pre-existing conditions, you may be at a higher risk for adverse effects with epinephrine.

Your allergist will provide you with a written emergency treatment plan that outlines which medications should be administered and when.

Once epinephrine has been administered, immediately call 911 and inform the dispatcher that epinephrine was given and that more may be needed.

Other medications may be prescribed to treat symptoms of a food allergy, but it is important to note that there is no substitute for epinephrine: It is the only medication that can reverse the life-threatening symptoms of anaphylaxis.

Managing Food Allergies in Children:

Because fatal and near-fatal food allergy reactions, like other food allergy symptoms, can develop when a child is not with his or her family, parents need to make sure that their child's school, daycare, or other program has a written emergency action plan with instructions on preventing, recognizing, and managing these episodes in class and during activities such as sporting events and field trips. A nonprofit group, Food Allergy Research & Education, offers has a list of resources for schools, parents, and students in managing food allergies. [20]

Medications and drugs allergies

Everyone reacts to medications differently. One person may develop a rash while taking a certain medication, while another person on the same drug may have no adverse reaction.

All medications have the potential to cause side effects, but only about 5 to 10% of adverse reactions to drugs are allergic.

Whether allergic or not, reactions to medications can range from mild to life-threatening.

It is important to take all medications exactly as your physician prescribes. Call your doctor if you have side effects that concern you, or you suspect a drug allergy has occurred. If your symptoms are severe, seek medical help immediately.

Allergic Reactions

Allergy symptoms are the result of a chain reaction that starts in the immune system. Your immune system controls how your body defends itself. For instance, if you have an allergy to a particular medication, your immune system identifies that drug as an invader or allergen. Your immune system may react to medications in several ways. One type of immune reaction is due to production of antibodies called Immunoglobulin E (IgE) specific to the drug. These antibodies travel to cells that release chemicals, triggering an immediate allergic reaction. This reaction causes symptoms in the nose, lungs, throat, sinuses, ears, lining of the stomach or on the skin and usually occurs within minutes to a few hours of taking the drug.

The most common immune response to a drug is due to the expansion of T cells, a type of white blood cell that recognize the drug as foreign. These T cells orchestrate a delayed immune response that most often affects the skin, causing itchy rashes, and occurs days to weeks after exposure to the drug.

Most allergic reactions occur within hours to two weeks after taking the medication and most people react to medications to which they have been exposed in the past. This process is called "sensitization." However, rashes may develop up to six weeks after starting certain types of medications.

The most severe form of immediate allergic reactions is anaphylaxis (an-a-fi-LAK-sis). Symptoms of anaphylaxis include hives, facial or throat swelling, wheezing, light-headedness, vomiting and shock.

Most anaphylactic reactions occur within one hour of taking a medication or receiving an injection of the medication, but sometimes the reaction may start several hours later. Anaphylaxis can result in death, so it is important to seek immediate medical attention if you experience these symptoms.

Antibiotics are the most common culprit of anaphylaxis, but more recently, chemotherapy drugs and monoclonal antibodies have also been shown to induce anaphylaxis.

The most severe form of delayed drug reactions not only cause rashes but may also involve other organs including the liver, kidneys, lungs, and heart. Blisters may be a sign of serious drug reactions called Stevens - Johnson syndrome and Toxic epidermal necrolysis (TEN), where the surfaces of your eye, lips, mouth and genital region may be eroded.

However, not all drug allergic reactions involve a specific immune reaction. Some people experience flushing, itching or a drop in blood pressure from intravenous dyes used in x-rays or CT scans. If you take angiotensin converting enzyme (ACE) inhibitors for high blood pressure, you may develop a cough or facial and tongue swelling.

In addition, some people are sensitive to aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs). One type of aspirin or NSAID sensitivity may cause a stuffy nose, wheezing and difficulty breathing. This is most common in adults with asthma and in people with nasal polyps (benign growths). Other reactions to NSAIDs can result in hives or in rare instances, severe reactions can result in shock.

A number of factors influence your chances of having an adverse reaction to a medication. These include: genetics, body chemistry, frequent drug exposure or the presence of an underlying disease. Also, having an allergy to one drug predisposes an individual to have an allergy to another unrelated drug. Contrary to popular myth, a family history of a reaction to a specific drug typically does not increase your chance of reacting to the same drug. [21]

Allergies and genetics

Allergic conditions are very common in modern society and up to half of all children in the UK have been diagnosed with at least one of asthma, atopic eczema, and hay fever or food allergies. With this increase in the prevalence of allergies, the development of these conditions is coming into question to help in the prevention and management.

