

History and classification of anaphylaxis

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Abstract. Anaphylaxis is the maximal variant of an acute allergic reaction involving several organ systems. The phenomenon itself is old, but it was recognized and named at the beginning of the 20th century by Richet and Portier. The clinical symptoms of anaphylaxis affect various organs, most commonly starting in the skin and proceeding to the respiratory tract, to gastrointestinal involvement and to cardiovascular symptoms, and finally to cardiac and/or respiratory arrest. Anaphylaxis *stricto sensu* is an immunological reaction, mostly mediated by IgE antibodies, but also by IgG or IgM antibodies (immune complex anaphylaxis). There are cases with similar clinical symptomatology without detectable immunological sensitization which are called pseudo-allergic or anaphylactoid reactions. In the newer nomenclature, some authors tend to include these under the heading of ‘anaphylaxis’ which has then to be defined as an acute systemic hypersensitivity reaction. The most common elicitors of anaphylaxis include drugs, foods, additives, but also other allergens as well as physical factors (cold, heat, UV radiation). The clinical outcome—the intensity of the reaction—is not only influenced by the degree of sensitization, but also by concomitant other factors: sometimes, individuals only develop anaphylaxis after simultaneous exposure to the allergen and an infection, physical exercise, psychological stress or concomitant medication (e.g. β blockers). The term ‘summation anaphylaxis’ has been proposed for this phenomenon which probably underlies many cases of so-called idiopathic anaphylaxis. In patients with insect venom anaphylaxis, decreased levels of plasma angiotensin have been measured in inverse correlation to the severity of the reaction. Certain differential diagnoses have to be distinguished from anaphylaxis. Every patient with a history of anaphylaxis should undergo allergy diagnosis with the aim to detect the eliciting agent, characterize the relevant pathomechanism (e.g. IgE-mediated reaction) and to offer a tolerable alternative (in food or drug allergy). In clear-cut IgE-mediated anaphylaxis, allergen-specific immunotherapy (hyposensitization) is the effective causal treatment, with success rates of 90% in insect venom anaphylaxis.

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Allergic diseases have been increasing in prevalence in most countries over the last few decades (Ring et al 2001) and are often not taken seriously because they are not regarded as contributory to increased mortality rates. This rather superficial

opinion has been contradicted by a variety of life-threatening emergencies in allergology (e.g. fatal asthma attack, anaphylaxis, laryngeal [angio-]oedema, severe serum sickness with vasculitis and nephritis, bullous drug eruptions like toxic epidermal necrolysis) among which anaphylaxis undoubtedly represents the most acute condition.

History

The phenomenon of anaphylaxis is old and has been described in ancient Greek and Chinese medical literature. The first documented anaphylactic patient might have been pharaoh Menes who died 2640 BC from the sting of a wasp, as hieroglyphs tell (Wadell 1930).

The phenomenon was only clearly recognized in 1901 when Charles Richet and Paul Portier were doing their experiments on the yacht of the prince of Monaco and later on in the laboratory in Paris, trying to immunize dogs with *Actinia* extracts (Portier & Richet 1902). When, contrary to the expectation, after repeated injections, the animal died under dramatic circumstances, Richet—who was called by Portier into the lab—immediately recognized that there was something new ('C'est un phénomène nouveau, il faut le baptiser!') and wanted to find a name for it. What he wanted to express was 'lack of protection' and should have been 'aphylaxis' (Greek α privativum = negation); however, for euphonic reasons, he preferred 'anaphylaxis', a term which rapidly spread all over the world; for its description Richet won the Nobel prize in 1913.

This discovery, describing an obvious damage by immunization—while earlier immunization was only connected with the positive and desired effect of protection against pathogenic organisms—subsequently led to the creation of the term 'allergy' by Clemens Freiherr von Pirquet in 1906 (von Pirquet 1906).

Later on, researchers realized that similar symptoms (Hanzlik & Karsner 1920) can be elicited by the injection of histamine in individuals or could occur in animals not previously sensitized ('anaphylactoid reactions') (Lorenz et al 1977, Kind et al 1972).

Epidemiology

There is limited knowledge about the exact prevalence and incidence of anaphylaxis in the general population and in different age groups. Some estimates of insect-sting anaphylaxis range between 1 and 3% (Müller 2001, Yocum et al 1999). For drug-induced anaphylaxis, different incidence rates have been reported for different drugs (e.g. prevalence of penicillin allergy 2%; fatal anaphylaxis 1:50 000–1:100 000).

Clinical symptoms

Clinically, anaphylaxis represents a syndrome of different symptoms involving various organs which may develop either alone or simultaneously or subsequently, most commonly

- starting in the skin (pruritus, flush, urticaria, angioedema) and the neighbouring mucous membranes (itchy palate, paraesthesia in pharynx, genital mucosa) are often the first symptoms
- proceeding to the respiratory tract (sneezing, rhinorrhoea, hoarseness, dysphonia, laryngeal oedema, cough, laryngeal obstruction, bronchospasm, respiratory arrest)
- abdominal symptoms (nausea, cramps, vomitus, defecation, diarrhoea, also miction and uterus cramps occur)
- and cardiovascular symptoms (tachycardia, blood pressure changes—not necessarily hypotension, but also transient-type hypertension has been observed as first symptom—arrhythmia, shock, cardiac arrest). Primary cardiac manifestation in anaphylaxis has been observed in ECG-changes (T-flattening, supraventricular arrhythmia, AV block) (Pavek et al 1982, Marone et al 1995). Marked changes of central venous pressure are common. During anaphylaxis, myocardial infarction has occurred (Cistero et al 1992, Wagdi et al 1994).

