Immuno -

ANAPHYLAXIS

While endeavouring to determine the toxic dose of extracts, we soon discovered that some days must elapse before fixing it; for several dogs did not die until the fourth or fifth day after administration or even later. We kept those that had been given insufficient to kill in order to carry out a second investigation upon these when they had recovered. At this point an unforeseen event occurred. The dogs which had recovered were intensely sensitive and died a few minutes after the administration of small doses. The most typical experiment, that in which the result was indisputable, was carried out on a particularly healthy dog. It was given at first 0.1 ml of the glycerine extract without becoming ill: twenty-two days later it was in perfect health, I gave it a second injection of the same amount. In a few seconds it was extremely ill; breathing became distressful and panting; it could scarcely drag itself along, lay on its side, was seized with diarrhoea, vomited blood and died in twenty-five minutes.

C. Richet

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Internal Medicine Grand Rounds

University of Texas Health Science Center at Dallas

August 11, 1983

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HISTORICAL PERSPECTIVE

Until the discovery of experimental anaphylaxis in 1902, the term "immunity" was used in a literal sense - protection from injury (1). Clinical descriptions of what are likely to have been anaphylaxis and other allergic diseases date to antiquity. Perhaps the earliest recorded instance of anaphylaxis occurred in 2621 B.C. - hieroglyphs depict Egyptian king Mene's fatal wasp sting (2). "Yet the history of what we are today begins not with accidental observations, no matter how fundamental, but with the emergence of a precise and perceptive mind which has not just stumbled on promised land but has been able to chart it" (3).

In 1902 Portier and Richet demonstrated that repeated injections of toxic extracts of Actinaria (sea anemone) provoked progressively more severe reactions in dogs rather than protection (4). They coined the term anaphylaxis - meaning without (ana) protection (phylaxis). Formal recognition of allergy, a multitude of immunopathologic reactions, followed on the heels of these experiments and the revolutionary concept they revealed (1).

Table I summarizes the observations that set the stage for the recent expansion of knowledge of human anaphylaxis. In 1907 Otto (5) and Friedman (6) produced anaphylaxis in normal animals several hours (the latent period) after injection of serum from a sensitive animal. Clearly some circulating factor conferred specific anaphylactic sensitivity. Schultz in 1910 (7) and Dale in 1913 (8) noted that tissues from sensitized animals reacted measureably, even visibly to the addition of antigen in vitro. Dale noted the similarity of the in vitro reactions to antigen to reactions to histamine. He proposed that antigen-antibody interactions in sensitized tissues caused the release of endogenous histamine, or a similarly acting substance, resulting in the tissue responses seen in aggregate in vivo as anaphylaxis.

This remarkably accurate hypothesis has been proven and refined in subsequent years. Bartosch was the first of many to actually demonstrate free extracellular histamine in antigen stimulated tissues (9). Riley and West linked tissue histamine to the mast cell (10) and Uvnas demonstrated the release of histamine from actively-sensitized isolated mast cells after antigen challenge (11).

The phenomenon of passive transfer of anaphylactic sensitivity with serum was extended to humans by Prausnitz and Kustner in 1921 (12). These investigators showed that injection of serum from an allergic donor into the skin of a non-allergic recipient conferred local specific antigen sensitivity. An immediate wheal and flare response ensued at antigen challenged sensitized sites but not at unsensitized sites. This experimental maneuver permitted a physicochemical characterization of the antibody involved and was an essential step in the identification of IgE.

TABLE I

CRITICAL EVENTS IN THE DEVELOPMENT OF OUR CURRENT UNDERSTANDING OF ANAPHYLAXIS

1902	Recognition of the phenomenon of anaphylaxis Portier and Richet
1907	Passive transfer of anaphylactic sensitivity with serum Otto and independently Friedmann
1910	Antigen-induced *in vitro* responses of tissues from sensitized animals Schultz
1913	Recognition of similarity of *in vitro* anaphylaxis to the actions of histamine Dale
1921	Demonstration of passive transfer of anaphylactic sensitivity from human to human with serum Prausnitz and Kustner
1932	Demonstration of free histamine in the tissues of antigen-stimulated sensitized animals Bartosch
1940	Recognition of "slow reacting substance of anaphylaxis" Kellaway and Trethewie
1953	Identification of the mast cell as the principal repository for preformed histamine Riley and West
1959	Isolation of mast cells from sensitized animals and demonstration of histamine release after antigen challenge Uvnas and Thon
1967	Isolation and characterization of human IgE Ishizaka and Ishizaka
1977	Recognition that "slow reacting substance of anaphylaxis" is derived from arachidonic acid Parker

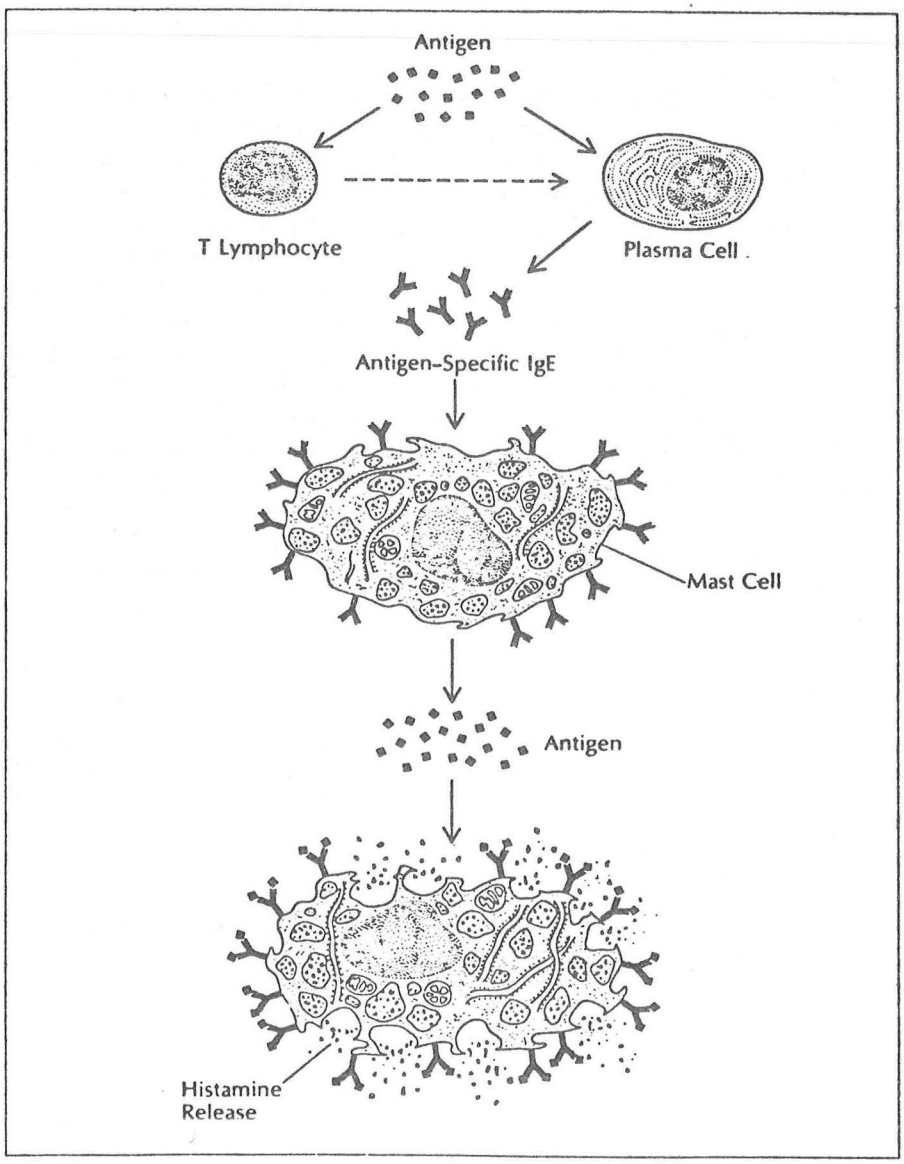
In 1967 the Ishizakas isolated, characterized, and named the IgE class of antibodies (13). Using the P-K test as an assay and the limited techniques for protein isolation available at the time, they isolated IgE antibody to ragweed antigens from human serum. This discovery permitted the development of assays such as the RAST for the detection of antigen specific human IgE. Qualitative and quantitative methods for the demonstration of specific IgE placed assessment of the immunologic basis of anaphylaxis in the clinical arena.

In the years following the delineation of IgE antibodies, IgE binding to mast cells, and antigen-triggered release of mast cell histamine, a better understanding has emerged of the full range of mast cell mediators released during anaphylaxis. In 1940 Kellaway and Trethewie noted the presence of a "slow reacting substance of anaphylaxis" (SRS-A) in the extracellular space during experimental anaphylaxis (14). Analysis of this activity was slow for many years. The critical breakthrough in this area came in 1977 when Dr. Charles W. Parker discovered that SRS-A is derived from arachidonic acid (15). Later work by Parker revealed that SRS-A is a C-6 glutathionyl thioether adduct of arachidonic acid and that SRS-A exists in three forms (see below). Murphy et al., demonstrated that the arachidonic acid derived portion of the molecule is a conjugated triene with a hydroxy substituent at the C-5 position. Parker's studies of arachidonic acid derived mediators also led to the discovery by his group and by others that prostaglandin D_2 is the principal oxygenated product of arachidonic acid formed by mast cells.

These developments in knowledge have permitted a gargantuan, accelerating expansion in our knowledge of the cellular and biochemical basis of anaphylaxis (16). For the purposes of this review, the details of many of these recent developments will be cited only to the extent of noting recent reviews, since their clinical impact remains years distant. We are moving from empiric, through experimental, to quantitative understanding of anaphylaxis. This "new" allergy would not have been possible without the contributions noted above. Nor would a modern understanding of anaphylaxis be possible without knowledge of the principles defined in these experimental systems.

MEDIATOR RELEASE FROM MAST CELLS

IgE-mediated reactions become possible when antigen processing leads to an IgE response, and mast cells become sensitized. Reexposure to antigen results in mediator release (Figure 1).



The first step in the immediate-hypersensitivity reaction occurs when antigen stimulates plasma cells and T cells to produce specific immunoglobulin E (IgE), which attaches to a mast cell or basophil. On subsequent exposure, the antigen will attach to "its" specific cell-bound IgE, thus stimulating release of histamine and other mediators.

L.M. Lichtenstein. Hospital Practice, March 1975

Figure 1

Two concepts with particular relevance to anaphylaxis have emerged from recent research on mast cell mediator release. First, human mast cells release a similar spectrum mediators after stimulation by antigen-IgE interactions; the anaphylatoxins C3a, C4a and C5a; as yet poorly defined lymphokines; hormones such as gastrin; adenosine diphosphate and triphosphate; and a variety of drugs also can cause mediator release (16-17). Diverse stimuli can cause mast cell mediator release. The clinical manifestations would be expected to be similar or identical regardless of the inciting force.

TABLE II

MAST CELL MEDIATORS

Preformed:

- Histamine
- Heparin
- Proteases (trypsin, chymotrypsin)
- Glycosidases
- Other enzymes (peroxidase, superoxide dismutase, arylsulfatase)
- Chemotactic factors (neutrophil chemotactic factor, eosinophil chemotactic factors).

Newly formed:

- PGD_2
- Leukotrienes B,C,D,E
- 5 HETE
- 12 HETE
- (Platelet Activating Factor)

A second important concept is that unlike many secretory cells that release a single product, mast cells release a diverse group of mediators into the microenvironment (Table II). To date no evidence has been presented indicating that mast cells can selectively release mediators during anaphylactic secretion - the entire spectrum of mediators appears to be unleashed in concert. As depicted in Table II mast cell mediators can be divided into two groups - preformed and newly formed mediators. Preformed mediators are located in membrane enclosed cytoplasmic granules. Release to the extracellular space is accomplished by exocytosis - noncytotoxic fusion of the perigranular membranes with the cell surface. Most of the newly formed mediators are oxygenation products of arachidonic acid. A series of lipolytic reactions are set in motion by secretory signals that result in the cleavage of arachidonic acid from membrane lipids. Cyclooxygenase enzymes convert this fatty acid to PGD_2. The 5-lipoxygenase system becomes activated resulting in the generation of 5-HETE, LTB_4, and LTC_4. LTD4 isformed from LTC_4 and LTE_4 is formed from LTD4 (16, 18-20).

