ALLERGIES

A Aggrawal, Maulana Azad Medical College, New Delhi, India

Introduction

The term allergy was first used in 1906 by an Austrian child specialist, Clemens von Pirquet (1874–1929) to denote exaggerated sensitivity of certain persons to innocuous exogenous particles such as animal dander, pollen, milk, jewelry, or washing powder. About 20% of all people, on coming into contact with such particles, exhibit symptoms like severe breathing difficulties, rashes, urticaria, or stomach upsets. von Pirquet coined this word from the Greek *allo,* meaning different, and *ergon,* meaning work. Literally, therefore, an allergy is something that "works differently" from the normal. Substances such as pollen or chemicals in washing powder, which elicit such abnormal responses, are called allergens. Allergens can enter the body in four principal ways: (1) ingestion (milk, peanuts); (2) inhalation (pollen, hay); (3) injection (bee stings, venoms); and (4) contact (washing powder, cosmetics). Allergic reactions would usually give rise to symptoms related to the exposed organ system. Thus ingested allergens may cause nausea, vomiting, and abdominal distress; inhaled allergens, bronchial asthma and respiratory distress; injected allergens, local redness and swelling; and contact allergens, dermatitis. All allergens can cause generalized life-threatening symptomatology, such as hypotension and shock.

A secondary allergen is an agent that induces allergic symptoms because of cross-reactivity with an allergen to which the individual is sensitive.

Allergoids are formaldehyde-modified allergens in order to favor the induction of immunoglobulin G (IgG: blocking antibodies) rather than IgE (antibodies causing most allergic reactions). These are analogous to toxoids prepared from bacterial exotoxins.

Allergen Nomenclature

In the initial days of allergy research, allergens were being discovered so rapidly that their nomenclature had become confusing, haphazard, and parochial. To bring a uniformity to its nomenclature, the Subcommittee for Allergen Nomenclature of the International Union of Immunological Societies (IUIS) recommended that all biologically derived allergens be designated by the first three letters of the genus (italicized), followed by a space; the first letter of the species name (again italicized), followed by a space; and a Roman numeral indicating the order of discovery of that antigen in that species. Thus, the allergen *Amb a* II indicates that it is the second antigen isolated from the ragweed *Ambrosia artemisiifolia*. Other common allergens are *Lol p* I to *Lol p* IV from perennial ryegrass pollen *Lolium perenne*, *Fel d* I from the domestic cat *Felis domesticus*, *Rat n* I from the rat *Rattus norvegicus*, *Equ c* I to *Equ c* III from the horse *Equus caballus*, *Der p* I and *Der f* I from two house dust mites *Dermatophagoides pteronyssinus* and *D. farinae* respectively, *Alt a* I from the fungus

Alternaria alternata, and *Gad c* I from the codfish *Gadus callarias*.

Classification of Allergies

The term allergy is quite commonly used interchangeably with hypersensitivity. A number of hypersensitive or immune disorders are known to clinicians. These can be classified in four principal ways. One of the simplest is to classify the reactions by source of antigen (Table 1). Levine in 1966 proposed a classification based on the time of onset of allergic symptoms (Table 2).

A third classification is according to their predominant clinical manifestations (Table 3).

Gell and Coombs in 1975 classified allergic reactions according to the immune mechanism involved (Table 4). This classification is most widely used by clinicians today.

Type I reactions are mediated by IgE, type II and III by IgG, and type IV by antigen-specific effector T cells. IgG are by far the most abundant immunoglobulins in the serum, and IgE the least. The levels of variousimmunoglobulins in human serum are: IgG 600–1400 mg dl^{-1}, IgA 60–380 mg dl^{-1}, IgM 40–345 mg dl^{-1}, IgD 3 mg dl^{-1}, and IgE 5×10^{-3} mg dl^{-1}.

Each of the above classifications helps us to understand and gain useful insights into the nature and diversity of allergic reactions.

It is important to appreciate that the term allergy has been used by various authorities in a variety of ways. Different authors mean different things when they use the term allergy. It has been noted above that the term allergy is used as a synonym of hypersensitivity by several authorities. This implies an adverse and idiosyncratic reaction to a substance – mostly foreign, but in some cases the body's own constituent too. Most pathologists however use the term allergy to describe only the IgE-mediated mast cell degranulation and corresponding clinical disorders. In this usage allergy is synonymous with immediate hypersensitivity.

In a medicolegal context, however, allergy should be used in the former sense, i.e., any adverse and idiosyncratic reactions to a substance, since all four categories (mentioned in Table 4) can have medicolegal implications. Examples include anaphylactic shock following drug injections such as penicillin (type I), mismatched blood transfusions and drug-induced lesions (type II), serum sickness (type III), and transplant rejection (type IV). It is in this sense that the term allergy will be used in this article. In addition, we would also include anaphylactoid reactions, which include non-IgE-mediated mast cell degranulation, such as those caused by neuromuscular blocking agents, opiates, radiocontrast media, dextrans, and a myriad of other low-molecular-weight chemicals, since these are also important from a medicolegal point of view. These agents do not cause a true IgE-mediated anaphylactic reaction. Instead, they act directly on the mast cells and basophils, causing degranulation, and all associated signs and symptoms.