Prodromi of anaphylaxis comprise paraesthesia on palms and soles, a metallic 'fishy' taste, anxiety, sweating, headache or disorientation.

Several attempts have been made to develop grading scales for severity scoring of anaphylaxis which differ in some respects (Mueller 1966, Ring & Messmer 1977, Ansell 1990). We proposed in a study describing 248 anaphylactoid reactions and observing 200 906 intravenous infusions of colloid volume substitutes, a simple scoring system from I to IV which is immediately useful with regard to acute therapy without need for long reflection (Table 1).

Although the clinical symptoms of anaphylaxis are rather characteristic, some differential diagnoses have to be considered (Table 2).

Pathophysiology

Anaphylaxis *stricto sensu* is an immunological reaction mostly mediated by IgE antibodies on the surface of mast cells and basophil leukocytes which, after a bridging with an at least bivalent allergen, trigger the secretion of preformed and newly synthesized mediators. In spite of our knowledge of mast cell activation and IgE antibodies, the exact mechanisms of amplification are not yet understood

TABLE 1 Grading of anaphylactic reactions according to severity of clinical symptoms

<i>Symptoms</i>				
<i>Grade</i>	<i>Dermal</i>	<i>Abdominal</i>	<i>Respiratory</i>	<i>Cardiovascular</i>
I	Pruritus Flush Urticaria Angioedema			
II	Pruritus Flush Urticaria Angioedema (not mandatory)	Nausea Cramping	Rhinorrhoea Hoarseness Dyspnoea	Tachycardia (> 20 bpm) Blood pressure change (> 20 mmHg systolic) Arrhythmia
III	Pruritus Flush Urticaria Angioedema (not mandatory)	Vomiting Defecation Diarrhoea	Laryngeal oedema Bronchospasm Cyanosis	Shock
IV	Pruritus Flush Urticaria Angioedema (not mandatory)	Vomiting Defecation Diarrhoea	Respiratory arrest	Cardiac arrest

bpm = beats per minute.

TABLE 2 Differential diagnoses of anaphylactoid reactions

- Pharmacological/toxic drug effects
- Hyperventilation
- Vasovagal reaction
- Globus hystericus
- Syncope (cardial, cerebral)
- Carcinoid syndrome
- Seizure diseases
- Bolus aspiration
- Pulmonary embolism
- Hypoglycaemia
- Artificial anaphylaxis (Munchausen syndrome)

which allow a healthy individual to be killed by a few micrograms of an allergen within minutes.

Apart from IgE, other antibodies may also elicit anaphylaxis via immune complex formation and complement activation (immune complex anaphylaxis), (Smedegard et al 1979, Richter et al 1980, Ring 1978). Clinical examples are anaphylactic reactions to blood products, xenogeneic proteins as well as dextran (Ring & Messmer et al 1977, Hedin et al 1976).

Apart from these clear-cut immunologically mediated reaction patterns, there are cases with very similar clinical symptomatology of anaphylaxis without detectable immunological sensitization (antibodies or sensitized cells) which have been called pseudo-allergic or anaphylactoid reactions. The mechanisms of these reactions are much less well-understood (Table 3) and include direct liberation of vasoactive mediators (e.g. histamine), general mast cell or basophil activation with release of other mediators, activation of the complement or other plasma protein systems (coagulation, kallikrein-kinin) as well as neuropsychogenic reflex mechanisms. It is known that psychological stress alone can lead to increased plasma histamine levels (Irie et al 2002).

In the end phase of the anaphylactic reaction, similar pathophysiological changes occur which are relevant for the clinical symptoms with post-capillary plasma exudation, microcirculatory disturbance with decreased capillary pressure and perfusion and erythrocyte stasis (Withers et al 1998, Endrich et al 1979, Fisher 1986, Sudhakaran et al 1979). Mast cell dependent anaphylactic reactions go along with the secretion of mast cell tryptase — preferably β -tryptase — in the serum which still can be detected even hours (sometimes post mortem) after a reaction (Schwartz et al 1994, Brockow et al 1999).

The amount of mediator release from mast cells and basophils depends not only on the serum concentration of IgE antibodies or the concentration of allergen or other elicitors, but is influenced by non-specific factors like acute infection, physical exercise, psychological stress, concomitant medication, such as β blockers or angiotensin-converting enzyme (ACE) inhibitors. These influences

TABLE 3 Possible mechanisms of non-immune anaphylactic (pseudo-allergic) reactions

Direct release of mediators (e.g. histamine)
Direct activation of complement system
Activation of the coagulation system
Interaction with kallikrein-kinin system
Shift in eicosanoid metabolism toward leukotriene formation
Platelet activation
Psychoneurogenic reactions

may — by the action of cytokines, like interleukin 3, 4, 13 or others — influence the ‘releasability’ of mediator-secreting cells and help to explain the well-known clinical fact that sometimes patients only react under certain circumstances when several eliciting factors act simultaneously (e.g. infection+allergen, exercise+allergen; Sheffer & Austen 1980, simultaneous exposure to different relevant allergens, etc). The term ‘summation anaphylaxis’ or ‘augmentation anaphylaxis’ has been proposed for this phenomenon which seems to be much more common than previously thought and probably underlies many cases of so-called ‘idiopathic anaphylaxis’ (Table 4).

Recently, some authors have included the non-immunologically mediated immediate-type reactions also under the heading ‘anaphylaxis’; then, anaphylaxis would have to be defined as ‘acute generalized immediate-type hypersensitivity reaction’ (Johansson et al 2001).