Recent unpublished studies of human pulmonary mast cells suggest that mast cells also make 1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphoryl-choline (also know as AGEPC, platelet activating factor, PAF, and PAF-acether). Antigen inhalation by allergic subjects does appear to lead to platelet activation in vivo (21), but the roles of the mast cell and PAF remain obscure. This is potentially a very important observation since PAF is an extremely potent mediator in experimental animals (22).

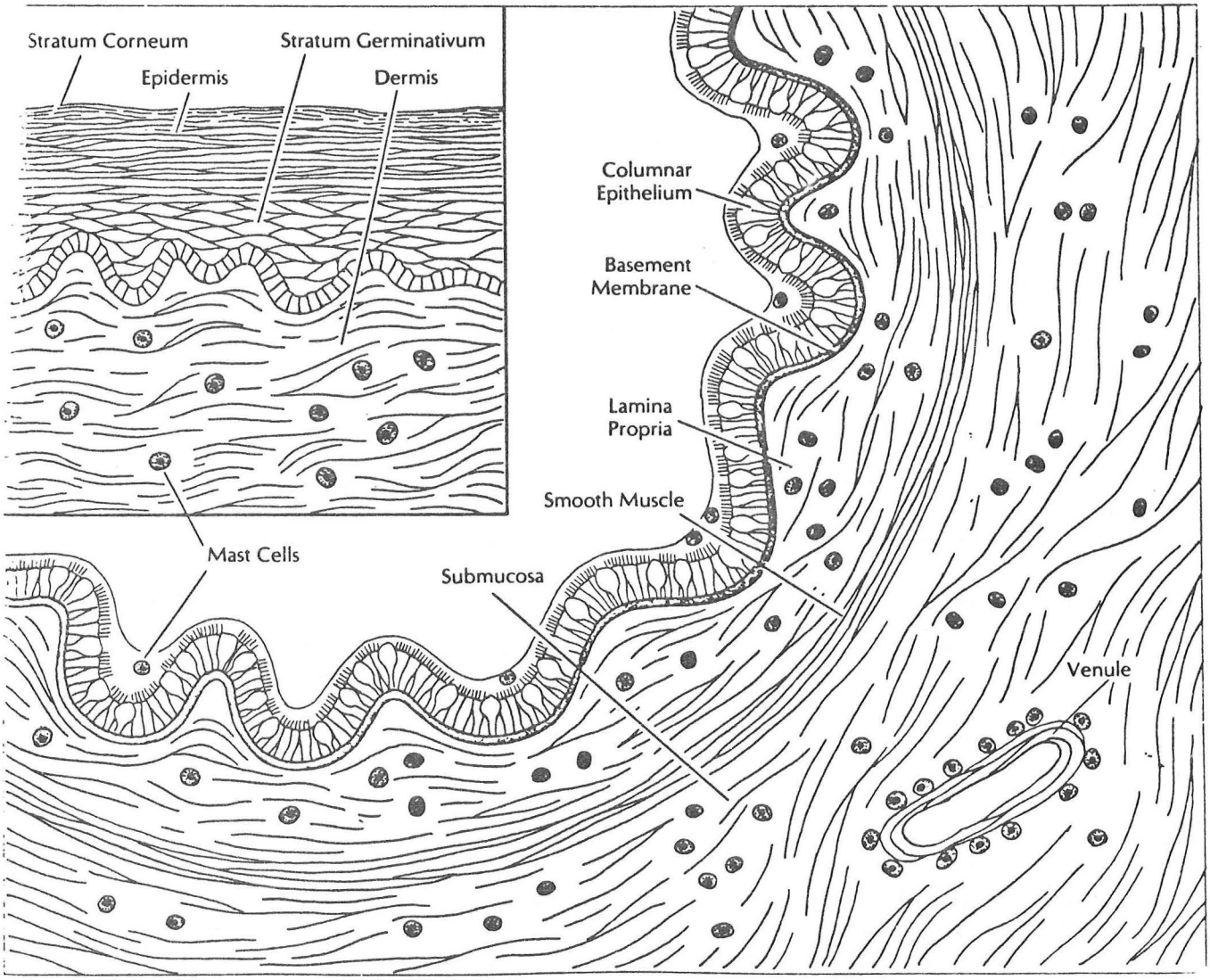
Among the implications of this knowledge for clinical anaphylaxis are the concepts that 1.) Anaphylaxis can be triggered by a variety of immunologic and non-immunologic signals. Clinical anaphylaxis strongly suggests marked mast cell mediator release has occurred, but does not implicate a specific kind of stimulus. 2.) Since anaphylaxis seems to result from the simultaneous actions of several powerful mediators (see below), pharmacologic interdiction of a single mediator (antihistamines for histamine or cyclooxygenase inhibitors for PGD_2 for example) is unlikely to be effective in controlling the entire syndrome (23).

Mast cells vs basophils. Human basophils appear to be derived from a cell line different from that of mast cells. Basophils contain histamine, but do not produce PGD_2 or PAF. There is dispute about their ability to form leukotrienes. These cells may contribute to increased vascular permeability and accelerate dissemination of antigen or other stimuli to mast cells, but there is no evidence that they are directly involved in anaphylaxis in an important way. Basophils are assigned this position primarily because the number of basophils is low and the total amounts of mediators generated are trivial.

BIOLOGICAL PROPERTIES OF MEDIATORS OF ANAPHYLAXIS

The release of mast cell mediators into the extracellular space induces a multifacted change in the microenvironment. Since mast cells are strategically located particularly around vessels and near epithelial secretory cells (Figure 2), the appearance of these potent regulatory molecules in the extracellular space can have immediate and profound impact (24). As depected in Figure 3, mast cell mediators can increase vascular caliber and permeability (histamine, PGD_2, LTC, LTD, LTE); induce the localization of eosinophils, neutrophils, and lymphocytes (ECF, NCF, LTB_4); and chemically modify molecules and cells in the region (heparin, enzymes). Normally this process is beneficial and subclinical. If the magnitude and duration of mediator release is exaggerated, inflammation may appear - clinically recognized as phenomena such as urticaria, angioedema, allergic rhinitis or asthma. If the mediator release process is explosive, clinical anaphylaxis ensues. This reaction currently is believed to be attributable primarily to the vasoactive mediators-histamine, PGD_2, LTC_4, LTD_4, LTE_4 and possibly PAF.

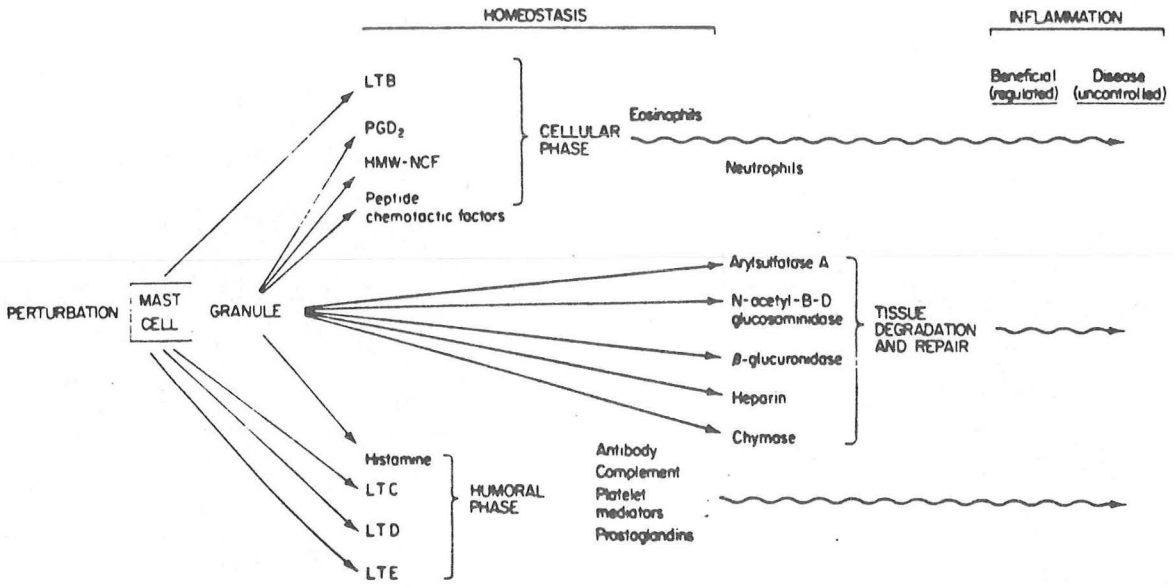
Late phase mast cell mediated reactions. Before focusing on the actions of these vasoactive mediators, the phenomenon of late phase reactions should be addressed. Recent studies of vigorous antigen challenge of the skin, lung, and nose of sensitive (IgE) subjects has



Mast cell distribution is appropriate for "sentinel" functions as schematized in bronchus and skin (inset). In the bronchial tissue, the mast cells are found near the mucosal surfaces and in the submucosa, as well as around venules. Skin mast cells are in the dermis. Thus they are near interfaces with external environment or between venous and arterial circulations.

K.F. Austen, Hospital Practice, November, 1982

Figure 2



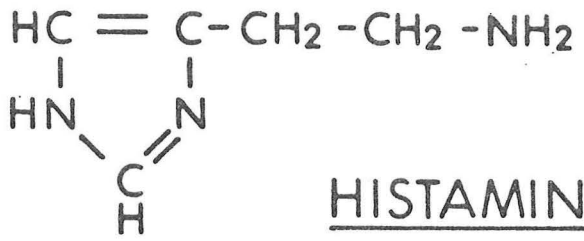
Schematic representation of the role of tissue mast cells in regulating the microenvironment in subclinical (homeostatic) manner and of the possible amplification of this role to produce inflammation, either beneficial (host resistance), or detrimental (inflammatory disease).

K.F. Austen, 1982

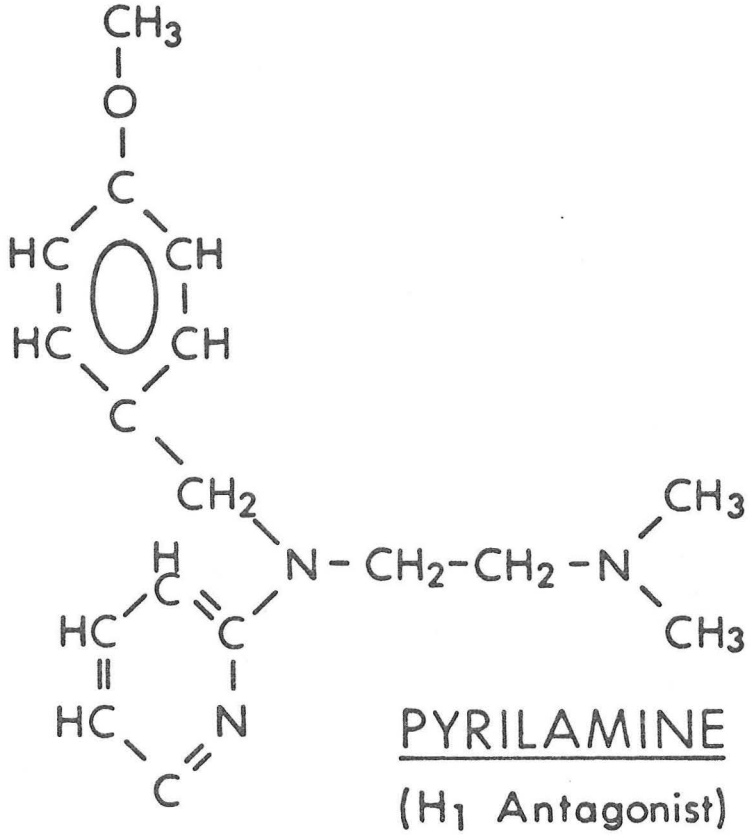
Figure 3

revealed a biphasic response. Immediately after antigen challenge a wheal and flare, fall in FEV_1, or obstruction is seen respectively. After partial or complete remission 1 to 2 hours after challenge a second phase of inflammation is observed. In the skin, an area of induration, erythema, and tenderness appears peaking 6 to 12 hours after challenge and remitting in 1 to 2 days. Reactions with similar kinetics occur in the lung (a fall in FEV_1) and the nose (obstruction). These reactions have been studied most extensively in the skin where mast cell dependence of both phases has been demonstrated (25-30). Interestingly, glucocorticoids suppress the second or late phase but not the first phase of the reactions.