Table 1 Allergic reactions classified by the source of antigen

Source of antigen	*Typical examples*
Exogenous	Reactions to plant pollens, milk, animal dander
Homologous	Reactions to isoantigens such as transfusion reactions
Autologous	Autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, etc.

Table 2 Allergic reactions based on their time of onset

Reaction type	*Time of onset*	*Clinical presentation (allergic symptoms)*
Immediate	0–1 h	Anaphylaxis, laryngeal edema, fall in blood pressure, urticaria/angioedema, wheezing
Accelerated	1–72 h	Urticaria/angioedema, laryngeal edema, wheezing
Late	>72 h	Hemolytic anemia, serum sickness, drug fever, exfoliative dermatitis, Stevens–Johnson syndrome, interstitial nephritis

Table 3 Allergic reactions classified according to their predominant clinical manifestations

Allergic reaction	*Predominant clinical manifestation*
Anaphylaxis	Bronchospasm, laryngeal edema, hypotension
Cutaneous reactions	Vasculitis, pruritus, maculopapular rash (also known as morbilliform rash), photosensitivity reactions, exfoliative dermatitis
Destruction of blood elements	Hemolytic anemia, neutropenia, thrombocytopenia
Pulmonary reactions	Interstitial/alveolar pneumonitis, fibrosis
Renal reactions	Nephrotic syndrome, glomerulonephritis, interstitial nephritis
Hepatic reactions	Hepatocellular damage, cholestatic reaction
Serum sickness	
Drug fever	
Lymphadenopathy	
Systemic vasculitis	

Table 4 Allergic reactions classified by mechanism involved

Type	*Typical example*	*Immune mechanism involved*
Type I Anaphylactic type	Anaphylaxis, atopy such as allergic conjunctivitis, rhinitis, some forms of asthma, urticaria, angioedema	Immunoglobulin E-mediated disorder. Release of vasoactive amines from mast cells
Type II Cytotoxic type	Transfusion reactions, erythroblastosis fetalis, myasthenia gravis, drug-induced lesions such as anemia caused by alpha-methyldopa and sedormid purpura	IgG and/or IgM bind to cell surface, causing lysis or phagocytosis
Type III Immune complex type	Serum sickness, Arthus reaction, rheumatoid arthritis	Antigen–antigen complexes bind to tissues and activate complement system. Tissue destruction occurs
Type IV Cell-mediated (delayed) hypersensitivity	Tuberculosis, transplant rejection	T lymphocytes are sensitized on a previous exposure and release lymphokines, causing tissue destruction

Tests for Allergy

A number of tests are available for allergy. They are broadly classified as *in vivo* and *in vitro* tests. Common forms of *in vivo* tests include immediate skin tests, delayed skin tests, patch skin tests, conjunctival challenge, oral challenge, and bronchial challenge. Among the *in vitro* tests, one of the most common and frequently performed tests is the radioallergosorbent test (RAST).

RAST

First introduced in 1967, RAST measures circulating allergen-specific IgE antibody. The term allergosorbent means that the allergen of interest (say, penicillin, insulin, or latex) is bound to a solid support, forming an allergosorbent. This solid support could be a carbohydrate particle, paper disk, a cotton thread, plastic ball, synthetic membranes, or even the wall of polystyrene testtubes or plastic microtiter wells.

If the allergist wants to diagnose a patient's allergy to, say, penicillin, he/she would use an allergosorbent containing the antigen of interest – in this case, penicillin. The allergosorbent is then exposed to the patient's serum. If the serum contains antibodies (IgE) against penicillin, they would bind to the allergosorbent. Excess serum is washed away. The allergosorbent is then reacted with a radiolabeled, highly specific antihuman IgE antibody. The amount of anti-IgE binding to the allergosorbent is proportional to the amount of IgE bound to the allergosorbent. Thus, by measuring the radioactivity levels, true levels of IgE against penicillin can be found. Currently RAST is available for a number of allergens, among them penicillin, insulin, chymopapain, muscle relaxants, thiopental, protamine, trimethoprim, and latex (Figure 1).

The radio label (in the radiolabeled, antihuman IgE antibody) is usually ^{125}I. More recently, enzymatic labels have become increasingly popular, producing enzyme-linked immunosorbent assay (ELISA). If an enzyme is used to label the anti-IgE, one more step is used, in which a proper substrate, which changes color in the presence of enzyme, is added. The intensity of color would then indicate the levels of IgE present in the blood.

Improper Use of RAST and its Attendant Medicolegal Implications

Increasing allergy litigations against doctors have seen increased use of RAST in recent times. It has led to commercialization and subsequent abuse of RAST. Companies have been selling RAST kits for drugs and chemicals which do cause anaphylactoid reactions, but have not been demonstrated to cause true IgE-mediated anaphylactic reactions (such as radiocontrast media). Performance of RAST in such cases is not only superfluous, but misleading. Increasing reliance of doctors on RAST in such cases would not prevent anaphylactoid reactions, and can invite unnecessary litigation.

Medicolegal Considerations in Allergy

Allergic disorders have a wide variety of inherent medicolegal implications, which are of relevance to forensic and legal personnel. Examples illustrating the different phenomena are given below.