Problems in terminology arise from the fact that classifications are attempted at different levels, either coming from clinical symptoms or from pathophysiology. So the terms may have different meanings and furthermore, our knowledge, especially regarding pseudo-allergic reactions, is so limited that classifications always remain speculative in nature. It should be stressed that the term ‘pseudo-allergic’ or ‘non-immune’ anaphylaxis is negatively defined in that it is not possible to detect immunological sensitization in the serum or at the cellular level. Possibly, with advanced technology, such reactions may be turned from pseudo-allergic anaphylactoid reactions into allergic anaphylactic reactions. From a clinical point of view, the broader meaning of ‘anaphylaxis’ seems acceptable and should not lead to confusion when the further distinction into immunologically mediated (IgE, IgG or others) or non-immunological (pseudo-allergic) is kept in mind!

During anaphylaxis, the organism has a variety of systems to counteract the untoward effects of the suprarenal hormones (stress), but also the rennin–angiotensin system. We could show that during drug-induced anaphylaxis under controlled conditions, angiotensin II concentrations sharply increase in urine together with clinical symptoms; this also could explain why sometimes initial

TABLE 4 Summation anaphylaxis (symptoms only after exposure to a combination of influencing factors)

Acute infection
Mental stress
Emotional stress
Physical exercise
Concomitant allergen exposure (indoor, outdoor, food)
Intake of medications (cyclo-oxygenase inhibitors, β -blocking agents)

hypertension is observed prior to hypotension in severe anaphylaxis (Rittweger et al 1994). In a series of patients with insect-venom anaphylaxis, we found significantly decreased plasma levels of components of the rennin-angiotensin system, and also in a patient with unexplained idiopathic anaphylaxis (Hermann & Ring 1993).

Allergens and elicitors

The most common elicitors of anaphylaxis are drugs, proteins, foods, aeroallergens, additives, body fluids, latex and microbial antigens, but also physical factors (Table 5). However, the total spectrum of elicitors is much broader, even anaphylaxis to ethanol has been described (Przybilla & Ring 1983). Rare cases of passive transfer by IgE antibodies via blood transfusion as well as attempted suicide (penicillin-allergic nurse) have been reported. Murder has been attempted by eliciting anaphylaxis in the detective literature. Also anaphylaxis factitia ('Munchausen's syndrome') exists (Ireland et al 1967). The eliciting agent may contact the organism via the air (fish allergens in volatile form around fish stores, latex allergens in operation theatres or rooms decorated with balloons), via the skin surface (contact anaphylaxis) (Ring et al 1986) but mostly after oral or parenteral intake.

TABLE 5 Elicitors of anaphylaxis (including anaphylactoid reactions)

Drugs
Foods
Drug and food additives
Occupational substances (e.g. latex)
Animal venoms
Aeroallergens
Seminal fluid
Contact urticariogens
Physical agents (cold, heat, ultraviolet radiation)
Exercise
Echinococcal cyst
Summation anaphylaxis
Underlying disease
Complement factor 1-inactivator deficiency
Systemic mastocytosis
Idiopathic (?)

Patient management

Every patient with a history of anaphylaxis should undergo allergy diagnosis which has to include three steps:

- detection of the eliciting agent
- characterization of the relevant pathophysiology
- offering a tolerable alternative (Ring & Behrendt 1999).

For prophylaxis, this means abstaining from polypragmatic pharmacotherapy. Equally important are endeavours of the pharmaceutical industry to produce better and less allergenic drugs. Predictive testing for these purposes (namely, characterization of IgE-inducing allergens) has to be improved.

Knowledge of possible complications is the basis of successful therapy. This implies education of the informed patient and his surroundings as well as improved declaration laws.

In clear-cut IgE mediated anaphylaxis, allergen-specific immunotherapy is the effective causal treatment with success rates of over 90% (Przybilla et al 1987). Attempts of 'hyposensitization' in certain types of drug allergy have been successful. In only few cases, specific induction of tolerance against xenogeneic horse immunoglobulin (Ring et al 1974, Jones et al 1976) or by hapten inhibition in dextran anaphylaxis have been proven successful (Laubenthal 1986).

Treatment of the acute anaphylactic episode follows the severity of symptoms (Messmer 1983) and includes the intramuscular use of epinephrine (adrenaline) as soon as severe respiratory involvement or hypotension occurs. However, it has to be recalled that epinephrine, even if used correctly, does not guarantee a successful outcome. In spite of early and adequate epinephrine, fatal anaphylaxis has been described (Lockey et al 1987). Furthermore, epinephrine may induce severe cardiac arrhythmia up to ventricular fibrillation, especially in elderly patients (Sullivan 1982).

Outlook: problems still to be solved

In spite of all our increasing knowledge in modern experimental and clinical allergology, anaphylaxis still represents a major problem both for researchers and clinicians.

Many more studies regarding pathophysiology, especially with regard to the non-IgE-mediated or IgE-independent mechanisms in the development of anaphylaxis, are needed.

Better techniques to study the involvement of different cell populations and mediators (differential release, such as increased histamine release with normal eicosanoid secretion or vice versa) have to be considered.

In diagnostic work, the detection of the eliciting agents is a major difficulty. Reliable skin tests or *in vitro* tests only exist for some protein allergens and few drugs as haptens. There is no *in vitro* or skin test for pseudo-allergic reactions.

Provocation tests under blinded conditions are the only reliable tool in many cases, but go along with a significant risk and, therefore, have to be performed under emergency and, preferably, in-patient conditions. Particularly difficult is the question of provocation tests in parenterally applied substances such as volume substitutes, radiographic contrast media or anaesthetic agents where the performance of a provocation in adequate dose poses also ethical questions.