Histamine. This preformed mediator (Figure 4) is a dibasic vasoactive amine generated in mast cells by decarboxylation of histidine. This molecule exerts its effects by binding to cellular receptors. These receptors are pharmacologically defined (Figure 4) and are designated H_1 and H_2 receptors (31-34). The actions of histamine relevant to anaphylaxis are summarized in Table III. Clearly histamine can mediate

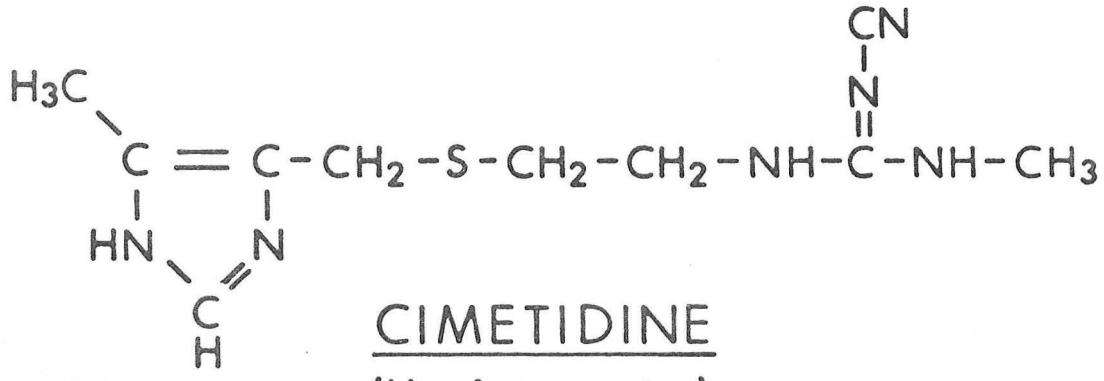


HISTAMINE



PYRILAMINE

(H_1 Antagonist)



CIMETIDINE

(H_2 Antagonist)

Figure 4

many of the common manifestations of anaphylaxis (34). The precise roles of H_1 and H_2 receptors are not entirely clear in each tissue, but H_2 receptors as well as H_1 receptors seem to be involved in many responses.

TABLE III

ACTIONS OF HISTAMINE

Peripheral vasodilation

Increased vascular permeability

Altered cardiac electrical impulse conduction

Contraction of bronchial and intestinal smooth muscle

Induction of cutaneous pruritus

Increased glandular secretion in bronchi and nasal mucous membranes

Of particular note, the alteration in blood pressure induced by an infusion of histamine (Table IV) is inhibited markedly by H_1 and H_2 receptor blockade, but not significantly by H_1 or H_2 blockade alone (31). As noted below this may have considerable importance in refractory hypotension or when β-adrenergic blockade impedes responses to epinephrine.

TABLE IV

Plasma levels of histamine required to elicit symptoms

Symptoms	Pretreatment			
	None (n = 12)	Cimetidine (n = 7)	Hydroxyzine (n = 7)	Cimetidine + hydroxyzine (n = 6)
	Plasma histamine levels (ng/ml)*			
Flush, headache	2.39 ± 0.52	3.10 ± 1.07	2.95 ± 0.19	5.76 ± 0.78 ($p < 0.001$)†
Increased heart rate (+30%)	1.61 ± 0.30	2.31 ± 0.35	4.15 ± 0.40 ($p < 0.001$)	6.07 ± 0.46 ($p < 0.0001$)
Widened pulse pressure (+30%)	2.45 ± 0.13	2.20 ± 0.26	1.63 ± 0.36	>6.07 ($p < 0.0001$)

n = number of patients studied.
*Data presented as mean ± SEM.
†Compared with baseline by paired sample t test.

From reference 31

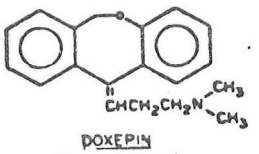
TABLE V

Tricyclic antidepressants as antihistamines

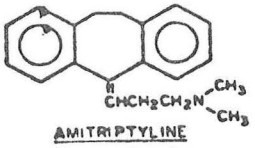
Tricyclic Antidepressant Affinities for Some Neurotransmitter Receptors: Comparisons With Selective Antagonists

Drug	Receptor		
	Histamine		Muscarinic
	H_1	H_2	
Tricyclic antidepressants			
Doxepin	3,100	0.6	1.3
Amitriptyline	770	2.2	5.5
Histamine H_1 antagonists			
Pyrilamine (Sleep-Eze, Sominex)	50		
Diphenhydramine (Benadryl)	4		
Histamine H_2 antagonists			
Cimetidine (Tagamet)		0.1	
Metiamide		0.1	
Muscarinic receptor antagonists			
Atropine			55
Scopolamine			53

From E. Richelson, Mayo Clin. Proc. 58: 40-46, 1983.



DOXEPIN
(Adapin, Sinequan)



AMITRIPTYLINE
(Elavil, Endep)

H_1 antihistamines commonly used to treat allergic diseases are very weak inhibitors compared to tricyclic antidepressants (32,35,36). As summarized in Table V doxepin is probably the drug of choice for acute allergic reactions where combined H_1 and H_2 blockade is desireable. However, no parenteral forms are available and no studies of effectiveness in anaphylaxis have been reported.

Prostaglandin D_2. This molecule is a bronchoconstrictor (37,38), increases pulmonary artery pressure (37), and is a vasodilator (Table VI) thought to contribute to episodes of hypotension in patients with mastocytosis (23, 39). The full array of pharmacologic properties and the role of PGD_2 in anaphylaxis is unknown, but this agent may play an especially important role in the hypotension resulting from loss of peripheral resistance (39). Aspirin (2400 mg/day) markedly decreases PDG_2 formation, as expected.

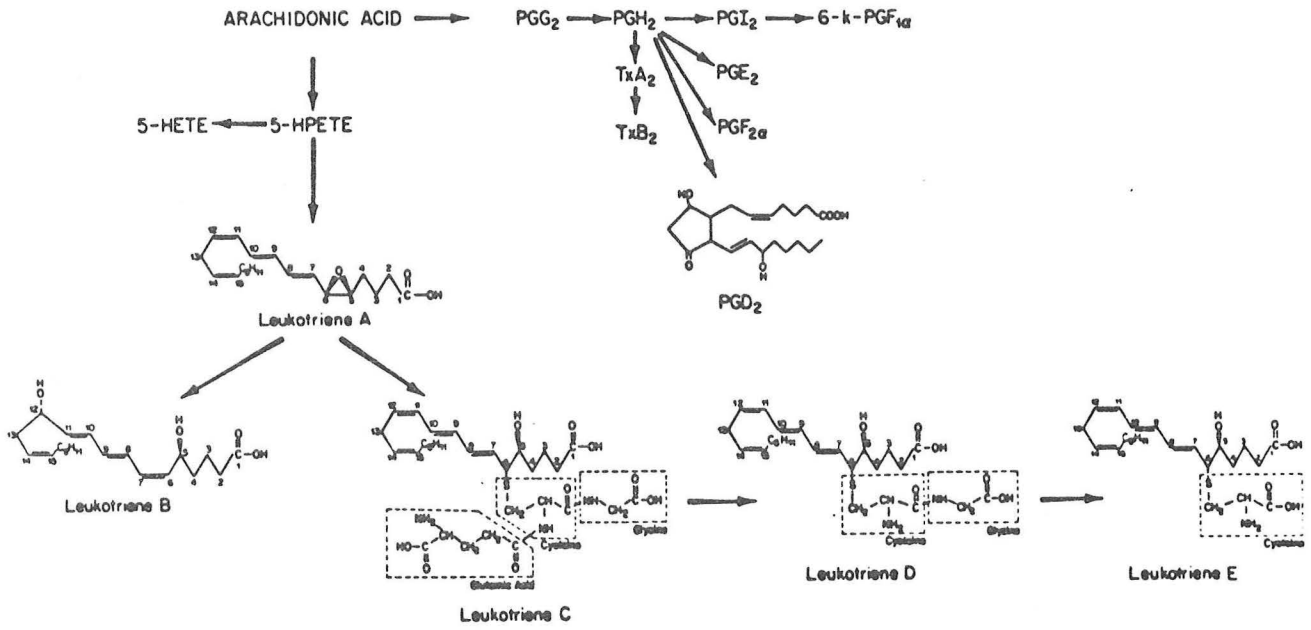
TABLE VI

Actions of PGD_2

* Bronchial constriction
* Increase in pulmonary artery pressure
* Peripheral vasodilation

Leukotrienes. The origins, structures and functions of leukotrienes have been reviewed several times in recent years (20,40). Figure 5 summarizes the synthesis and structures of these molecules. Several early pharmacologic studies with biologically derived leukotrienes gave conflicting results. With the recent availability of synthetic leukotrienes, definition of the full properties of these molecules is in progress. A summary of the properties of leukotrienes is presented in Table VII. Recent data (41,42) also indicate that low concentrations of intravascular leukotrienes are potent coronary artery constrictors in vivo and after cardiac function in vitro. No inhibitors are available for general clinical use at this time.

Platelet activating factor. The novel structure of this molecule is presented in Figure 6. The biologic properties of PAF are summarized in Tables VIII and IX. The extraordinary range of actions of this mediator at very low concentrations suggests that this agent may play an important role in anaphylaxis and several forms of inflammation (22, 43-45). No clinically useful pharmacologic antagonists have been identified.



Structural depiction of the leukotriene products of the oxidative metabolism of arachidonic acid and of PGD_2.