Allergic Asthma

One of the most common conditions seen by doctors is allergic asthma. Generally, physicians rely on their clinical judgment to gauge the severity of their symptoms and the effectiveness of medications. In 1991, however, the US National Institute of Health

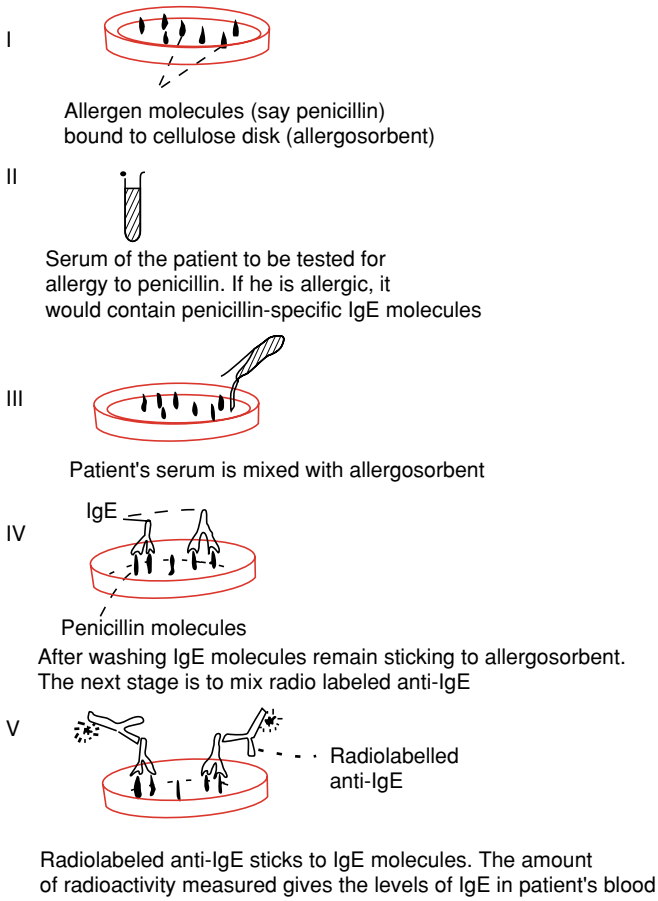

Figure 1 Principle of radioallergosorbent test (RAST).

published *Guidelines for the Diagnosis and Management of Asthma* and mailed it to 150 000 pediatricians, internists, pulmonologists, family practitioners, and allergists. These guidelines prescribed a set of recommendations which seem to set a standard of care for doctors. For instance, it is recommended that office spirometry be conducted in the initial assessment of all patients, and periodically thereafter, as appropriate. It was also recommended that clinicians consider using peak expiratory flow rate (PEFR) as measured by peak flow meters at home to monitor patients over 5 years old with moderate to severe asthma. The recommendations also said that peak flow measurements provided a simple, quantitative, reproducible measure of airway obstruction that can be obtained using inexpensive, portable peak flow meters. They correlate well with forced expiratory volume in 1 s (FEV_1) and provide an objective measurement. These measurements were considered akin to measuring glucose levels in a diabetic, or blood pressures in a hypertensive patient.

It was noted that neither patients' reporting of severity of symptoms nor physicians' clinical judgment were the true indicator of the severity of disease. The only objective criteria were the pulmonary function tests as noted above. Patients' responses to medication were also to be assessed by these tests.

A case is on record where a young asthmatic woman in her 20s died of an exceptionally severe attack. It was later discovered that her physician and the emergency medicine doctors had failed to conduct the objective pulmonary function tests outlined above in the report. Had they done the tests, they may have probably discovered that the patient was not responding well to treatment, and may have considered hospitalization, which could have saved her life. The woman's relatives sued the doctors, and the case was settled for a substantial sum.

Occupational Allergies and Compensation

Most countries now have laws regarding general aspects of health and safety at work. Employers are

required by law to look after the health of their employees. In the event of an employee becoming ill in the workplace, the employer will be responsible and liable for compensation, especially if negligence on the employer's part is proved. Some important acts catering to workers' safety are Health and Safety at Work Act 1974 and Control of Substances Hazardous to Health Regulations 1988 in the UK, Health and Safety at Work Act 1977 in Sweden, Worker Health and Environment Act 1977 in Norway, and The Workmen's Compensation Act 1923, and The Factories Act 1948 in India.

Allergic manifestations occurring in work environments may attract various medicolegal provisions of the above acts, relating to compensation, relocation, or premature retirement. Examples are given below.

Hypersensitivity pneumonitis Hypersensitivity pneumonitis is a lung inflammation induced by antibodies specific for substances that have been inhaled. If these inhaled substances are related to work, and/or are present in the work environment, they would attract relevant legal provisions relating to compensation.

Bagassosis The fungi *Thermoactinomyces saccharic* and *T. vulgaris* thrive in pressings from saccharis. Subjects working in sugarcane mills may inhale dust from molding hot sugarcane bagasse and develop type III (Arthus reaction) hypersensitivity. The condition is expressed as a hypersensitivity pneumonitis.