There are major problems regarding the prognosis as well as the definition of risk factors for anaphylaxis. Up to now, apart from history, there is almost no reliable diagnostic test giving adequate information on the risk of future reactions after repeated contact. The question whether atopic individuals are at higher risk for anaphylaxis is still controversially discussed. Most likely, food anaphylaxis and anaphylactic reactions with predominantly respiratory involvement may occur more frequently in atopics, while parenterally elicited anaphylactic reactions (insect stings, penicillin, etc.) are not related to atopy.

Problems in acute treatment include the question as to who should use epinephrine, when and in what dosage. Novel approaches would be desirable. Application of angiotensin II may be an alternative for the future. In causal treatment approaches, avoidance is only possible if the patient is well-educated and the elicitors are declared in drugs, foods or other substances. Allergen-specific immunotherapy for many elicitors of anaphylaxis does not exist. Studies are needed for food allergy and many cases of drug allergies. Studies with biologicals such as monoclonal antibodies against IgE seem promising and have to be performed at a larger level (Leung et al 2003).

At the level of industry — not only pharmaceutical, but also general — the problem of predictive testing with regard to IgE-inducing allergens is still unsolved and deserves attention and research. Education of the public with regard to the nature of anaphylaxis and immediate first aid manoeuvres (e.g. posture) are mandatory!

References

- Ansell G 1990 Adverse reactions to contrast agents. Scope of problem 1970. *Invest Radiol* 25:381–391
- Brockow K, Vieluf D, Püschel K, Grosch J, Ring J 1999 Increased postmortem serum mast cell tryptase in a fatal anaphylactoid reaction to nonionic radiocontrast medium. *J Allergy Clin Immunol* 104:237–238
- Cistero A, Urias S, Guindo J et al 1992 Coronary artery spasm and acute myocardial infarction in naproxen-associated anaphylactic reaction. *Allergy* 47:576–578
- Endrich B, Ring J, Intaglietta M 1979 Effects of radiopaque contrast media on the microcirculation of the rabbit omentum. *Radiology* 132:331–339

- Fisher MMD 1986 Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care* 17:17–21
- Hanzlik PJ, Karsner HAT 1920 Anaphylactoid phenomena from the intravenous administration of various colloids, arsenicals and other agents. *J Pharmacol Exp Ther* 14:379
- Hedin H, Richter W, Ring J 1976 Dextran-induced anaphylactoid reactions in man: role of dextran reactive antibodies. *Int Arch Allergy Appl Immunol* 52:145–159
- Hermann K, Ring J 1993 The renin angiotensin system and Hymenoptera venom anaphylaxis. *Clin Exp Allergy* 23:762–769
- Ireland P, Sapira JD, Templeton B 1967 Munchausen's syndrome. Review and report of an additional case. *Am J Med* 43:579–592
- Irie M, Nagata S, Endo Y 2002 Effect of isolation on classical conditioned histamine release in guinea pigs. *Neurosci Res* 44:31–35
- Johansson SG, Hourihane JO, Bousquet J et al 2001; EAACI (the European Academy of Allergology and Clinical Immunology) nomenclature task force. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 56:813–824
- Jones VE, Lance EM, Abbosh J, Graves HE 1976 Tolerance to equine IgG after immunosuppression in patients with multiple sclerosis. *Postgrad Med J* 52(suppl 5):136–138
- Kind LS, Kaushal PK, Drury P 1972 Fatal anaphylaxis-like reaction induced by yeast mannans in nonsensitized mice. *Infect Immun* 5:180–182
- Laubenthal H 1986 Dextrananaphylaxie, Pathomechanismus und Prophylaxe. Ergebnisse einer multizentrischen Studie. Springer, Berlin
- Leung DYM, Sampson HA, Yunginger JW et al 2003 Effect of Anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 348:986–993
- Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC 1987 Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 79:666–677
- Lorenz W, Doenicke A, Dittmann I, Hug P, Schwarz B 1977 Anaphylaktoide Reaktionen nach Applikation von Blutersatzmitteln beim Menschen. Verhinderung dieser Nebenwirkung von Haemacel durch Praemedikation mit H₁- und H₂-Antagonisten. *Anaesthesist* 26:644
- Marone G, Patella V, de Crescenzio G et al 1995 Human heart mast cells in anaphylaxis and cardiovascular disease. *Int Arch Allergy Immunol* 107:72–75
- Messmer K 1983 Plasma substitutes and indications for their use. In: Tinker J, Rapin M (eds) *Care of the critically ill patient*. Springer, Berlin, p 569–575
- Mueller HL 1966 Diagnosis and treatment of insect sensitivity. *J Asthma Res* 3:331–333
- Müller U 2001 Spätkomplikationen bei Anaphylaxie. In: Ring J, Darsow U (eds) *Allergie 2000: Probleme, Strategien und praktische Konsequenzen*. Dustri, München, Germany, p 249–252
- Pavek K, Wegmann A, Nordström L, Schwander D 1982 Cardiovascular and respiratory mechanisms in anaphylactic and anaphylactoid shock reactions. *Klin Wochenschr* 60:941–947
- Przybilla B, Ring J 1983 Anaphylaxis to ethanol and sensitization to acetic acid. *Lancet* 1:483
- Przybilla B, Ring J, Griesshammer B, Braun-Falco O 1987 Rush hyposensitization with Hymenoptera venoms. Tolerance and results of therapy. *Dtsch Med Wochenschr* 112:416–424
- Portier P, Richet Ch 1902 L'action anaphylactique de certains venins. *CR Soc Biol* 54:170
- Richter W, Hedin H, Ring J, Kraft, D, Messmer, K 1980 Anaphylaktoide Reaktionen nach Dextran I. Immunologische Grundlagen und klinische Befunde. *Allergologie* 3:99
- Ring J 1978 Anaphylaktoide Reaktionen nach Infusion natürlicher und künstlicher Kolloide. Springer, Berlin
- Ring J 1987 Anaphylaxis and anaphylactoid reactions. In Baethmann A, Messmer K (eds) *Surgical research: recent concepts and results*. Springer, Berlin, p 210–221
- Ring J, Messmer, K 1977 Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1:466–469