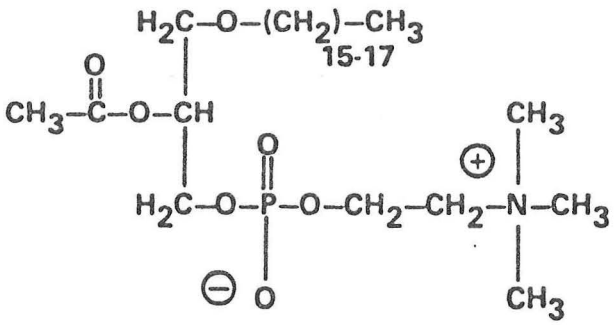
K.F. Austen, 1982

Figure 5

TABLE VII

Leukotriene mediators of immediate type hypersensitivity reactions in human tissues

Mediators	Structural Characteristics	Assay(s)	Other functions
LTB	5S,12R-dihydroxy-6-14-cis-8,10-trans eicosa-tetraenoic acid	Bioassay: chemotactic attraction of eosinophils and neutrophils; radioimmunoassay: direct or after reverse high performance liquid chromatography	
LTC	5(S)-hydroxy,6(R)-S-glutathionyl-7,9-trans,11,14-cis eicosa-tetraenoic acid	Bioassay: guinea pig ileum pre-treated with atropine and H_1 antihistamine; radioimmunoassay: direct or after reverse high performance chromatography	Constriction of pulmonary parenchymal guinea pig strips and isolated human airways; aerosol-induced constriction of human airways; increased venular permeability in guinea pig and human skin
LTD	5(S)-hydroxy,6(R)-S-cysteinylglycyl-7,9-trans,11,14-cis eicosa-tetraenoic acid	As for LTC	As for LTC
LTE	5(S)-hydroxy,6(R)-S-cysteinyl-7,9-trans,11,14-cis eicosatetraenoic acid	As for LTC	As for LTC, except no human aerosol studies to date



1–*O*–hexadecyl/octadecyl–2–acetyl–*sn*–glyceryl–3–phosphorylcholine (AGEPC)

R.N. Pinckard, 1982

Figure 6

TABLE VIII

Biological Activities of AGEPC In Vitro

Platelets	Aggregation, serotonin and PF4 secretion, production of thromboxane B_2.
Neutrophils	Aggregation, chemotaxis, lysosomal enzyme secretion, production of superoxide anion
Guinea pig ileum	Contraction: prolonged; not antagonized by H1, muscarinic or leukotriene blockers or by indomethacin
Guinea pig parenchymal lung strips	Contraction

TABLE IX

Biological Activities of AGEPC In Vivo

Intravenous Administration	
Intravascular	Thrombocytopenia Neutropenia Basopenia Increased Hematocrit Decreased Plasma Protein PF4 and TxB_2 Release
Cardiovascular	Bradycardia, cardiac arrhythmias Elevated right ventricular and pulmonary artery pressures Decreased cardiac output Prolonged systemic hypotension
Pulmonary	Decreased respiratory frequency Increased total pulmonary resistance Decreased dynamic lung compliance Respiratory arrest and death
Intracutaneous Administration	
	Vasoconstriction Pain and pruritis Vasodilatation Increased vascular permeability; not blocked by H1 antagonists Neutrophil infiltrates

R.N. Pinckard, 1982

CLINICAL ANAPHYLAXIS

Definition. Systemic anaphylaxis has been defined as, "...an acute antibody-mediated reaction leading to the release of histamine and other mediators of immediate hypersensitivity. Multiple organ systems systems are usually affected, including the skin (pruritus, urticaria, and angioedema), respiratory tract (bronchospasm and laryngeal edema), and cardiovascular system (hypotension and cardiac arrhythmias). All or nearly all human anaphylactic reactions are thought to be mediated by IgE immunoglobulins, although in some animal species (and possibly man) IgG immunoglobulins also have this capability. Anaphylactoid reactions are clinically similar, non-antibody-mediated reactions, apparently involving the same or pharmacologically similar mediators" (46). A similar definition was offered by a National Institute of Allergy and Infectious Diseases Task Force (47).

While this definition has some merit for situations where specific IgE can be demonstrated (e.g. penicillin or insect venoms), this cumbersome definition falls short on two accounts. First, a diagnosis of anaphylaxis is made entirely on the basis of clinical criteria. Demonstration of the presence of specific IgE does not absolutely prove a causal relationship. Methods for the detection of histamine, PGD_2 metabolites, heparin and its effects and the mast cell high molecular weight neutrophil chemotactic factor are reaching the point where direct evidence of mast cell mediator release can be obtained. This information still will have only retrospective value, as will IgE assessments. Diagnosis that permits timely intervention will remain a clinical diagnosis.

Secondly, increasing evidence indicates that many "anaphylactoid" reactions are the consequence of nonimmunologic stimulation of mast cell mediator release. By current light, the clinical consequences of mast cell mediator release should be similar, possibly decorated with additional effects of the agents involved.

Perhaps a better definition and the definition used in this review would take anaphylaxis to be a clinical state resulting from the acute release of pathologic amounts of mast cell mediators. Clinical criteria would be the basis for a tentative diagnosis and mobilization of therapy, while subsequent biochemical evidence of mediator release would confirm the impression, and demonstration of the presence of relevant IgE would indicate the cause of mast cell activation. Careful studies particularly of penicillin and insect venom induced anaphylaxis via IgE-stimulation formally disclosed the clinical manifestations associated with massive mast cell mediator release. Once demonstrated, there is no need to cling to the original route to insight as an essential part of the definition.

Epidemiology. Estimates of the incidence of anaphylaxis among individuals in this country usually place the lifetime risk at approximately 0.4% (47). In a study of over 20,000 healthy men to be published in the fall of 1983, 0.49% of the men examined were said to have experienced anaphylaxis. Table X presents a list of reported causes of anaphylaxis. This catalog is not meant to be comprehensive. Rather, it is intended to demonstrate the remarkable variety of agents,

conditions, or stresses that appear to be capable of inducing clinically similar anaphylaxis.

TABLE X

Reported Causes of Human Anaphylaxis

Chemical Therapeutic or Diagnostic Agents

Penicillin and related β-lactam antibiotics

Amphotericin, aminophenazone, arsphenamine, p-aminosalicylic acid, arginine, acelylsalicylic acid, bacitracin, bromsulphalein, chloramphenicol, chlorpropamide, Congo Red, declomycin, dextrans, diphenhydramine, decholin, estradiol, ethylene oxide, folic acid, fluorescein, gelatin, gentamycin, hydrocortisone, hyperalimentation solutions, iron (parenteral preparations), kanamycin, local anesthetics, mercurials, muscle relaxants, methylprednisolone, neomycin, noramidopyrine, nitrofurantoin, pentothal, probenecid, protamine, progesterone, radiocontrast media, streptomycin, succinylcholine, tetracycline, thiamin, triphenylmethane, vancomycin, vitamin B_{12}, zomepirac.

Stinging and Biting Insects

Venoms of bees, hornets, wasps, yellow jackets, and fire ants.

Protein Therapeutic Agents

Horse antisera (snake bite, rabies, diphtheria, botulism, gas gangrene, antilymphocyte serum), allergen extracts, ACTH, calcitonin, Factor VIII, growth hormone, insulin, prothrombin, parathormone, posterior pituitary extracts, IgA (into IgA deficient patients), IgG, asparginase, chymopapain, chymotrypsin, penicillinase, trypsin, heparin.

Vaccines

Diphtheria-pertussis, influenza, measles, mumps, rabies, typhoid, typhus, yellow fever.

Foods

Eggs, fish, gluten, milk, melons, nuts, peanuts, potatoes, soybeans, tea.

TABLE X (continued)

Rare Causes

Allotypically mismatched platelets, leukocytes, erythrocytes.
Human seminal fluid
Ruptured echinococcal cyst
Diethylcarbamazine treatment of filarial disease
Exercise
Cold urticaria
Mastocytosis
Ideopathic

Despite a brief respite, Zomax is available for use in this country again. This agent is capable of inducing marked anaphylaxis, usually without antecedent mild episodes. The mechanism that stimulates anaphylaxis is unknown. Patients should be alerted to this potentially fatal problem and physicians should be alert for such reactions.

Predisposing factors. Why do patients with apparently similar stimulation, in some circumstances with apparently similar IgE? sensitivity, range from no detectable response through fatal anaphylaxis Why do patients who express anaphylaxis after simulation on one occasion fail to express serious or even detectable reactions after similar challenge on another occasion? In general no satisfactory answer is available. Critical forces appear to exist about which we know nothing.

One recognized factor influencing the expression of anaphylaxis is β-adrenergic blockade (48-50). Anaphylaxis appears to be more frequent, more severe and more difficult to treat in β-blocked patients. Recognizing this, physicians should consider replacing β-blockers with alternative drugs in patients at risk for anaphylaxis (e.g. insect venom allergic subjects or patients receiving allergy desensitization injections).

Asthma appears to affect the mortality from anaphylaxis (51, 52). No clear increase in incidence of anaphylaxis has been noted among asthmatics, but they are roughly twice as likely to die from anaphylaxis, usually from intractable bronchial obstruction. Again, physicians should take special precautions with asthmatics to avoid anaphylaxis or to treat anaphylaxis very aggressively.

TABLE XI

ANATOMICAL ABNORMALITIES FOUND AT AUTOPSY OF
100 PATIENTS WHO DIED OF FATAL INSECT VENOM-INDUCED ANAPHYLAXIS

Site	Abnormality	Percent Positive
Upper respiratory tract (pharynx, epiglottis, larynx)	Edema Secretions	56%
Lower respiratory tract (Trachea, bronchi, parenchyma)	Edema Secretions Alveolar rupture	58%
Cardiovascular system	Myocardial Infarction Generalized hemorrhage Engorgement of the organs Edema	12%
Central nervous system	Necrosis Edema Hemorrhage Infarction	7%

Pathology. The anatomic alterations detected at postmortem examination of patients dying of anaphylaxis are variable. At times no abnormalities are detected. A review of the autopsy finding in 100 fatal reactions to insect stings (53) is presented in Table XI. Other reports of anatomical changes in fatal anaphylaxis of diverse specific cause (54-57) also have indicated that findings are variable. In approximatley one-fourth of cases interstitial pulmonary edema and infiltration with eosinophils was noted, occasionally with hemorrhagic fluid in the alveoli. Acute tubular necrosis has been observed, as one would predict. Occasionally urticaria and angioedema are detectable at postmortem examination. Eosinophilic infiltration in the lungs, liver and spleen, a distinctive finding in this setting, may suggest the diagnosis of anaphylaxis.

Clinical manifestations. The onset of anaphylaxis usually is within 30 minutes following exposure to the offending agent although the onset of ultimately fatal anaphylaxis can be delayed for over an hour (51, 53).

Often flushing and then generalized pruritus (or pruritus of the scalp or hands or soles) is the first indication of the reaction. The common manifestations of anaphylaxis are summarized in Table XII. Symptoms of anaphylaxis may remit within minutes, continue for hours, or rarely continue for more than 1 day.

TABLE XII

CLINICAL MANIFESTATIONS OF ANAPHYLAXIS

System	Manifestation
Skin	Pruritus, flushing, angioedema, urticaria other pruritic rashes
Eye	Conjunctival suffusion, lacrimation, pruritus
Nose	Rhinorrhea, congestion, sneezing, pruritus
Upper airway	Oropharyngeal or laryngeal edema, hoarseness, stridor
Lower airway	Tachypnea, dyspnea, wheezing, use of accessory muscles of respiration, intercostal or sternal notch retractions, cyanosis
Cardiovascular	Tachycardia, irregular pulse, hypotension
Gastrointestinal	Nausea, vomiting, diarrhea, bloody diarrhea
Neurological	Fear of impending death, dizziness, syncope, seizure, weakness

Cardiac rhythm disorders. Antigen-induced systemic anaphylaxis in man has been associated with several forms of cardiac dysfunction (58-63). Atrial disorders observed include supraventricular tachycardia, wandering atrial pacemaker, atrial premature beats, and atrial fibrilation. Nodal rhythms, right axis deviation, intraventricular conduction defects, ventricular dysrhythmias including ventricular fibrillation, ST and T wave disturbances, transient electrocardiographic changes suggesting myocardial infarction and well-documented myocardial infarction also have been reported. These disturbances in cardiac function have been attributed to intracardiac release of mast cell mediators, hypotension, hypoxia, pre-existing cardiac disease, and to possible effects of pharmacologic agents administered to reverse the allergic reactions. Virtually no data have been presented to clarify the relative importance of these or other factors in specific episodes of cardiac dysfunction observed during human anaphylaxis.

Biphasic anaphylaxis. As noted above, acute severe mast cell secretion may be followed by a second phase of mast cell mediated inflammation that peaks 6 to 12 hours after stimulation in the skin, lungs and nose. This led to speculation that biphasic anaphylactic reactions might occur. Further, since glucocorticoids suppress the second phases in other tissues, speculation arose that these agents should be given to attempt to suppress this potential complication. In recent years we have kept patients under observtion for at least 12 hours and have treated them with the equivalent of two 60 mg doses of prednisone - one dose when stable and a second dose 6 hours later. No published data has provided evidence for or against these conjectures.

We have, however, detected two instances of recurrent anapylaxis despite glucocorticoid therapy - hypotension 8 hours after severe anaphylaxis to penicillin and hypotension 10 hours after severe anaphylaxis to Zomax. Thus the phenomenon of recurrent or biphasic anaphylaxis appears to exist, as predicted. Clearly patients should be kept under direct observation for at least 12 hours after the onset of anaphylaxis.