Farmer's lung This is another instance of hypersensitivity pneumonitis. Farmer's lung is caused by *Actinomycetes* (or other organic dusts), which thrive in moldy hay. Subjects working in such environments may develop antibodies to the mold spores. Subsequent inhalation of dust containing spores may induce hypersensitivity pneumonitis characterized by nausea, chills, fever, coughing, tachycardia, dyspnea, and cyanosis. Treatment would include standard antiallergic regimens such as those consisting of cromolyn sodium and corticosteroids.

Humidifier lung This condition, also known as air-conditioner lung, is common among workers involved with refrigeration and air-conditioning equipment. The hypersensitivity is due to the various species of the fungi *Micropolyspora* and *Thermoactinomyces*. Symptoms of the acute form consist of chills, cough, fever, dyspnea, anorexia, nausea, and vomiting. The chronic form of the disease is characterized by fatigue, chronic cough, dyspnea on exercise, and weight loss.

Bird fancier's lung Known variously as bird breeder's lung, pigeon breeder's lung, or hen worker's lung, this form of hypersensitivity pneumonitis is due to antigens in bird droppings.

Tables 5 and 6 list these and some other cases of hypersensitivity pneumonitis, along with the antigen involved. In all these cases, the subject experiences flu-like symptoms, with productive cough and weight loss. Specific precipitating antibodies can be demonstrated in some cases. Pulmonary function tests show a restrictive defect in early disease and a restrictive, obstructive, or mixed defect in late disease. Chest X-rays would show signs of pneumonitis. If the disease is recognized early, the employee may be relocated in service or considered for premature retirement. If the disease is not recognized, it may progress to interstitial fibrosis, which could invite heavy compensation.

Employers in these professions must conduct a regular check-up of all their prospective employees, including chest X-rays, complete blood profile, and pulmonary function tests before inducting them in work. Once an employee is inducted, the same tests must be conducted at regular intervals, perhaps every 6 months. As seen above, if pulmonary function tests are not conducted regularly, and occupational hypersensitivity pneumonitis develops, it may be difficult to convince the jury that the employer was not negligent with regard to employees' health.

Finally, it may be added that certain forms of hypersensitivity pneumonitis may not necessarily be associated with a particular profession. The most recent example is the so-called "hot tub lung" caused by *Mycobacterium avium* complex (MAC), which thrives in hot tubs. Hot tubs provide an excellent growth environment for MAC; the warm temperature promotes growth. The steam and bubbles generated efficiently vaporize the organism, facilitating easy inhalation.

It has recently been recommended that physicians maintain a high index of suspicion for hot tub lung and include questions about hot tub use in their routine review of symptoms in patients with respiratory problems. Not doing so may invite charges of medical negligence.

Allergy to laboratory animals (ALA) ALA is a well-known occupational disease in subjects working with these animals. The most common animals to which personnel are allergic include mice, rats, guinea pigs, rabbits, hamsters, dogs, cats, and monkeys. About 20% of all workers exposed to animals display allergies. The most common clinical manifestation is rhinoconjunctivitis which comprises sneezing, nasal

Table 5 Some common instances of hypersensitivity pneumonitis (HP) due to biologically derived antigens, which may attract medicolegal provisions

Disease name	*Antigens*	*Exposure*
Antigens originating from bacteria and fungi		
Bagassosis	Thermophilic actinomycetes	Moldy bagasse (pressed sugarcane)
Cheese-washer's lung	Fungus (*Pencillium casei* or *P. roqueforti*)	Cheese casings
Compost lung	Fungus (*Aspergillus*)	Compost
Farmer's lung	Thermophilic actinomycetes fungus (*Aspergillus* spp.)	Moldy hay
Humidifier (air-conditioner) lung	Bacteria (*Bacillus subtilis, B. cereus, Klebsiella oxytoca*), fungus (*Aureobasidium pullulans*), amebae (*Naegleria gruberi, Acanthamoeba polyhaga, A. castellani*)	Mists from standing water
Japanese summer-type HP	Fungus (*Trichosporon cutaneum*)	Damp wood and mats
Malt worker's lung	Fungus (*Aspergillus clavatus*)	Moldy barley
Maple bark-stripper's lung	Fungus (*Cryptostroma corticale*)	Moldy wood bark
Metal-working fluids HP	*Mycobacterium chelonae*, fungi	Microbially contaminated, water-based metal-working fluids
Mushroom worker's lung	Thermophilic actinomycetes	Mushroom compost
Sequoiosis	Fungi (*Graphium* spp., *Pullularia* spp.)	Moldy wood dust
Suberosis	Fungus (*Penicillum frequentans*)	Moldy cork dust
Wood pulp worker's lung	Fungus (*Alternaria* spp.)	Moldy wood pulp
Wood trimmer's disease	Fungus (*Rhizopus* spp.)	Moldy wood trimmings
Antigens comprising proteins other than from bacteria and fungi		
Mollusc shell HP	Aquatic animal proteins	Mollusc shell dust
Bird breeder's lung	Avian proteins	Bird droppings and feathers

Table 6 Some common instances of hypersensitivity pneumonitis (HP) due to chemicals acting as antigens, which may attract medicolegal provisions