- Ring J, Behrendt H 1999 Anaphylaxis and anaphylactoid reactions: classification and pathophysiology. *Clin Rev Allergy Immunol* 17:387–399
- Ring J, Seifert J, Lob G et al 1974 Intensive immunosuppression in the treatment of multiple sclerosis. *Lancet* 2:1093–1095
- Ring J, Galosi A, Przybilla B 1986 Contact anaphylaxis from emulgade F. *Contact Dermatitis* 15:49
- Ring J, Krämer U, Schäfer T, Behrendt H 2001 Why are allergies increasing? *Curr Opin Immunol* 13:701–708
- Rittweger R, Hermann K, Ring J 1994 Increased urinary excretion of angiotensin during anaphylactoid reactions. *Int Arch Allergy Immunol* 104:255–261
- Schwartz LB, Bradförd TR, Rouse C et al 1994 Development of a new, more sensitive immunoassay for human tryptase: use in systemic anaphylaxis. *J Clin Immunol* 14:190–204
- Sheffer AL, Austen KF 1980 Exercise-induced anaphylaxis. *J Allergy Clin Immunol* 66:106–111
- Smedegard G, Ravenäs B, Arfors KE 1979 Anaphylaxis in the monkey: hemodynamics and blood flow distribution. *Acta Physiol Scand* 106:191–198
- Sudhakaran K, Viswanathan R, Subramanian TA 1979 Plasma histamine levels under hypoxic stress: further studies on pulmonary oedema of high altitude. *Respiration* 37:91–96
- Sullivan TJ 1982 Cardiac disorders in penicillin-induced anaphylaxis: association with intravenous epinephrine therapy. *J Am Med Assoc* 248:2161–2162
- von Pirquet C 1906 Allergie. *Münch Med Wochenschr* 30:1457
- Wadell LA 1930 Egyptian civilisation. Luzac & Co., London
- Wagdi P, Mehan VK, Burgi H, Salzmann C 1994 Acute myocardial infarction after wasp stings in a patient with normal coronary arteries. *Am Heart J* 128:820–823
- Withers GD, Kubes P, Ibbotson G, Scott RB 1998 Anaphylaxis-induced mesenteric vascular permeability, granulocyte adhesion, and platelet aggregates in rat. *Am J Physiol* 275:H274–H284
- Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DS, Silverstein MD 1999 Epidemiology of anaphylaxis in Olmsted county: a population-based study. *J Allergy Clin Immunol* 104:452–456

DISCUSSION

Galli: Could you expand on the concept of summation anaphylaxis? Have there been any prospective studies that have looked at defined combinations, or is this concept primarily based on clinical observations?

Ring: I'm not aware of good studies, except for summation in the sense of exercise-induced anaphylaxis. The combination of exercise plus food has been studied best.

Müller: There is a paper by Hepner et al (1990), which is a case-control study looking at the effect of β blockers in patients on allergen immunotherapy. They found no increase in the frequency of systemic allergic side effects in the group on β blockers but concede that side effects in these patients may be more severe and more difficult to treat.

Galli: Hugh Sampson, have you seen a summation effect in cases of food allergies that you have studied?

Sampson: As Johannes Ring mentioned, we see food-associated exercise-induced anaphylaxis. There are some children who had milk allergy early on, appear to have outgrown it, but retain evidence of IgE antibody. In some cases, if they consume milk and then exercise, they will experience anaphylactic symptoms whereas if they are not exercising they are fine. No one has worked out the mechanism underlying this phenomenon.

Galli: What is your speculation about the angiotensin II connection?

Ring: It's a fascinating observation. Novartis produces an angiotensin II drug called 'hypertensin'. It is rarely used, but it would be a useful addition to our emergency kit. It is independent of epinephrine.

Fisher: Have you looked in any groups other than Hymenoptera allergy?

Ring: Yes, we've looked at drug-induced anaphylaxis.

Fisher: Did they also have low levels of rennin/angiotensin?

Ring: No, they didn't have generally decreased angiotensin levels, but the angiotensin levels increased during anaphylaxis.

Marone: I was very impressed by your data showing that the renin-angiotensin system can be involved *in vivo* during systemic anaphylaxis. This is an important issue for several reasons. First, I remember that Urata et al (1993) showed several years ago that chymase can efficiently convert angiotensin I to angiotensin II. More recently we have shown that mast cell chymase released from immunologically activated cardiac mast cells can efficiently convert angiotensin I to angiotensin II. (Marone et al 1998). It is possible that certain mediators such as chymase released from mast cells can play an important role in the homeostatic control of anaphylaxis.

Schwartz: It is a fascinating observation that chymase could be a source for generating angiotensin II in tissues. It has been difficult for people doing research on this area to show that such an event is pathophysiologically important. Along the same lines, there is a second angiotensin converting enzyme (ACE), ACE2, that has now been described to counterbalance ACE. When those two enzymes are out of balance, problems ensue. ACE2 makes an inactive or less active form of angiotensin. It is a smaller peptide that has less activity, so it ends up reducing the potential amount of angiotensin II. Thus, the system has become more complex; I'm not sure what role chymase plays.

Ring: I should add that the patients I described had normal ACE levels, although they had reduced angiotensin I and II in the plasma.