Complications. Anaphylaxis resulting in sustained hypoxia or hypotension can be complicated by myocardial infarction, cerebral infarction, hypoxic cerebral injury, acute tubular necrosis, or hepatic necrosis. Cardiac rhythm disorders, as noted above, are important and frequent aspects of anaphylaxis and its therapy (see below).

Causes of fatal outcomes. As discussed in detail below, upper respiratory tract obstruction, pulmonary dysfunction, hypotension or complications such as myocardial infarction are the usual causes of death. Case-fatality rates appear to be highest in the 40 to 70 year age group (47).

Laboratory abnormalities. Routine studies disclose abnormalities in keeping with the abnormalities detected by history and physical examination, with no distictive features attributable to anaphylaxis. As noted above research laboratories now can measure histamine in blood

and urine, PGD_2 urinary metabolites, high molecular weight neutrophil chemotactic factor activity in blood, circulating heparin and its effects. These measures can confirm or dispute a clinical diagnosis of anaphylaxis but these values are not readily obtained.

Diagnosis. Since a decision about therapy usually must be made immediately, the diagnosis of anaphylaxis usually rests on clinical criteria. A distinction should be made between an acute generalized allergic reaction, for example urticaria or angioedema, and a life endangering reaction. Some authors use the term anaphylaxis to encompass all acute systemic reactions, regardless of severity. Most, however, reserve the term for reactions with life-endangering components - upper airway obstruction, pulmonary dysfunction, hypotension or cardiac rhythm disorders. The presence of recent exposure to the agents or conditions listed in Table X and manifestations listed in Table XII facilitate recognition of anaphylaxis.

Conditions commonly confused with anaphylaxis include vasovagal syncope, myocardial infarction, pulmonary embolism, cardiac dysrhythmias not caused by anaphylaxis, stroke, aspiration, poisoning, occult hemorrhage, pheochromocytoma and hereditary angioedema (46). Physicians should keep in mind that these and similar conditions might mimic anaphylaxis or alternatively that anaphylaxis may be misidentified as one of these conditions.

APPROACHES TO THE AVOIDANCE OF ANAPHYLAXIS

General measures. The diversity of mechanisms and specific stimuli leading to anaphylaxis in susceptible patients makes identification of patients at risk and methods to avoid reactions a formidible task.

A careful inquiry into adverse reactions associated with previous exposures to an agent selected for therapy and immunologic assessments, when feasible, are used to identify allergic patients. Five general approaches are taken to bypass reactions in susceptible individuals: avoidance of specific agents or groups of agents, premedication, change in activity (e.g. exercise), immunization and desensitization.

The diversity of potential immunologic and nonimmunologic reactions triggered by drugs presents a formidable obstacle to effective general premedication or identification of patients at risk. Premedication and immunologic or genetic screening are not sufficiently developed to be applied to all drug therapy. As noted below, however, in some circumstances immunologic screening and premedication have proven effective.

Assessment of history of drug allergy. Positive histories of adverse reactions to drugs should be scrutinized carefully to distinguish allergic reactions from untoward but non-allergic reactions. Isolated gastrointestinal complaints associated with erythromycin therapy, diarrhea associated with ampicillin therapy, pain at the site of a drug injection, headache associated with nitroglycerine therapy, malaise and local discomfort for two days after a tetanus toxoid injection, and similar predictable untoward reactions to drugs do not indicate an allergic reaction. If a patient has experienced an allergic reaction during an earlier exposure, the role of the agent in question should be assessed. Identification of the offending agent may be difficult. Some patients have underlying illnesses such as systemic lupus erythematosis that might cause symptoms resembling allergic reactions. In some instances primary allergic diseases are mistakenly treated as infections or other diseases; subsequent inflammatory or destructive reactions are mistakenly attributed to drugs. Often multiple drugs have been given simultaneously. Penicillin G, semisynthetic penicillins, cephalothins and gentamicin are common causes of drug allergy (over 1% of treated patients). A diagnosis of IgE-mediated β-lactam antibiotic allergy often can be confirmed by skin testing before the administration of H_1 antihistamines (see below). Indomethacin, heparin, nitrofurantoin, chloramphenicol, glutethimide and barbiturates also provoke reactions in a significant fraction of patients (0.5 to 1% of those treated). Demonstration of positive immunologic tests for allergy to β-lactam antibiotics, insulin, and selected other agents may clarify the situation (see below). If prior adverse reactions are not indicative of an allergic reaction, the drug of choice can be used.

Alternative drugs. If a reasonable likelihood of allergy to a current drug of choice is found, alternative approaches should be

considered. Since immune reactions are highly specific, drugs with similar actions but distinctly different structures usually are appropriate alternatives. Structurally different antibiotics often can be used in place of β-lactam drugs. Alternative diagnostic maneuvers such as CT scanning or ultrasound may prove adequate to delineate disorders usually assessed by radiocontrast studies. Some aspirin-sensitive patients can be treated with sodium salicylate or perhaps benoxyprophen, depending on the indication for aspirin. If clinically effective, relatively nontoxic alternatives are available, they should be selected.

Assessment of relative risks of allergic reactions and alternative drugs. If valid tests for allergy are unavailable, or if such tests are positive, but potential alternatives are not as effective as the drug of choice or carry serious potential hazards, consideration should be given to cautiously administering the drug of choice despite the risk of an allergic reaction. Determination of relative risks must be highly individualized. Attention should be given to the patient's age, clinical condition, concurrent therapy (particularly with β-adrenergic blocking agents), the nature of the problem being treated, concurrent illnesses, and relative efficacies and toxicities of the alternatives.

Desensitization. Acute desensitization, or the cautious administration of progressively larger doses of a substrate, has been applied successfully with chemical activators of mast cells such as aspirin, haptens (e.g. penicillin), insulin, heteroantisera, and other preformed antigens. Insulin allergy, a relatively common problem, can be used as an example of the principles applied to desensitization to macromolecules. Patients with a history of immediate hypersensitivity reactions to insulin who are on insulin therapy are removed from insulin and allergic reactions are allowed to subside (if possible). Prick and then intradermal skin tests are performed using serial ten-fold dilutions of U-100 regular bovine, porcine, or human insulin, to identify the least reactive insulin species and to establish the highest concentration of insulin that does not cause an immediate intradermal wheal and flare response. This solution is administered S.C. beginning with 0.05 ml. Progressively doubled doses of insulin are administered at 30 minute intervals until therapeutic doses are achieved. If allergic symptoms appear during desensitization, a more gradual increase in dosage can be considered.

Aspirin sensitive patients can be desensitized if a compelling indication for a nonsteroidal anti-inflammatory agent is present (64,65). If asthma is active, the patient should be treated vigorously to achieve maximal normalization of pulmonary function. Desensitization usually should not be attempted if a severe impairment of pulmonary function persists since asthmatic responses usually occur during desensitization. Pulmonary functions should be measured before the procedure and regularly during the proedure. Using 3 hour intervals between doses 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, 320 mg, and then 650 mg of aspirin should be administered P.O. If the schedule is interrupted at night the procedure can be resumed the next morning beginning with the last tolerated dose. The patients should be

monitored by clinical assessment and spirometry. A clinical reaction usually occurs at some point in this process. Such a response should be allowed to subside, or if necessary conventional means should be used to suppress the reaction. The dose that provoked the response should be administered again 3 hours or more later. In most instances no response occurs after rechallenge and the procedure can continue. Occasionally a second milder response appears. These reactions are addressed as described above. The desensitization procedure continues until full dose therapy is achieved. Once desensitization to aspirin is accomplished, any of the nonsteroidal anti-inflammatory agents can be used. The state of desensitization usually persists for days after the last dose. Caution should be exercised if more than a day elapses between doses, and the desensitization procedure should be repeated if more than two days elapse.

Specific approaches to the avoidance of anaphylaxis. Progress has been made in identifying patients at risk for some forms of anaphylaxis and for avoiding or minimizing the risk. Five representative situations and approaches will be reviewed: 1.) Penicillin and related drugs - skin testing and desensitization; 2.) Insect sting hypersensitivity - skin testing and immunization against venoms; 3.) Local anesthetics - selection of a structurally dissimilar agent; 4.) Exercise-induced anaphylaxis - modification of activity; 5.) Radiocontrast medium reactions - premedication.

Penicillin and other β-lactam antibiotics. Since penicillin allergy was discussed in detail at these rounds on July 23, 1981, this review will be restricted to critical concepts and progress in this area. Additional copies of the earlier grand rounds protocol are available in the Allergy Division office as a bulky supplement to this document.

A history of an apparently allergic reaction to penicillin or closely related β-lactam antibiotics is offered by approximately 7% of the adults in this country. Acute allergic reactions to penicillin are noted in approximately 2% of courses of therapy with this agent (Table XIII). These drugs are a major cause of acute systemic allergic reactions, and a dominant cause of fatal and nonfatal anaphylaxis.

Skin tests to detect IgE to penicillin were developed in the late 1950's and early 1960's by Charles W. Parker and independently by Bernard B. Levine (66). This was a very difficult task since antibodies react with drug determinants covalently coupled to endogenous proteins, not free drug. The immunochemistry of penicillin had to be established before tests could be developed. Since that time considerable experience with these techniques has been obtained (reviewed in 67). The reagents used at this institutuion are comercial Pre-Pen (peniciloyl-poly-L-lysine 6 x 10^{-5}M), Penicillin G or any other β-lactam drug of interest (5,000 units/ml or approximately 10^{-2}M, 3.3 mg/ml), and Penicilloic Acid (3.3 mg/ml, 10^{-2}M). The methods used and criteria for positive are detailed in reference 67. Clearly immediate wheal and flare skin testing offers a potential bedside method for assessing current immunologic status with information sufficient to make therapeutic decision available within 40 minutes.

TABLE XIII

Incidences of penicillin allergy[a,b]

Overall incidence	2%
Late reactions[b]	1.4%
Accelerated reactions	0.3%
Immediate reactions	0.3%
Anaphylaxis	0.4% (1:2,500)
Anaphylactic deaths	0.001% (1:100,000)
Anaphylactic deaths per annum U.S.A.[c]	400 to 800

[a]These are estimates based on literature and authors' experience (see text).
[b]Immediate reactions begin between 2 to 30 minutes after the first dose of penicillin. Most are diffuse urticaria. Accelerated reactions occur between 1 to 72 hours after onset of therapy. Most are urticarial in nature. Late reactions begin later than 72 hours after onset of drug therapy. Most manifest as skin rash.
[c]Based upon 70-80 million therapeutic courses of penicillin (or semisynthetic penicillin or cephalosporin) given per annum in the U.S.A.

From reference 47

How useful is this technique? The incidences of acute allergic reactions in skin test positive patients trated with full therapeutic doses of penicillin has ranged from 39% to 73% with an aggregate of 27 of 54 or 50% (68-72). In these same series the incidences of acute reactions in skin test negative subjects ranged from 0% to 2.9% with an aggregate of 12 reactions in 1967 treated patients or 0.6%. To date anaphylaxis has never been reported in a penicillin-treated, skin test-negative patient. Thus penicillin skin testing is a very useful tool for identifying patients at risk for acute allergic reactions.

The issue of the risks of giving cephalosporins or semisynthetic penicillins to penicillin allergic patients remains incompletely resolved. On one hand cross-reactions with IgE to penicillin as assessed by skin tests is common (67, 72-77) and clinical cross reactions are well documented (74, 78-84). Our own experience is presented in Table XIV. On the other hand, many physicians administer cephalothins to patients with a history of penicillin allergy with an apparently low rate of crossreaction. No studies have prospectively examined the fate of penicillin skin test positive patients given full doses of cephalothins.

TABLE XIV

Skin-test reactivity to ampicillin, cephalothin, and carbenicillin in patients also skin tested for penicillin reactivity

Degree of penicillin reactivity	Skin-test results*					
	Ampicillin		Cephalothin		Carbenicillin	
	+	−	+	−	+	−
Negative	0	14	4	45	1	7
Intradermal positive	25	15	26	35	1	3
Percutaneous positive	16	0	12	1	0	2

*Skin tests with these agents were performed with the same concentrations that were selected for skin tests with Pen G. Reactions to percutaneous or intradermal tests were combined as a total.