There are several allergic conditions that are often grouped together when discussing the link between allergies and genetics, including asthma, atopic eczema, hay fever or food allergies. These conditions appear to be linked and follow a similar pattern in relation to genetic susceptibility.

Children affected by allergies often follow a pattern where they will progress through a series of allergic conditions, known as the allergic march. For example, they may initially experience atopic eczema with then subsides, followed by the presentation of asthma and then rhinitis. Some children will also develop several of the allergic conditions and retain them for life

Familial Link:

Some families appear to be more likely to be affected by allergic conditions than others and children born into these families have a higher risk of developing an allergic condition. This familial tendency to develop allergic conditions is thought to have a genetic link known as atopic.

It is estimated that more than half of children born into atopic families will develop an allergic disease, whereas the incidence of children with no family history of allergic disease is one in five. The risk is elevated even further for families where both parents are affected by an allergic condition.

Notably, children do not always develop the same allergic condition as the other members of the family and research tends to indicate a susceptibility to allergies, rather than a specific allergic condition.

Genetic Research:

Genome-wide association studies (GWAS) have helped to enlighten our understanding of genes in the development of allergic conditions.

Specific gene variations that alter the encoding of epithelial cell-derived cytokines such as interleukin-33 and thymic stromal lymphopoietin may be involved in the pathogenesis of allergies. Additionally, variations in the ORMDL3 and GSDML genes have been linked to an increased risk of early-onset asthma.

These finding help to identify children with the highest susceptibility to allergies, which can be useful in targeting preventative techniques or being aware of allergies symptoms that require treatment.

However, there remains a lot to be discovered in the research field of allergies and genetics. Further studies are required to continue broadening the understanding of the genetic development mechanisms of allergic conditions, and begin to implement techniques to lessen the impact of allergies on the modern population. [22]

Allergies and parasitic infections

A popular explanation for the increase in the prevalence of allergy is the hygiene hypothesis that attributes the allergy epidemic to a failure to develop appropriate immune regulation because of reduced exposures to microbes and their products in childhood. There is considerable interest in the potential role of helminth infections in reducing allergy prevalence – certainly, helminth infections have strong regulatory effects, are highly prevalent, and first occur in early life in endemic areas.

The most common helminth infections are caused by Geohelminthes parasites (also known as intestinal and soil-transmitted helminthes). Geohelminthes parasites include Ascaris lumbricoides, Trichuris trichiura, and hookworm (Ancylostoma duodenale and Necator americanus) have a worldwide distribution, are estimated to infect a quarter of the World's population , and are most prevalent among children living in areas of the rural Tropics with poor access to sanitation and clean water. Other important helminth infections include schistosomiasis and filariasis have a more focal distribution within endemic countries.

Allergic inflammation directed against helminthes:

The human immune response to helminth infections is associated with elevated levels of IgE, tissue eosinophilia and mastocytosis, and the presence of CD4+ T cells that preferentially produce IL-4, IL-5, and IL-13. Th2-mediated mechanisms are considered to mediate protective immunity against these parasites. Parasites in the tissues stimulate a strong localized Th2 response, characterized by an eosinophil-rich inflammatory infiltrate. A classic example is the Th2 granoluma that develops around schistosome eggs in the liver or wall of the intestine.

Individuals exposed to helminth infection may have allergic inflammatory responses to parasites and parasite antigens. Individuals with limited exposures to helminthes such as expatriates or recent migrants often develop allergic-type clinical manifestations, a probable host response to isolate and kill the parasites. A classic example is the asthma-like illness, Loeffler's syndrome, caused by the passage of A.lumbricoides larvae through the lungs. Helminth parasites in endemic areas tend to cause chronic infections - individual adult parasites may survive for many years in their human host - that are associated with few allergic-type reactions and a more tightly controlled Th2 response. Regulation of the Th2 response may be important for parasite survival and may allow the host to escape potentially damaging inflammation in the tissues.

For example, during infections with the tissue helminth, Onchocerca volvulus, the skin may be populated by millions of larval microfilariae and these appear to elicit little in the way of a host inflammatory response. This state of hyporesponsiveness may be reversed rapidly after the killing of microfilariae by chemotherapy - treated individuals may develop allergic-type reactions that are associated with the development of eosinophilic abscesses in the superficial dermis within hours after treatment. The onset and severity of these reactions are associated with the release of allergic mediators such as tryptase and eosinophil degranulation products into the peripheral circulation. The hyporesponsiveness associated with chronic helminth infections appears to be actively regulated and may require the presence of live parasites.