Disease name	*Antigens (chemical involved)*	*Exposure*
Isocyanate HP	• Toluene diisocyanate (TDI): most dangerous • Hexamethylene diisocyanate (HDI): less dangerous than TDI • Methylene bisphenyl diisocyanate (MDI): least dangerous and the preferred substitute for TDI and MDI	Paints, resins, polyurethane foams
TMA HP	Trimellitic anhydride (TMA)	Plastics, resins, paints

congestion, and itchy, watery eyes. It occurs in up to 80% of symptomatic workers. Dermatologic symptoms, including contact urticaria (hives) itchy maculopapular eruption, occur in up to 40% of symptomatic workers. About 20–30% of the symptomatic workers suffer from respiratory symptoms, including asthma, wheezing, cough, and chest tightness. Asthma is the most serious symptom and may not be reversible after removal from exposure.

Symptoms usually start within 1 year of the beginning of exposure (in one-third of all cases). Most who develop allergies will do so within 3 years of employment (up to 70%).

In the case of allergy to mouse (*Mus musculus*), the most common allergen involved is *Mus m* I, found primarily in mouse urine, but also in dander and hair, and *Mus m* II, found mostly in hair and dander. In the case of guinea pig, the allergens are *Cav p* I and *Cav p* II, found in hair, dander, and urine; in the case of rabbit, *Ory c* I, found in hair, dander, and saliva, and *Ory c* II, found in hair, dander, and urine; in the case of cat, *Fel d* I, found in hair, dander, and saliva; and in the case of dog, *Can f* I, found in hair, dander, and saliva.

It is important to remember that most animal allergens are only a few microns in size (between 1 and 20 μm) and, as such, can remain airborne for hours. Removal of animals from the work environment therefore may not bring immediate relief.

It is recommended that there should be a pre-employment medical examination of all prospective employees. Very few laboratories are currently doing these examinations. Even those which are conducting such examinations are found lacking in

conducting specialized tests for animal allergies. For instance, in one study it was found that less than 5% of preemployment examinations included skin testing for hypersensitivity. The tests should be thorough, including lung function tests, blood profile (for increased IgE levels), and skin tests. In addition job applicants must be required to furnish information regarding personal history of allergy, asthma, and, most importantly, allergy to animals. A history of allergy to animals must be an immediate disqualifier.

If an employee develops ALA despite all screening tests, immediate steps must be taken to limit the exposure. The steps may include limiting the hours of exposure, withdrawing the individual from those procedures most likely to put him/her at risk, use of respiratory protection and other personal equipment, use of a safety cabinet where possible, increased periodic monitoring, and monitoring the progress of disease. If possible, shifting the employee to administration may be considered.

It is important to realize that if an employee develops an allergic disease to a laboratory animal, in several countries it may be required by law to report this to the proper authorities. For instance, in the UK occupational asthma resulting from working with laboratory animals must be notified to the Health and Safety Executive under the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations of 1985. Occupational asthma (such as that developing from exposure to laboratory animals) is a prescribed occupational disease in most countries and qualifies for disability benefit.

Latex allergy Natural latex is the sap of the tropical rubber tree *Hevea brasiliensis*. It is a colloidal dispersion of rubber particles (*cis*-1,4-polyisoprene) in water, and contains a complex mixture of organic substances including many proteins. Allergy to natural rubber latex (NRL) proteins (latex allergy) was first reported to cause glove-related contact urticaria in 1979. Later there were several reports of fatal reactions to latex enema tips. The incidence of latex allergy in recent years seems to have increased due to increased condom and glove use (both latex products) in the wake of acquired immunodeficiency syndrome (AIDS) and hepatitis epidemics. In high-quality, costlier latex gloves, leachable chemicals and water-soluble proteins are removed with a costly process. Poorly manufactured gloves may have a higher protein content, causing more reactions.

Latex allergy can be detrimental to both healthcare workers (doctors, surgeons, nurses) and their patients. Patients with spina bifida are 500 times more prone to latex allergy than the general population. This could be due to their repeated exposure to latex. The incidence in the general population is less than 1%.

The most common symptoms of latex allergy are localized contact urticaria, pruritus, erythema, and urticarial wheals. Cornstarch used as glove powder adsorbs NRL allergens, rendering them airborne, and this can cause an acute attack of asthma in susceptible persons. The UK Medical Devices Agency has advised against its use. It is further recommended that sensitized individuals should use NRL gloves with a low extractable protein content ($<50\,\mu g\,g^{-1}$), or gloves made from alternative material such as neoprene (polychloroprene) or elastyrene (styrene butadiene). However these have financial implications, as they could be more expensive.

If a doctor finds that a patient is allergic to latex, he/she should immediately inform the patient about this. The patient should also be told to wear a Medic-Alert bracelet stating "allergy to latex." Hospitals should make sure that staff are not allergic to latex. If an employee is found to be allergic, gloves made of alternative material should be provided.

Recently a nurse from South Wales, UK, successfully sued her employers because she was allergic to latex. Interestingly the hospital had provided her with vinyl gloves, but contact with colleagues wearing latex or with latex-contaminated dust was enough to trigger an allergic reaction in her. The appellate court held that in such cases the employer held a strict liability.