From reference 67

Two important features of this issue should be mentioned. Many patients who have had penicillin reactions years ago are skin test negative and could receive any β-lactam drug without incident (67). In addition the likelihood that a true crossreaction would be accurately identified in the context of acute serious infections is speculative.

While an accurate estimate of the degree of risk of a crossreaction is not possible, patients allergic to penicillin as determined by a positive skin test are at some risk of anaphylaxis to cephalothins or semisynthetic penicillins.

When B-lactam drugs are needed for therapy of allergic patients an acute desensitization procedure can be considered (85-87). The rationale for the oral desensitization method used at this institution is presented in Table XV and in detail in reference 85.

TABLE XV

Rationale for Oral B-Lactam Antibiotic Desensitization

* Only half of skin test positive patients have an acute reaction when given full dose therapy
* Most reactions are not anaphylactic
* Most anaphylactic reactions are treatable
* Initial doses need not be large doses
* Only 6 reported deaths from oral β-lactam therapy
* No serious acute allergic reactions in 65 patients desensitized by the oral method

In most instances alternative antibiotics can be given. However in rare cases the risk of not using a β-lactam drug appears greater than the risk of using the drug. An estimate of the risk of a fatal reaction to full dose therapy in a skin test positive person is (0.50 react x 0.1 at most have anaphyalxis x 0.03 chance of a fatal reaction in skilled hands) approximately 0.15% or 1 in 667. The desensitization procedures appear to reduce this risk substantially. Indications for desensitization have included bacterial endocarditis, Pseudomonas infections, osteomyelitis, central nervous system syphilis, and syphilis in pregnancy.

An example of the kind of procedure we have used is presented in Table XVI. If the agent selected for treatment is not available in an oral form, we usually use oral benzylpenicillin, switching to the agent of choice when parenteral doses are given. Patients with a history of anapylaxis are started at a 100-fold lower dose.

TABLE XVI

Protocol for Oral Desensitization

Dose	Units	Route
1	100	P.O.
2	200	P.O.
3	400	P.O.
4	800	P.O.
5	1,600	P.O.
6	3,200	P.O.
7	6,400	P.O.
8	12,500	P.O.
9	25,000	P.O.
10	50,000	P.O.
11	100,000	P.O.
12	200,000	P.O.
13	400,000	P.O.
14	800,000	P.O.
	Wait 30 minutes	
15	100,000	I.V.
16	200,000	I.V.
17	400,000	I.V.
18	800,000	I.V.

These doses are given at 15 minute intervals with continuous monitoring for signs of an allergic reaction. Conventional therapy then can begin.

IgE-mediated complications of the procedure and then therapy have been restricted to urticaria in one third of the subjects. Only one patient had urticaria during the procedure. No deaths, anaphylaxis, or other serious IgE-mediated reaction has occurred. Full courses of therapy were completed in 63 of the 64 subjects treated by this general protocol. The one patient withdrawn developed a severe immune hemolytic anemia while receiving nafcillin, a known complication of high dose β-lactam antibiotic therapy (86).

The mechanism of acute desensitization appears to be antigen specific mast cell desensitization (86). We have suggested that a form of hapten inhibition, as depicted in Figure 7, becomes established with univalent materials blocking crosslinking of IgE. Implicit in this concept is the notion that lapses in therapy must not occur or sensitivity will return. Skin tests usually become negative after desensitization but revert to positive quickly (hours to days) after cessation of therapy. Usual dosing intervals appear satisfactory, but there should be no more than 12 hours between doses.

Thus, patients at risk for anaphylaxis to β-lactam antibiotics can be identified with a considerable degree of precision. If β-lactam drugs are needed in allergic patients, acute desensitization appears to be an acceptably safe procedure for avoiding anaphylaxis.

Insect venoms or saliva. Allergic reactions to stinging or biting insects afflict approximately 0.3% of the adults in this country and account for a significant number of instances of anaphylaxis. Fatal anaphylaxis is reported 30 to 40 times per year, but may be more common since most such deaths are not routinely reported and could easily be mistaken for other problems if the sting was not known to anyone but the victim.

The taxonomy of the animals involved in these reactions is presented in Figure 8. The Hymenoptera most commonly causing anaphylaxis are honeybees, yellow jackets, hornets, wasps, and fire ants.

The contents of the Hymenoptera venoms characterized to date are presented in Table XVII, derived from reference 89. The major antigen in each venom appears to be phospholipase A, but several other antigens are involved in most cases (89).

The physiology and pathology of acute reactions to Hymenoptera are similar to those in anaphylaxis from other causes (89, 90).

A fascinating controversy arose in the mid 1970's over methods for diagnosis and treatment of Hymenoptera sensitivity. From 1930 until that time, extracts of whole insect bodies (wings, antlers, adherent pollen, and all) were used for diagnostic skin testing and for immunotherapy. Development of effective methods for the isolation of venoms permitted an assessment of their value in diagnosis and treatment. As one might expect, venoms were proven appropriate test reagents and venoms were proven effective for immunotherapy (80-94). In the process whole body extracts were demonstrated to be poor diagnostic reagents and no better than placebo for immunotherapy (Table XVIII). Adherents to the whole body extracts still exist, but are an endangered species.

The mechanism of protection from anaphylaxis after immunotherapy appears to be simple immunization. IgG anibodies raised by gradual immunization with venoms appear to neutralize venom before it can interact with cell bound IgE (Figure 9). Passive administration of immune IgG protects bee venom sensitive subjects from anaphylaxis (95). Protection from anaphylaxis after treatment appears to correlate with the level of venom specific IgG (96).

Postmortem diagnosis of Hymenoptera anaphylaxis can be assisted by using RAST procedures to search for venom specific IgE (99). The uncertainty reflected in the case in Figure 10 emphasizes the potential value of this maneuver. The presence of IgE supports the diagnosis, its absence argues against the diagnosis.

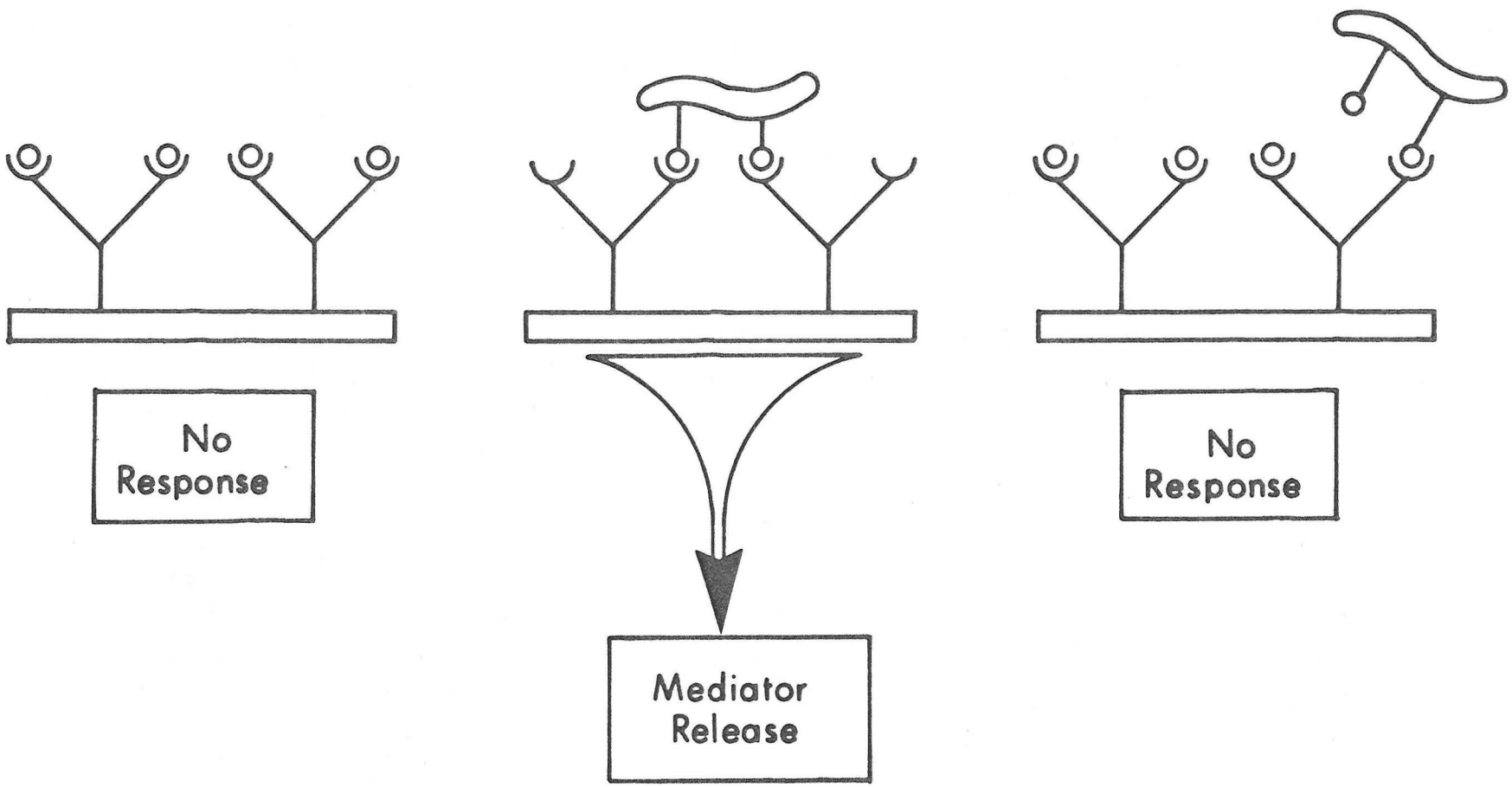


Figure 7 Inhibition of drug induced mediator release by free drug or univalent conjugates.

Taxonomy of order Hymenoptera – insects whose stings can cause systemic allergic reactions*