Austen: There are two issues I would like to speak about briefly. The overall context to my comment is that I am dismayed by the idea that we would mix distinct biochemical and immunological disease mechanisms and that we would use the terms pseudo-allergic and anaphylactoid synonymously with the term 'anaphylaxis'. They can be used as separate terms for descriptive purposes. Anaphylaxis is an immunological term that

excludes, for example, the non-steroidal anti-inflammatory adverse reactions and also adverse reactions to the ACE inhibitors. With regard to the non-steroidal anti-inflammatory agents, we know that the adverse reactions which have clinical characteristics of anaphylaxis are precipitated by inhibition of cyclooxygenase type 1 resulting in attenuation of PGE2 generation and increased generation of cysteinyl leukotrienes; this adverse reaction can be blocked by preventing the generation of the cysteinyl leukotrienes, or by antagonism of their receptor-mediated action. That does not mean that there cannot be the occasional patient who recognizes an epitope in a true immunological reaction to the non-steroidal (NSAID) drug but the vast majority of adverse reactions to the NSAIDs are not structurally specific but rather share a common biochemical mechanism. This is a wonderful example of why one shouldn't lose sight of mechanism by either clinically or intellectually lumping a lot of different pathways together. We'll never sort them out if we do that.

As to life-threatening angioedema, targeted disruption of the inhibitor of the first complement component (C1INH) has shown that the augmented permeability is due to the elaboration of kinins. Indeed, a double 'knockout' lacking C1INH and a kinin receptor is protected (Han et al 2002). At the human level the data are not yet as far along, but a number of laboratories have shown elevated kinin levels in hereditary C1INH. The ACE inhibitors not only block the function for which they are named but also a kininase, which is responsible for the inactivation of the kinins. Furthermore, this pathway has been implicated in a subfraction of patients with idiopathic anaphylaxis. My point is that we will be able to dissect mechanistically clinically similar adverse reactions and then introduce rational management in biochemical terms. The adoption of a nomenclature that buries our thinking, both clinically and scientifically, is a mistake that neither serves our clinical field nor our patients.

Galli: Johannes, did I understand correctly that the proposal is to refer to all of the reactions that are clinically similar to anaphylaxis without attempting to break out anaphylactoid reactions?

Ring: That is right. I am a member of this task force and we have had a lot of discussion about this. I was in favour of Frank Austen's mechanistic distinction. For me, anaphylaxis is an immunological reaction. Yet, the argument from the other side is a clinical one. You see the patient and you have to write a letter to the relatives telling them, for example, how the patient died. You can only uncover the mechanism days or weeks later, so you have to use the term anaphylactoid irrespective of a mechanism.

Lee: Part of this debate about nomenclature stems from the fact that we don't understand the pathophysiological mechanisms. Management wise, it is critically important to know the mechanism, so if it is an IgE-mediated phenomenon we

now have anti-IgE therapies. In the discussions over the next few days we will be hearing a lot about the effector arm of the response. What we may not hear much about is the target tissue response. In other words, are there situations in very severe anaphylaxis or allergy whereby there is a hypersensitivity of the target tissue, caused for example by greatly enhanced receptor expression. I believe there is in aspirin intolerance (Sousa et al 2002). In order to provide insight on ways in which we can stop people dying from anaphylaxis we have to understand both sides of the equation.

Fisher: We have wrestled with this nomenclature issue for many years. In the first papers that we wrote we talked about severe histamine-mediated reactions, which is probably the first two or three minutes. Then we talked about clinical anaphylaxis. The problem in practice with the anaphylactoid/anaphylaxis classification is that often anaphylactoid can mean many things. It means that there is no immunological basis to that reaction, but what it really means is that there is no immunological basis that I have found to this reaction. It often means that I haven't looked, or that I haven't looked with the appropriate technology. There are documented cases where someone has assumed a reaction was anaphylactoid, or not immune mediated, on the basis of it occurring on first exposure. This has led to the deaths of patients. On the warning bracelet we write 'anaphylaxis'. Everyone knows to be frightened of that. But for scientific papers it is a different ball game.

Simons: I would like to comment on the issue of diagnosis. Johannes Ring mentioned that diagnosis of anaphylaxis is easy. However, I'd like to suggest that there is at least one group of patients in whom this isn't the case, namely infants and pre-school children. I was concerned for many years by the fact that few infants and young children were included in the retrospective studies of anaphylaxis episodes from all triggers in all ages that have been published (Yocum et al 1999, Kemp et al 1995). The mean age in these studies was 29–39 years. There are two small studies and one recent large study of anaphylaxis from all triggers in children (Dibs & Baker 1997, Novembre et al 1998, Simons et al 2003). Recently, we have completed a prospective surveillance study of anaphylaxis within the Canadian Pediatric Surveillance Program. During an 18 month period, 747 cases were reported, two thirds of which involved children under the age of six years. A new picture of anaphylaxis in the very young is emerging from this study. The fact is that infants and very young children often can't describe their symptoms and if they do describe them, they use a non-traditional vocabulary. Itching, for example, is described as burning, hurting, scratching, tickling, tingling or hot or is reported when caregivers observe rubbing, pulling or clawing at the itchy part by those too young to verbalize. I mention this in order to draw attention to the fact that diagnosis of anaphylaxis may not be easy in infants and young children (Simons et al 2003).

Pumphrey: I agree with that. Of patients that are referred to us that have been given treatment for anaphylaxis, over half have been misdiagnosed. For example, I do my anaesthetic reaction clinic with an experienced consultant anaesthetist, and in two-thirds of cases referred following a ‘reaction’ we find an alternative cause for the event and no evidence for anaphylaxis.

Galli: In these cases are the patients presenting with the clinical picture of anaphylaxis because of mast cell activation by a non-immunological mechanism, or do they have something else entirely?

Pumphrey: There are many causes during anaesthesia for someone’s blood pressure falling rapidly or sudden difficulty with ventilation.