Drug Allergy and Anaphylaxis

Allergy to drugs is a very important issue from a medicolegal standpoint. A number of medical negligence suits have been filed against doctors who failed to conduct sensitivity tests before injecting, say, penicillin. A number of other drugs can cause allergy, and the practicing physician would do well to keep them in mind.

Type I hypersensitivity reactions (anaphylaxis) These are the most serious and dramatic allergic reactions to drugs such as penicillin, cephalosporins, allergenic extracts, and insulin. Anaphylactoid reactions can be caused by radiocontrast media and aspirin. It is vital for radiologists to take an informed consent from the patient before administering radiocontrast media. Two types of radiocontrast media are currently available. One is the conventional high-osmolar radiocontrast media (HORCM). Their osmolality is seven times that of plasma. Anaphylactoid reactions to HORCM (urticaria, wheezing, dyspnea, hypotension, death) occur in 2–3% of individuals receiving intravenous or intraarterial injections. If there is a

previous history of reactions to HORCM, the chances of having a repeat reaction on reexposure are as high as 33%. Death occurs in about 1:50 000 intravenous procedures. It is hypothesized that the high osmolality of HORCM may cause direct degranulation of mast cells.

It might be prudent for radiologists to use low-osmolality radiocontrast media (LORCM), which is a relative new entrant in the field. The osmolality of these agents is only twice that of plasma. The incidence of a repeat reaction with LORCM is just about 2.7%, even in patients who have shown a previous reaction to HORCM. However, their cost is 20 times that of HORCM.

Type II hypersensitivity reactions Certain drugs, such as penicillin, quinidine, and methyldopa, can cause type II hypersensitivity reactions causing antibody-mediated destruction of red blood cells (hemolytic anemia) or platelets (thrombocytopenia). The drug binds to the cell surface and serves as a target for antidrug IgG antibodies, causing destruction of the cell. Penicillin is known to cause all four types of hypersensitivity reaction.

Allergy to antisnake venom (type I, type III hypersensitivity) Antisnake venom is prepared by hyperimmunizing horses against snake venom. The sera from these horses are then used to manufacture antisnake venom. Since it contains foreign proteins, it can induce violent anaphylaxis (type I hypersensitivity) or serum sickness (type III hypersensitivity). Adequate testing must be done before injecting antisnake venom. This includes injecting 0.1 ml of the antisnake venom intradermally. A wheal of 1 cm surrounded by erythema of about the same width developing in 5–20 min would indicate that the subject is allergic.

If the subject is found to be allergic, antisnake venom must be given with great caution. Medications for anaphylaxis must be available.

Most snakes are nonpoisonous and giving generalized polyvalent antisnake venom in every instance of a snakebite may not be very good practice. If the relatives and friends have killed the snake, and have brought it with them, it must be identified. A good emergency physician must know the basic differences between a poisonous and a nonpoisonous snake for this reason. Doing so may avoid unnecessary medicolegal complications.

Herxheimer reaction (type III hypersensitivity) This is a form of serum sickness (type III form of hypersensitivity), which occurs following the successful treatment of certain infections such as syphilis, trypanosomiasis and brucellosis. During infection antibodies are formed against these organisms. A successful drug therapy will cause lysis of these organisms, releasing into the circulation a significant amount of their antigens. This may cause a violent antigen–antibody reaction, which may have medicolegal connotations. Before starting treatment in such cases, it is always advisable to inform the patient of the possibility of these reactions. Furthermore, it is advisable for the physician to obtain a written signed consent form from these patients.

Allergy to Human Seminal Plasma

This bizarre condition, first described in 1958 by Specken, has led to successful divorce suits. The female is allergic to her partner's seminal plasma. This causes a stinging, burning, or itching sensation in the vagina immediately after intercourse, with pain in some cases. Local redness, swelling, severe vulvovaginitis, rhinitis, dyspnea, wheezing, and even life-threatening asthma after intercourse have been reported. Many women experience the symptoms for the first time during their honeymoon. These symptoms have also been reported following intrauterine insemination.

In an interesting case, a concurrent allergy to human seminal plasma and latex in a woman has been described. Though the condition is rare, its existence could lead to successful divorce suits. The condition effectively means that a woman cannot have sex. She would experience allergic symptoms after sexual intercourse irrespective of whether the partner used a condom or not. If a condom was used, latex allergy would be the culprit, and if not, it would be the seminal allergy.

Bestiality and Allergy to Animal Sperm

In an extremely unusual case, allergy to dog sperm has been reported. In October 1971, a 42-year-old divorced woman, who had four children and who was pregnant for the fifth time by her boyfriend, reported dizziness and syncope. Her attending physician found her to be hypotensive. She admitted to having had sexual contact with her German Shepherd dog 20 min before her arrival. A scratch test with dog sperm was found to be positive.

Peanut Allergy

Peanut allergy is a known phenomenon, and has invited several successful litigations against doctors. The allergy is due to proteins found in peanuts. These proteins are not destroyed by cooking, so fresh, cooked, and roasted peanuts can cause an allergic reaction. About 1% of all people could be allergic to peanuts.