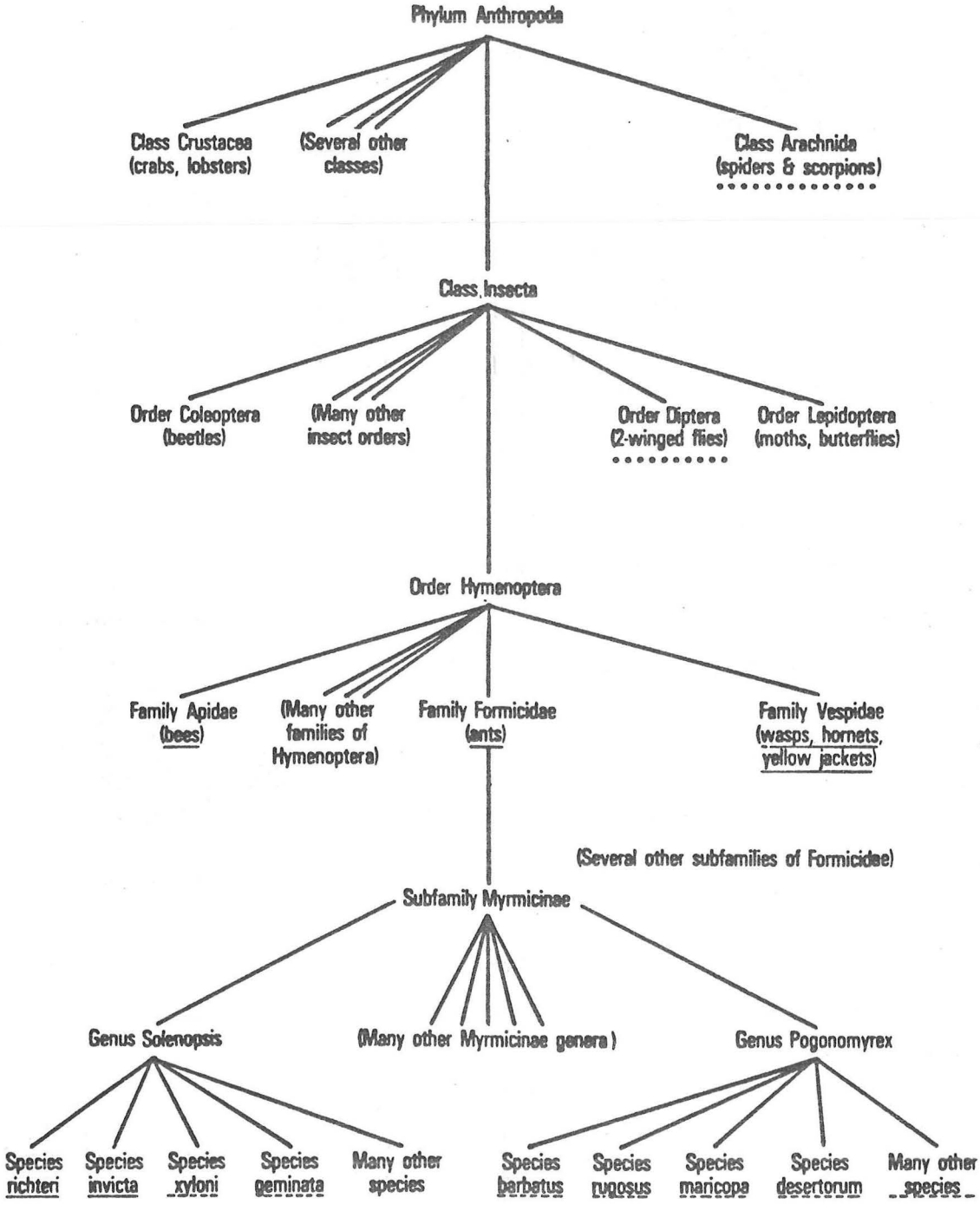


Figure 8: From reference 89

TABLE XVII

IDENTIFIED VENOM CONTENTS

Honeybee	Yellow Jacket	Hornet	Wasp*
Phospholipase A	Phospholipase A	Phosphoilpase A	Phospholipase A
Hyaluronidase	Phospholipase B	Phospholipase B	Phospholipase B
Acid phosphatase	Hyaluronidase	Hyaluronidase	Serotonin
Melittin	Acid phosphatase	Acid phosphatase	Histamine
Apamin	Kinin	Kinin (hornet)	Hyaluronidase
Mast cell degranulating peptide (MCD)	Histamine	Histamine	Kinin
	Serotonin	Serotonin	
	Dopamine	Acetylcholine	
† Minimine?	Norepinephrine	Dopamine	
Norepinephrine	Epinephrine	Norepinephrine	
Dopamine	Cholinesterase	Epinephrine	
Histamine	Histidine decarboxylase	Protease	
	Protease		

* Small number of identified components probably reflects limited studies.
† Minimine has been described as a minor polypeptide that retards the development of Drosophila. Its existence has not been confirmed.

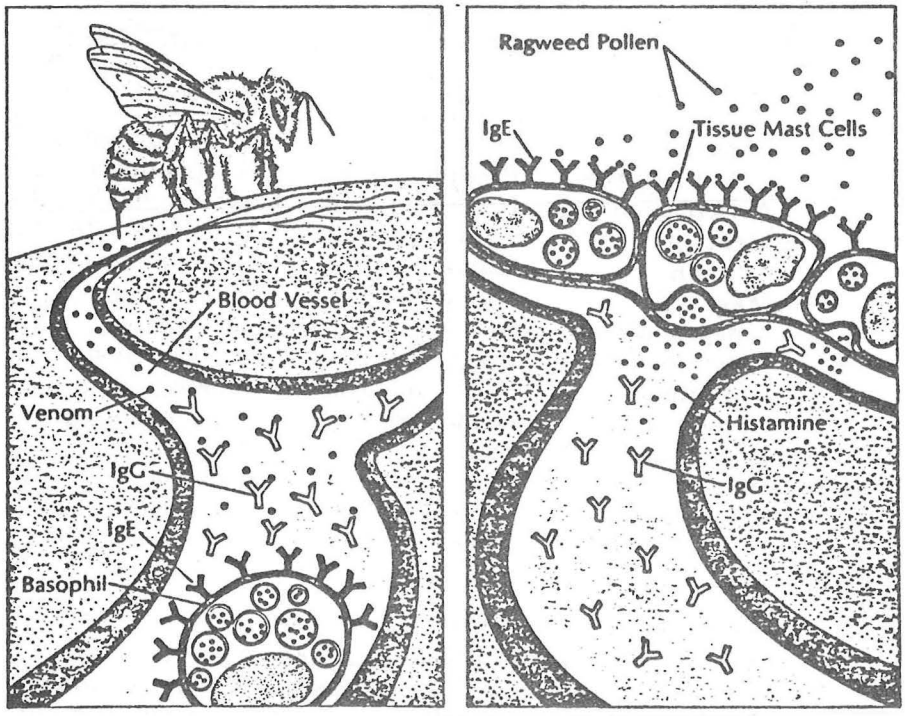
From reference 89

TABLE XVIII

Summary of Sting Challenges with Venom (Group I), Whole-Body Extract (Group II) and Placebo (Group III).

Group	Patients Treated	Patients Stung	Systemic Reactions
I	19	18	1 (5%)
II	20	11	7 (64%)
III	20	12	7 (58%)

From reference 93



With high IgG levels in blood, venom antigen is neutralized before reaching basophil-bound IgE (left) and reaction is forestalled. In hay fever (right), pollen allergen falls directly on IgE-sensitized tissue mast cells; serum IgG cannot help.

Figure 9: L.M. Lichtenstein, Hospital Practice, 1982.

South Oak Cliff man dies after being stung by wasps

An elderly man died within minutes after he was stung by wasps as he trimmed hedges at his South Oak Cliff home, authorities said.

Ben Abner Gafford, 70, collapsed in his home Monday morning and was dead by the time an ambulance summoned by his wife arrived at their home in the 8100 block of Greenspan Drive, authorities said.

Pathologists with the Dallas County medical examiner's office, after conducting an autopsy, said they were not able to make a final ruling pending further tests. Gafford had been stung once on the right ear and once on the left hand.

Gafford's wife, Corrine Gafford, 65, told investigators her husband was trimming hedges about 10:15 a.m. when she noticed him dodging several wasps, whose nest in the hedges he apparently disturbed.

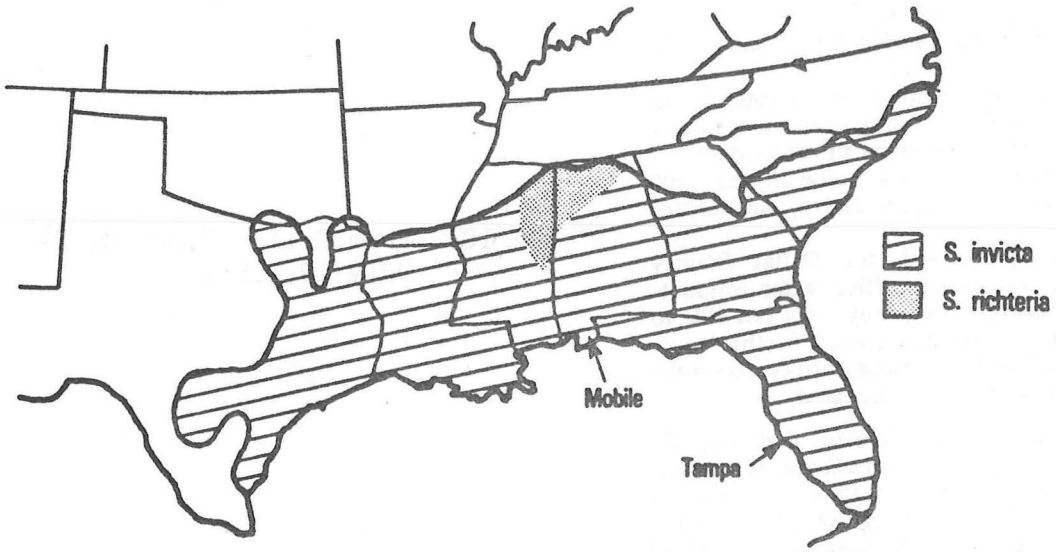
She told investigators she applied a medicinal lotion and cold compresses to the stings, but her distressed husband became unconscious within 15 minutes and she could not revive him.

Figure 10: From Dallas Times Herald July 19, 1983

Fire ant venom allergy is a problem of increasing significance in the warmer parts of the United States (Figure 11 and reference 98). Bites by fire ants often result in a slow healing sterile pustule, signalling the type of ant involved (98). Multiple bites are common (Table XIX). Many allergic subjects can be identified by skin testing and with RAST testing with whole body extracts (100,101), but venom (a difficult commodity to obtain) may detect a higher proportion of allergic individuals (101). Controlled trials are in progress assessing the value of immunotherapy, but no data are available for inspection. Avoidance and epinephrine for self-injection are the current approaches to minimizing reactions to fire ants.

Hymenoptera sensitivity represents allergy to preformed antigens that can be detected by direct skin testing. Immunization with venom antigens leads to classical protection by neutralizing IgG antibodies.

Local Anesthetic Allergy. Patients who experience untoward reactions of virtually any kind during treatment with local anesthetic agents often are told or believe they have experienced acute allergic reactions. A careful review of the setting and nature of these reactions often does not unequivocally assign prior reactions to IgE-mediated, pharmacologically-mediated, or vasovagal mediated categories. Possible bedside immunodiagnostic methods, such as skin testing, and in vitro diagnostic methods have not been vigorously characterized and must be regarded as experimental. In general these patients must be approached as if they had experienced IgE-mediated reactions and as if they are at risk for another IgE-mediated reaction if the same or a structurally related local anesthetic agent is administered.



Present distribution of *S. invicta* and *S. richteri* in southeastern United States (From Wojcik, D.P., Buren, W.F., Grissell, E.E., and Carlysle, T., *Entomology Circular*, Fla. Dept. Agr. and Consumer Serv. 173:4 1976.).

Figure 11

TABLE XIX

HISTORIES OF FIRE ANT HYPERSENSITIVITY

	Number	Percent
Number of patients	104	100
Male	52/104	50
Female	52/104	50
Age (1–72 years)	23 yrs [a]	
Children (0–18 years)	44/104	42
Time of onset of symptoms (1–60 min)	13 min [a]	
Number of bites (1–100)	10[a]	
History of allergy	28/83	34
History of other insect sensitivity	8/104	7
History of systemic reaction to previous ant bites	19/104	18
Pustules present at 24 hrs	62/72	86
Pustules not present at 24 hrs	10/72	14

a. Average.

Analysis of apparently allergic reactions to local anesthetics and cutaneous wheal and flare reactions to them (102) has suggested that cross-reactions are common among p-amino-benzoyl (PAB) group containing local anesthetics (Table XX). Reactions to local anesthetics not containing the PAB structure appear to be rare and crossreactions in this group appear to be rare. Vigorous efforts should be made to identify the agent associated with a prior reaction.

If the agent that provoked a reaction is known, a structurally unrelated agent can be selected. Table XX presents commonly used agents according to the presence or absence of the PAB group and according to the usual sites or routes of administration. If a PAB group agent was associated with a prior reaction, an agent without the PAB group can be selected. If a non-PAB agent was associated with a prior reaction, a PAB agent or another non-PAB agent can be selected. If the agent implicated in a prior reaction can not be determined, the agent or class of agent least likely to have been used is selected. Paraben preservatives in medications and procaine amide contain the PAB group and could conceivably cause a reaction in a PAB sensitive individual.