Galli: So this isn’t simply a debate about whether to call it an anaphylactoid reaction or anaphylaxis — they have a completely different pathophysiological mechanism.

Pumphrey: Yes.

Lasser: For many years the reactions that resulted from X-ray contrast material injections were termed ‘anaphylactoid’, although clinically they were indistinguishable from other anaphylaxis reactions. In the last few years we have found something that will enable us rightfully to call these reactions anaphylactic and with good reason.

Ring: In response to Estelle Simons’ comment, when I said diagnosis was easy I was speaking in relative terms. It can be difficult. Description is not just a problem in children. When adults describe their symptoms they use colourful terms. All doctors have a similar questionnaire with standard questions, but we don’t let the patients tell us themselves what they have experienced. One patient described to me that she saw ‘white mice’. They describe a lot of symptoms which we reject because they are outside of our usual thinking.

Sampson: Tak Lee mentioned about studying the target audience response. I think this is very important. One of the observations we have made over the years doing double-blind challenges is that in children who are allergic to more than a single food, we can see reproducible responses. For example, if someone is allergic to milk they may have a reproducible response in the skin and gastrointestinal (GI) tract, and if we then challenge them with egg which they are also allergic to, we might get a reproducible response in the lung and skin. One of the questions that we have always had is why, if they have IgE on the mast cells in all these target organs, do they have one reproducible target response with one food and another target response with other foods. In response to Estelle Simons’ comment about young children, one thing that is evident is that young children respond in a certain way and as they get older their anaphylaxis becomes more apparent. There are many children in the USA who respond to peanut early on, often with skin and GI symptoms, yet if they are exposed again a few years later will exhibit a full systemic response. One of the problems in the young children is

that they may not manifest all target organ responses early, but it will become much more evident later on.

Schwartz: We published a case report about an infant once with underlying systemic mastocytosis who presented with recurrent spells of apnoea. We were able to observe one of those in the hospital. Mature β tryptase levels went up markedly in the blood during one of these episodes, and then fell to baseline. Thus, in an infant with anaphylaxis, one of the presenting manifestations might be apnoea.

Simons: In particular, if skin signs are absent, you can imagine the difficulty the parent or nursery school teacher might have in diagnosing anaphylaxis. In our paediatric series: about 10% of children didn't have skin signs. I have a question. I saw a case report in which constitutive hyperhistaminaemia played a role in increasing the susceptibility of adults to anaphylaxis (Hershko et al 2001). Does anyone else think this is significant?

Ring: This raises the question of histaminase deficiency induced by diamino-oxidase blockers. When patients take many drugs, some of them block this enzyme and then the plasma histamine increases. Dr Ohtsu, you have knockout mice which might address this.

Ohtsu: Yes, I made mice lacking histamine by knocking out histidine decarboxylase. These mice are completely opposite from what we would expect. Now I am making transgenic mice which produce a lot of histamine, but I haven't checked them yet. Perhaps we could look at diamino oxidase in our transgenic mice.

Ring: How do the mice that don't have histamine react to anaphylaxis?

Ohtsu: I'll present some data on this later in the meeting.

Galli: Estelle Simons, in the case of the patient with high levels of histamine, was the origin of the high levels of histamine completely obscure? Was the patient examined for abnormalities of diamino oxidase or histaminase?

Simons: This was a patient who had elevated plasma histamine levels and impaired urinary histamine clearance. He had experienced anaphylaxis after eating fish. On other occasions, he had anaphylaxis from unknown causes and on yet additional occasions, he was able to eat fish without getting any symptoms (Hershko et al 2001).

Galli: Getting back to Hugh Sampson's point about the organ specificity of responses to different foods, I know that Hannah Gould has studied local production of IgE. Hannah, would you like to comment on the possibility that the local production of IgE, that might not yet be reflected in systemic sensitization of mast cells could in part account for this?

Gould: We have carried out a number of studies on nasal biopsies and blood from hay fever patients. Several observations suggest that the nasal mucosa is the primary source of allergen-specific IgE antibodies in these patients. (1) We have

incubated the nasal biopsies and observed the synthesis of IgE and allergen-specific IgE *ex vivo* (Smurthwaite et al 2001). (2) Locally synthesized IgE contains a significantly higher ratio of specific/total IgE than serum IgE from the same patients. (3) The relative frequency of IgE-expressing B cells in the nasal mucosa is several orders of magnitude greater than the frequency in circulating B cells: 5% of CD19⁺ B cells and 25% of CD138⁺ plasma cells in the nasal mucosa, compared to one in ten thousand B cells in the circulation, express IgE (Kleinjan et al 2000). The differentially expanded population of IgE-expressing B cells in the nasal mucosa is also observed at the mRNA level (Durham et al 1997). (5) Probing the biopsies for molecular markers (germline gene transcripts and switch circle transcripts) has provided evidence for local class switching to IgE (P. Takhar, S.R. Durham and H.J. Gould, unpublished results), likely accounting for the selective expansion of IgE-expressing cells in the tissue. (4) Analysis of IgE VH cDNA sequences reveals the presence of clonal families of B cells in the nasal mucosa of hay fever patients (H.A. Coker, S.R. Durham and H.J. Gould, unpublished results), suggesting that B cells in the nasal mucosa are activated by allergens and undergo clonal selection, proliferation, somatic hypermutation and class switching *in situ*.