It is the doctor's duty to inform the parents of children with serious food allergies that their condition is potentially life-threatening. They should also be taught how to use epinephrine (adrenaline) in cases of emergency. On January 24, 2002, a jury ordered two US Middlesex County physicians to pay $10 million to a 13-year-old boy Ray Varghese, who had suffered brain damage after eating peanut candy on Christmas day 1996, because they had failed to inform his parents of the severity of his allergy to peanuts. The parents of Ray Varghese successfully alleged in court that they were not prescribed an EpiPen (epinephrine) that could have prevented their son's brain damage.

Allergy and Sudden Infant Death Syndrome (SIDS)

A M Barrett, a pathologist at the University of Cambridge, UK, was the first to suggest, in 1954, that the cause of enigmatic SIDS could be hypersensitivity to milk. Six years later he, together with two of his colleagues, W E Parish and R R A Coombs (of Gell and Coombs classification fame), conducted a few ingenious experiments to show that milk allergy could indeed be the cause of SIDS. They showed that instillation of a very small amount of milk – too little to cause choking (say, about 0.25 ml) – over the glottis into the larynx of unsensitized conscious guinea pigs was without clinical effect. However, the same procedure repeated over guinea pigs sensitized to milk could result in characteristic anaphylactic reaction, often leading to death. The postmortem findings in such animals did not resemble those found in typical cot-death cases.

If, however, the guinea pigs were lightly anesthetized – an experimental condition used to simulate the condition of the sleeping child – milk introduced into the larynx had quite a different effect. In the unsensitized animal there was no effect, as before. In the sensitized animal, on the other hand, there was a complete lack of the anaphylactic reaction that was seen in the conscious animals. The animal stopped breathing after some time without any sign of struggle. Death sometimes occurred immediately, but the majority died within an hour. The pathological findings in these animals resembled those found in SIDS.

This definitely seemed to indicate that allergy to milk could be a causative factor in SIDS. Later, in November 1960, Parish, Barrett, and Coombs along with two more colleagues, Gunther and Francis E Camps, published a paper outlining their experiments to provide more experimental evidence in favor of their theory. They examined sera from actual cases of cot deaths for their level of milk antibodies. Instead of using milk, they used recovered stomach contents from actual cases of SIDS and used it for instillation in guinea pigs. They conducted experiments to see if individual milk proteins casein, α-lactalbumin, and β-lactoglobulin could produce a lethal effect. And finally, they compared the pathological findings in guinea pigs killed in this way with those found in human cot death.

They found that anesthetized guinea pigs sensitized to cow's milk died rapidly and without struggling when a small quantity (about 0.25 ml) of either cow's milk or stomach contents recovered from cases of SIDS was instilled over their larynx. A 1% solution of casein or a 1% solution of β-lactoglobulin introduced in the same way also produced death. The histopathological changes in the lungs of experimental animals resembled those found in cases of cot deaths. This seemed to prove quite conclusively that milk allergy was indeed the cause of SIDS.

Many workers in later years seemed to corroborate the allergy theory, but suggested different causative allergens. Some workers found increased levels of serum IgE antibodies to dust mite and *Aspergillus*, suggesting that these could be the possible offending allergens. Elevated serum tryptase levels were also found in many cases of SIDS, which seemed to indicate mast cell degranulation just before death, which in turn seemed to corroborate the allergy theory.

But several other workers produced evidence that allergy may not be the causative mechanism in SIDS at all. Elevated serum tryptase levels were explained by stating that it could be caused by a hypoxic stimulus due to the prone position of the child, or it could be due to terminal respiratory failure which would occur in all cases of death. It was suggested that elevated tryptase levels could also be due to passive diffusion from the lung after death, and could just be a postmortem artifact.

The allergy and SIDS controversy is still ongoing, and unresolved, with workers producing evidence for and against the allergy theory at regular intervals.

Exercise and Allergy

Allergy to exercise is a known condition, and may invite medicolegal considerations, especially in army personnel, sports coaches, and trainers, and other persons involved in strenous work. Exercise in susceptible people causes massive release of histamine in the body. Sometimes only exercise is needed, while at other times the person has to eat something before exercise. Occasionally the person has to eat a particular food before exercise to trigger the allergy.

Allergy to exercise can take very bizarre forms. A German group has recently reported a man who got this allergy every Friday while gardening, but not while gardening on other days. This was because he treated himself to a slice of poppyseed cake every Friday before his garden work. Allergy to poppy seeds was proved with tests, but it needed the extra trigger of exercise to accentuate the allergic manifestations.

Postmortem Examination in Allergic Deaths

Quite frequently, a forensic pathologist is faced with an anaphylactic death. Undoubtedly this is one of the most difficult situations to handle; an inexperienced pathologist can easily ruin the autopsy if he/she does not take some basic precautions.

Precautions

It is important to remember in such cases that the autopsy should be conducted as soon as possible after death, because the findings, especially those in the larynx, may recede rapidly after death. Medicolegal formalities may tend to take time, but the earlier they are completed, the better it is for the pathologist. If the body has to be embalmed, the neck organs should be removed before. A detailed history is very helpful, since it would determine proper sampling procedures. Most common allergic deaths encountered are deaths due to drug anaphylaxis (e.g., penicillin), anaphylactoid reactions (e.g., radiocontrast media), exposure to certain plants, and stings due to bees, wasps, and fire ants.