Geohelminthes parasites that are confined to the intestinal lumen may be less likely to induce strong systemic immune regulation although the tissue migratory life cycle stages of parasites such as Ascaris lumbricoides may induce strong allergic reactions in infected individuals living in regions where transmission of infection is seasonal. The comparative rarity of such reactions in endemic populations with year-round transmission may reflect difficulties in diagnosis or perhaps suppression of the inflammatory response.

Many zoonotic helminth infections cannot develop to maturity in the human host and the helminth larvae may migrate for prolonged periods in the tissues. Examples are infections with Toxocara spp, Ascaris suum, and dog hookworms. Such infections cause allergic type syndromes such as cutaneous and visceral larva migrans. Tissue damage is caused by allergic inflammation directed against the migrating larvae. During such infections there appears to be a failure of immune regulation probably because host and parasite have not co-evolved.

Factors affecting the effects of helminthes on allergy:

Four factors may determine the effect of helminthes on allergy: 1. Timing – the time of first infection and the duration of infection are likely to be important Early and/or long-lasting (chronic) infections may be more likely to induce immune modulatory effects that suppress allergic inflammation caused by parasite and non-parasite allergens while later and/or periodic infections may enhance allergy. The effect of Geohelminthes in suppressing atopy may be more important in the first years of life and the temporary elimination of infections later in childhood or adulthood may not affect a phenotype that is 'programmed' in infancy. 2. Intensity of infection – heavy parasite burdens may induce immune down modulation while light infections may be more likely to have the opposite effect – the effects are likely to be stronger for tissue helminth infections than for Geohelminthes infections. 3. Host genetics – the ability to induce specific host immune regulatory mechanisms may be partly determined by host genetics. Individuals that are genetically susceptible to atopic disease may be more likely to develop allergic responses to helminth and non-parasite allergens and may be genetically more resistant to infection. 4. The parasite – Different helminth parasites may have different effects on the risk of atopy and allergic disease.

Association of helminthes with allergic diseases:

Helminth antigens stimulate allergic inflammatory responses directed against the parasite in the human host and that this inflammation may be actively suppressed during chronic infection. A distinct question is whether helminth infections may modulate also allergic inflammatory responses directed against non-parasite allergens such as aeroallergens and affect allergic sensitization and the expression of allergic diseases.

Helminthes and atopy:

Epidemiological studies have shown inverse associations between allergen skin test reactivity and infections with A. lumbricoides and T. trichiura, hookworm, and schistosomiasis. Both active and past infections appear to mediate this effect. Infections with T. trichiura in the first years of life are associated with a reduced prevalence of allergen skin test reactivity later in

childhood independent of later infections. A study of European farm children showed an inverse association between sensitization to ascariasis (measured by the presence of specific IgG antibodies) and the presence of aeroallergen-specific IgE. Not all studies, however, have shown an inverse association and some have provided evidence for positive associations between the presence of Geohelminthes infection or Ascaris-specific IgE and allergen skin test reactivity or elevated allergen-specific IgE. One study showed that allergen skin test reactivity was positively associated with anti-Ascaris IgE and negatively associated with active A. lumbricoides infection.

Helminthes and asthma:

A meta-analysis of many of studies investigating the association between the presence of Geohelminthes eggs in stool samples and asthma provided some evidence for parasite-specific effects; A. lumbricoides eggs was associated with an increased prevalence of asthma, T. trichiura with no effect, and hookworm eggs with a reduced prevalence of asthma. All hookworm studies were conducted in Ethiopia and replication in other geographic regions is important.

Ascariasis may contribute to an increased risk of asthma either by causing directly inflammation in the airways (i.e. migrating larvae) or through increased atopy and Th2 inflammatory responses in the airways. Studies investigating the association between the presence of anti-Ascaris IgE and asthma or bronchial hyper-responsiveness (BHR) have shown a strong positive association that may be independent of endemicity and the presence of active infection (i.e. A. lumbricoides eggs in stool samples). Studies in urban Brazil have shown positive associations between A.lumbricoides infection and recent wheeze and BHR. The capacity to produce high levels of IgE on exposure to A. lumbricoides infection might simply be explained by a greater capacity to produce IgE on allergen exposure by (genetically susceptible) atopic children. A study in Venezuela showed that the presence of atopy to Ascaris (elevated specific IgE and skin test reactivity) was an important risk factor for BHR in rural children but not in urban children in whom BHR was associated with atopy to house dust mite. This could reflect a shift in the dominant allergen exposures to which children with atopic asthma are exposed. The presence of anti-Ascaris IgE in asthmatics in Costa Rica has been associated with asthma severity and morbidity. Monthly treatments of children with anthelmintic drugs in Venezuela may reduce BHR, symptoms of wheeze and the need for asthma medications.