We have observed that the production of grass pollen allergen-specific IgE in the nasal mucosa of grass pollen-sensitive hay fever patients persists between seasons, suggesting that the plasma cells (or their clones) are long-lived residents of the tissue. Long-lived plasma cells may be able to continually re-sensitize mast cells in the tissue for an immediate response to the allergen that originally drove the selection. The rate of IgE synthesis out of season in the nasal mucosa of grass pollen-allergic hay fever patients is sufficient to maintain the hypersensitivity of the nasal mast cells, taking into consideration the number of mast cells and the rate of IgE synthesis/volume of tissue, the number of molecules of the high-affinity IgE receptor, FcεRI, per mast cell and the rate of dissociation of IgE from the mast cells in tissues (Gould et al 2003).

The organ specificity of IgE responses may therefore stem from the chance migration of a B cell expressing a specific antibody to the target organ, clonal expansion, somatic mutation and class switching of the immunoglobulin genes, and IgE antibody synthesis *in situ*. It may not be a problem (in explaining the organ specificity of food allergens) that IgE antibodies of other specificities are present in the serum if these antibodies were not produced in the target organ. The IgE antibodies produced at a particular site in the tissue would be more likely to occupy IgE receptors on the neighbouring mast cells than IgE diffusing into the tissue from the circulation.

It would be very interesting and feasible to biopsy the three tissues mentioned by Hugh Sampson, the skin, GI tract and lung of the milk- and egg-allergic individuals and assay the levels and specificities of the IgE synthesised *ex vivo* (Smurthwaite et al 2001). This would reveal whether local

IgE production can account for the observed organ specificity of the reactions to these allergens.

Vercelli: One of the common objections to local switching has been that while B cells can switch in an organ, in reality they engaged in the process elsewhere. Thus time is of the essence. What I found impressive is that, in still unpublished work, Hannah Gould's lab is now able to identify in the nasal mucosa molecular events that define switching as a very recent occurrence. It is not as if these cells have had a lot of time to go very far. In a sense, the window of opportunity for switching to occur out of the nodes is getting narrower and narrower. This is important to answer the potential objection that the cells undergoing switching in the nose have been triggered in some other tissue. It is very likely that they have not.

Finkelman: If you are looking for reasons for different responses in different organs to different foods, it might not just be differences in the sites where IgE is produced but also differences in the populations of mast cells that are present. In addition, the cytokine environment in different organs may amplify responses to mediators released by mast cells. Curiously, in the lung and gut different cytokines seem to be responsible for mastocytosis.

Gould: The sites of IgE synthesis are probably linked to the presence of mast cells.

Galli: One of the issues here is the assumption that some of us make that both the antigens and also the reactive immunoglobulins will be systemically distributed. If the same antibody and effector cells are involved, why would one food activate a process in one organ and another food in another? With the possible exception that there may be local production of IgE in an individual organ that has not yet resulted in enough systemic distribution of IgE to sensitize mast cells in other sites, these clinical observations are difficult to explain.

Sampson: These children in whom we have observed this have circulating levels of IgE to these specific foods that are often greater than 100 kilo units per litre. At least when we look systemically, therefore, we don't see anything. This doesn't rule out the possibility that some local plasma cells are producing even higher levels locally, so we are getting differential binding to these receptors.

Finkelman: Perhaps another way of looking at it would be differences in locally produced IgG and/or IgA antibodies that may have blocking capacity.

Galli: The phenomenon of local activation of a response deserves some sort of a local explanation. The question is, what is that?

References

- Dibs SD, Baker MD 1997 Anaphylaxis in children: a 5-year experience. *Pediatrics* 99:E7
Durham SR, Gould HJ, Hamid QA 1997 IgE regulation in tissues. In: Vercelli D (ed) *IgE regulation: molecular mechanisms*. Wiley, Chichester, p 21–36

- Gould HJ, Sutton BJ, Beavil AJ et al 2003 The biology of IgE and the basis of allergic disease. *Annu Rev Immunol* 21:579–628
- Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE 3rd 2002 Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest* 109:1057–1063
- Hepner MJ, Ownby DR, Anderson JA, Rowe MS, Sears-Ewald D, Brown EB 1990 Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections. *J Allergy Clin Immunol* 86:407–411
- Hershko AY, Dranitzki Z, Ulmanski R, Levi-Schaffer F, Naparstek Y 2001 Constitutive hyperhistaminaemia: a possible mechanism for recurrent anaphylaxis. *Scand J Clin Lab Invest* 61:449–452
- Kemp SF, Lockey RF, Wolf BL, Lieberman P 1995 Anaphylaxis. A review of 266 cases. *Arch Intern Med* 155:1749–1754
- Kleinjan A, Vinke JG, Severijnen WWFM, Folkens WJ 2000 Local production and detection of (specific) IgE in nasal B-cells and plasma cells of allergic rhinitis patients. *Eur Respir J* 15:491–497
- Marone G, de Crescenzo G, Patella V, Genovese A 1998 Human cardiac mast cells and their role in severe allergic reactions. In: Marone G, Austen KF, Holgate ST, Kay AB, Lichtenstein LM (eds) *Asthma and allergic diseases. Physiology, immunopharmacology and treatment*. Academic Press, San Diego, p 237
- Novembre E, Cianferoni A, Bernardini R et al 1998 Anaphylaxis in children: clinical and allergologic features. *Pediatrics* 101:E8
- Simons FER, Chad ZH, Gold M 2003 Anaphylaxis in children: real-time reporting from a national network. *Int Immunol* 15, in press
- Smurthwaite L, Walker SN, Wilson DR et al 2001 Persistent IgE synthesis in the nasal mucosa of hay fever patients. *Eur J Immunol* 31:3422–3431
- Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH 2002 Leukotriene receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *N Engl J Med* 347:1493–1499
- Urata H, Boehm KD, Philip A et al 1993 Cellular localization and regional distribution of an angiotensin II-forming chymase in the heart. *J Clin Invest* 91:1269–1281
- Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD 1999 Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol* 104:452–456