It is useful to take a chest X-ray before starting an autopsy. In fact, the clinician would do well to take it immediately after pronouncing death in such cases; a delay can often cause remission of findings. Pulmonary edema and congestion in chest X-rays may indicate a possible anaphylactic reaction.

External Examination

On external examination, one must search for injection sites or sting marks. Time spent on this simple procedure is well worth it, and may save a lot of embarrassment to the pathologist later. Concentrate on areas like the cubital fossa, front of forearms, back of the hand, both gluteal regions, and areas which are swollen. These are the areas where an injection is likely to be given. Stings are more likely to be on the face and neck, although they can be on any exposed part. Such lesions on covered areas generally rule out insect stings, and indicate injections. If such lesions are found, they must be photographed and excised with a minimum 5 cm margin. The excised tissue should immediately be frozen at $-70\,^{\circ}C$, and submitted for antigen–antibody reactions. Observe for foam around the mouth and nostrils.

Internal Examination

Neck organs must be removed and a photograph of the rima of glottis taken from above, together with the epiglottis. This photographic record may prove very valuable in a court of law. This would also be useful in cases where a second autopsy may be ordered, which is not entirely unusual, given the raised suspicion levels of distressed relatives regarding medical negligence in such cases. Finally these photographs may be useful given the fact that laryngeal edema may subside very rapidly. By the time the pathologist has returned to the neck organs after dissecting the rest of the organs, he/she may find that laryngeal edema has subsided considerably. For histologic study, larynx and epiglottis must be fixed in Zenker's or Bouin's solution.

A detailed examination of the tracheobronchial tree and lungs may prove very rewarding. It is not unusual to find foamy edema in the trachea and bronchi. Lungs may show pulmonary edema and congestion. There may be diffuse or focal pulmonary distension alternating with collapse. A microscopic examination may reveal eosinophilic leukocytes. Just as in the case of trachea and larynx, it is useful to take photographs of the lungs for similar reasons. Weights of lungs must also be recorded; grossly overweight lungs point to pulmonary edema. Lungs should not be perfused with fixative as it may cause artificial distension.

A microscopic examination of the spleen may show eosinophilic leukocytes in red pulp.

Special Investigations

A sample of blood must be submitted for drug levels (or sting antigens) alleged to have been injected. Samples must also be frozen and submitted for IgE against the suspected drug/antigen.

See Also

Autopsy: Procedures and Standards; **Autopsy, Findings:** Sudden Infant Death Syndrome; **Drug-Induced Injury, Accidental and Iatrogenic**; **Drugs, Prescribed:** Product Liability; Testamentary Capacity; **Sudden Infant Death Syndrome, Etiology and Epidemiology**

Further Reading

Aggrawal A (1993) Allergies. In: Aggrawal A (ed.) *Some Common Ailments,* pp. 1–8. India: National Book Trust.

Buckley MG, Variend S, Walls AF (2001) Elevated serum concentrations of β-tryptase, but not α-tryptase, in sudden infant death syndrome (SIDS). An investigation of anaphylactic mechanisms. *Clinical and Experimental Allergy* 31: 1696–1704.

Galiher GO, DeRobertis LR (1999) The legal aspects of the latex protein allergy epidemic. *Hawaii Medical Journal* 58: 160, 167.

Gibofsky A (1996) Legal issues in allergy and clinical immunology. *Journal of Allergy and Clinical Immunology* 98: S334–S338.

Giroux-Slavas J (1999) Latex allergy: a potential liability issue. *Pennsylvania Dental Journal (Harrisburg)* 66: 14–17.

Guidelines for the Diagnosis and Management of Asthma (1991) *National Asthma Education Program Expert Panel Report*. Publication NIH 91-3042. Bethesda, MD: Department of Health and Human Services.

Holden TE, Sherline DM (1973) Bestiality, with sensitization and anaphylactic reaction. *Obstetric Gynecology* 42: 138–140.

Hunskaar S, Fosse RT (1993) Allergy to laboratory mice and rats: a review of its prevention, management and treatment. *Laboratory Animals* 27: 206–221.

Kohn P (1999) The legal implications of latex allergy. *Registered Nurse* 62: 63–65. Erratum in *Registered Nurse* 1999; 62: 9.

Parish WE, Barrett AM, Coombs RRA, Gunther M, Camps FE (1960) Hypersensitivity to milk and sudden death in infancy. *Lancet* ii: 1106–1110.

Rice B (2002) A $10 million allergy case. Could it happen to you? *Medical Economics* 79: 36–38.

Rubsamen DS (1993) The doctor, the asthmatic patient, and the law. *Annals of Allergy* 71: 493–494.

Schappi GF, Konrad V, Imhof D, Etter R, Wuthrich B (2001) Hidden peanut allergens detected in various foods: findings and legal measures. *Allergy* 56: 1216–1220.

Wakelin SH, White IR (1999) Natural rubber latex allergy. *Clinical and Experimental Dermatology* 24: 245–248.

Zemenick RB (1994) Medicolegal implications of pulmonary function testing. *Annals of Allergy* 73: 275–276.