An alternative explanation for the association between elevated Ascaris-specific IgE and asthma is infections with other common ascarid worms such as toxocariasis – antigen preparations from both worms show a high degree of immunological cross-reactivity. Toxocariasis is associated with asthma-like symptoms in children with visceral larva migrans and there is some evidence that Toxocara may be an important risk factor for asthma in some populations. Whether such asthma symptoms are caused directly by the parasite or by Th2 adjuvant effects of parasite antigens on responses to aeroallergens is not clear.

Other zoonotic infections associated with asthma and that may be an important risk factor in some populations or high-risk groups is Anisakis simplex. Anisakiasis is caused by the ingestion of live L3 larvae in inadequately cooked seafood or perhaps exposure to Anisakis proteins, and is considered to be an important cause of food allergy and BHR in Spain and Japan.

Helminthes and eczema:

Recent studies have shown both positive and negative associations between Geohelminthes infection and the prevalence of eczema. A small intervention study in Uganda showed that infants of mothers with helminth infection at the time of delivery had a reduced risk of eczema compared to those born of uninfected mothers, and also a non-significant trend of a reduced risk of subsequent atopic dermatitis in the offspring of the mothers given anthelmintic treatment during pregnancy.

Immunological mechanisms of helminth-mediated modulation of allergy

Helminth parasites could affect allergic inflammation in three ways:

1) By enhancing or suppressing allergic inflammation directed against the parasite:

Chronic helminth infections of humans suppress anti-parasite immune responses through regulatory immune cells such as regulatory T cells and alternatively activated macrophages and mechanisms that include the production of immune modulatory cytokines such as IL-10 and TGF-β.

2) Through immunological cross-reactivity between helminth allergens and aeroallergens:

Important allergens such as tropomyosin of helminth parasites and invertebrates demonstrate immunological cross-reactivity. A recent study of subjects infected with A. lumbricoides and asthmatics sensitized to American cockroach showed that although IgE antibodies from both groups were cross-reactive for American cockroach and A. lumbricoides tropomyosin, the cross-reactive IgE did not appear to be clinically relevant - none of the subjects with ascariasis had a positive skin test for American cockroach and none of the cockroach-sensitized asthmatic subject had ascariasis.

3) By affecting allergic inflammation directed against aeroallergens through bystander effects in the same tissues such as the lungs:

Helminth infections may contribute to ‘immune homeostasis. Early life exposures in particular could have important long-term effects. Immune homeostatic mechanisms affected might include the production of baseline levels of regulatory cytokines (e.g. IL-10) by immune cells in the tissues that could raise the thresholds for the induction of effector cell responses to aeroallergens. A study of children infected in Cameroon provided some evidence for elevated production of IL-10 and TGF-β1 by unstimulated peripheral blood leukocytes (PBLs) that was associated positively with Geohelminthes parasite burden and inversely with for immune reactivity. Regulatory homeostasis may be expected to be insensitive to short term fluctuations in parasite burdens (e.g. single dose anthelmintic treatment) but could be ‘reset’ by long-term changes in parasite levels (e.g. increases in parasite burdens or repeated anthelmintic treatments). Single anthelmintic treatments for Geohelminthes infections do not affect cytokine responses to parasite antigen but repeated doses over prolonged periods caused an increase in Th2 cytokine responses of PBLs from Ecuadorian children. Long-term anthelmintic treatment did not affect cytokine

responses to aeroallergens indicating that the suppressive effect was specific for antiparasitic responses.

Bystander suppression may be also a more active process that requires the continued presence of the parasite. Active immune regulation may be mediated through mechanisms such as the direct suppressive effects of parasite-secretions and parasite-specific regulatory immune cells in the tissues. Such suppression may be reversed rapidly after anthelmintic treatment or parasite death and appears to be an important survival mechanism for tissue helminth parasites. Such suppression may affect also immunity to aeroallergens and could explain the observation of an inverse association between the productions of parasite-antigen induced IL-10 by PBLs and skin test reactivity to house dust mite among children from Gabon living an endemic area S. mansoni. Further, a study in Brazil that compared asthmatics infected with S. mansoni and those not infected (from a different population) showed that D. pteronyssinus-stimulated PBLs from infected asthmatics produced less Th2 cytokines and more IL-10 compared to controls. However, studies conducted in areas where A. lumbricoides is the predominant helminth have not provided evidence for either enhanced IL-10 responses to aeroallergens or an increase in the frequency of regulatory T cell populations induced by aeroallergen stimulation of PBLs. [(23)]

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