TABLE XX

CLASSIFICATION OF LOCAL ANESTHETIC AGENTS BY PRESENCE OR ABSENCE OF p-AMINOBENZOYL GROUP

p-Aminobenzoyl Structure Present	p-Aminobenzoyl Structure Absent
Injectable Agents	
Procaine	Lidocaine
Chloroprocaine	Mepivacaine
Tetracaine	Dibucaine
	Bupivacaine
	Etidocaine
	Prilocaine
Ophthalmic Agents	
Benoxinate	Proparacaine
Topical Mucous Membrane and Cutaneous Agents	
Benzocaine	Dimethisoquine
Butamben	Cyclomethicaine
	Dyclonine
	Pramoxine
	Cocaine

The incomplete nature of our knowledge of allergic reactions to local anesthetics has led to the widespread use of a variety of provocative testing procedures before local anesthetics are used for anesthetic purposes (103). A protocol for provocative testing is presented in Table XXI. If a local or systemic reaction occurs, another agent is selected, if one is available, and provocative testing is repeated. If no alternative local anesthetic agents are available, cautious use of the least reactive agent, infiltration with a weakly anesthetic H_1 antihistamine, systemic analgesic therapy or general anesthesia should be considered depending upon the indication for analgesia. This general approach has been successful in permitting the use of local anesthetics in patients with histories of allergic reactions to local anesthetics.

TABLE XXI

Provocative Testing with Local Anesthetics

Dose	Concentration	Amount Route
1.	1:100 dilution	___ Prick test
2.	Undiluted	___ Prick test
3.	1:100 dilution	0.02 ml Intradermal
4.	1:100 dilution	0.5 ml Subcutaneous
5.	Undiluted	0.2 ml Subcutaneous
6.	Undiluted	1.0 ml Subcutaneous

a. The full protocol is used when the agent that provoked an allergic reaction is unknown. Doses 3, 5 and 6 are used when a structurally dissimilar agent is known.

b. Interval between doses, 15 minutes.

Exercise induced anaphylaxis. This bizzarre syndrome is characterized by a feel of cutaneous warmth and pruritus folowed by cutaneous erythema and urticaria followed by hypotension and or upper respiratory obstruction all of which occur during exercise (104-108). The wheals are a centimeter or more in diameter, do not appear with a rise in core body temperature and two thirds experience pronounced hypotension in distinction from cholinergic urticaria. Exercise in susceptible patients results in marked increases in plasma histamine levels (104), and occasionally a rash, but the full syndrome has not been induced in the laboratory. Some other variable seems to be necessary for full expression. In some patients that variable has been identified as a mild food allergy (105,106), in others the ingestion of any food (106,107), but for the majority of subjects the variable has not yet been identified. Neither exercise nor ingestion of food alone caused a clinically detectable reaction. Half of these subjects had personal atopic disease and two thirds had a positive history of atopy. A familial cluster has been reported (108).

Interestingly the syndrome can be aborted if exercise is halted with the appearance of the cutaneous component. Since episodes do not occur with each period of exercise, most subjects can continue to exercise, stopping if the initial signs appear. Treatment of advanced attacks is the same as other forms of anaphylaxis (see below).

Radiocontrast medium reactions. Anaphylactic reactions of varying intensity occur in approximately 2% of all intravenous radiocontrast studies (109-113). Recently important determinants of risk have been and estimates of relative risk offered (Table XXII; 113).

TABLE XXII

Risk Factors for Radiocontrast Medium Anaphylactic Reactions

Condition	Relative Risk			
	Minor	Intermediate	Severe	Death
History of allergy	1.6	2.6	3.91	---
Asthma	1.5	2.72	5.09	---
Hay fever	1.68	1.76	2.34	---
Urticaria	1.54	4.83	2.03	---
Eczema	1.30	1.16	4.69	---
Other allergies	1.44	1.75	3.35	---
Drug reactions	1.83	1.97	3.15	---
Prior RCM reactions	6.85	8.67	10.88	---
Cardiac disease	1.10	0.86	4.54	8.48
CHF	1.34	0.98	5.5	53.8
CAD	1.02	0.80	6.88	8.68
Arrhythmia	1.46	0.78	9.75	---

From reference 113

Patients who have experienced RCM reactions in the past have an approximately 30% chance of a reaction during another RCM procedure (109). Premedication with glucocorticoids according to the regimen in Table XXIII reduced the reaction rate to approximately 6% and most reactions have been much less severe than the initial reaction (109). Studies are in progress to determine whether or not all patients would benefit from premedication. The regimen is benign and I would recommend premedication of all subjects, at least those with significant risk factors (Table XXII). Further more for reasons stated above and below H_2 receptor blockade with cimetidine, ranitidine or doxepin is likely to be even more effective and preliminary studies of RCM premedication seem to confirm this hypothesis. While most investigators have not detected value in low dose IV pretesting with RCM (109), some workers advocate such a test (114).

RCM reactions are an example of chemically-induced anaphylaxis (112) in which clear risk factors have been identified and in which premedication significantly reduced the incidence and severity of reactions.

TABLE XXIII

Protocol for Premedication to Avert

Radiocontrast Medium Reactions

Hours Before Procedure	Pharmacologic Agent	Dose
13	Prednisone (Cimetidine)	50 mg PO (300 mg PO)
7	Prednisone (Cimetidine)	50 mg PO (300 mg PO)
1	Prednisone Diphenhydramine (Cimetidine)	50 mg PO 50 mg PO (300 mg PO)

Summary of avoidance measures. Methods to detect patients at risk for anaphylaxis and to avoid anaphylaxis when a class of agent is needed for therapy or diagnosis are diverse and depend upon the specific agent. The forces that lead to anaphylaxis are diverse and effective avoidance measures are specific force oriented; the clinical anaphylactic syndromes on the other hand are similar; and the treatment of anaphylaxis detailed below is similar.

TREATMENT OF ANAPHYLAXIS

At the outset in a discussion of the treatment of anaphylaxis, one should be aware that the commonly recommended plans for management of anaphylaxis are based upon varying measures of fundamental pharmacologic and physiologic principles, reported anecdotes, rumors, and the sometimes bizarre personal beliefs of the self-proclaimed experts who write the protocols, including this protocol. There are no controlled trials reported that prove the relative efficacy or relative safety of the approaches delineated below. These approaches are, however, sound in principle and have a substantial degree of apparent effectiveness.

Assessment. The appearance of an apparently allergic reaction should immediately initiate a determination of the nature of the reaction (Table XXIV) and careful assessment of what caused the reaction. If anaphylaxis has appeared near the beginning of the administration of a therapeutic or diagnostic agent, the drug should be stopped. Careful and repeated clinical assessment, as outlined in Table XXIV, is essential since diagnosis and successful management must be based on clinical observations. In addition to establishing the presence of specific manifestations, assessment must establish the severity of the manifestation and the rate of worsening or appearance of new manifestations. These cardinal features should be noted carefully, since the nature, severity and rate of development of manifestations of anaphylaxis determine the nature, methods and rate of treatment.

Urticaria and Angioedema. Often the first signs of anaphylaxis are flushing; generalized pruritus or pruritus of the scalp, palms or soles; urticaria; or angioedema. Even more often these cutaneous disorders will be the only clinical expressions of an acute systemic allergic reaction.

Aside from the passage of time there are no methods for distinguishing the onset of a life endangering reaction from acute urticaria and angioedema. Since epinephrine usually is quite effective for the treatment of acute urticaria and angioedema, if given in the first hours of the reaction, and since these phenomena can not be distinguished from the first signs of a more serious reaction, epinephrine usually is the drug of choice. If no signs of upper or lower airway disorders or signs of cardiovascular disorders have been detected within the first hour of the reaction, alternative approaches may be considered (Table XXV).

Pruritus usually is the indication for treating acute urticaria. An approach to suppressing acute urticaria and pruritus is presented in Table XXV. The role of tricyclic antidepressants in this context is not well defined, but these agents appear to be the most potent H_1-antihistamines available and they also exert potent anti-H_2 actions (32,34,35). Our experience with doxepin has been very favorable (32). As with other antihistamines, drowsiness is the principal side effect limiting the dose that can be tolerated. The oral suspension form of doxepin is convenient since infinite flexibility in dosage is

TABLE XXIV

Detection and Continuing Assessment of Anaphylaxis

Primary Clinical Manifestations:

Generalized pruritus, urticaria, flushing, rash, conjunctival suffusion, rhinorrhea and nasal congestion, dizziness, weakness, syncope, oropharyngeal or laryngeal edema, hoarseness, stridor, dyspnea, wheezing, irregular pulse, nausea, vomiting, diarrhea, hypotension.

Clinical Assessments made repeatedly during reaction:

Upper airway - hoarseness, stridor, tachypnea, dyspnea, use of accessory muscles of inspiration, intercostal and sternal notch retractions.

Lower airway - dyspnea, wheezing, prolonged expiration, tachypnea, cyanosis. If system involved: blood gas measurements and spirometry.

Cardiovascular system

Blood pressure, pulse

Cardiac rhythm - continuous ECG monitoring.

Other manifestations noted in initial assessment.

TABLE XXV

Pharmacologic Suppression of Acute Uncomplicated Urticaria and Angioedema

1. Epinephrine
   (e.g. Epinephrine 300 ug - 0.3 ml of 1:1000 - S.C.
   Usually effective in the first 1 to 2 hours after onset but not later in course)

-If this proves ineffective or is not indicated-

2. Conventional H_1 antihistamines
   (e.g. Chlorpheniramine 4 to 8 mg P.O. q 6 h or
   Diphenhydramine 50 to 100 mg I.M. q 6 h)

-If this proves ineffective-

3. H_1 antihistamine plus H_2 antihistamine
   (H_1 antihistamines as noted above plus Cimetidine 300 mg P.O. q 6 h)

-If this proves ineffective-

4. Tricyclic antihistamines
   (e.g. Doxepin 5 mg P.O. q 12 h or higher doses P.O. once daily)

-If this proves ineffective-

5. Antihistamine therapy plus short term glucorticoid therapy
   (e.g. Prednisone 40 mg P.O. once daily in a.m. for 4 days)

possible. The q 12 h dosage interval for 5 mg of doxepin or once daily dosage for 10 mg or higher also make this agent attractive.

Patients with acute urticaria may not be responsive to epinephrine or antihistamine therapy alone. Many of these individuals can be controlled by antihistamine therapy plus a short course of glucocorticoid therapy (Table XXV). Glucocorticoids, in these moderate doses for this short interval, seldom are contraindicated if the patients' other medical problems are controlled. A similar approach can be applied to the treatment of angioedema, with the exception of upper airway obstruction (see below).

If a β-adrenergic blocking agent such as propranolol is being administered, urticaria and other allergic reactions may be particularly difficult to suppress. Consideration should be given to using an alternative to β-blockers, such as nifedipine, if the reaction is not readily controlled.

Anaphylaxis - General Measures. Since fatal allergic reactions can evolve very rapidly, even when the onset of a reaction occurs hours after exposure to an antigen, particular attention should be given to determining the intensity and rate of progression of symptoms and signs. If symptoms and signs are confined to the skin and if the reaction appears stable, treatment can be instituted according to the protocol in Table XXV followed by careful clinical monitoring. If the acute reaction is explosive in onset or if the respiratory or cardiovascular systems are involved, the protocol outlined in Table XXVI and detailed below should be considered.

The four primary life-endangering aspects of acute systemic allergic reactions - upper airway obstruction, severe bronchial dysfunction, cardiac dysfunction, and hypotension - must be addressed in a systematic manner. Upper airway patency, pulmonary function, cardiac rhythm and blood pressure must be followed carefully until the reaction has subsided (Table XXVII).

Epinephrine. The drug of choice for anaphylactic reactions is epinephrine (115). This agent acts by suppressing mediator release from mast cells and basophils and by reversing many of the end-organ responses to mediators of anaphylaxis. Complete resolution of clinical manifestations often occurs within minutes after epinephrine administration. Effective use of epinephrine requires an appreciation of the potential hazards as well as the benefits of the agent. Intravenous or high doses (1 mg or more) of epinephrine may provoke serious or even fatal ventricular dysrhythmias. The use of alternative routes, appropriate doses, and cardiac monitoring minimize this problem. Initial doses of 300 to 500 μg (0.3 to 0.5 ml of 1:1000) of epinephrine in an adult usually can be given by the subcutaneous route. The peripheral vasodilation associated with anaphylaxis apparently facilitates rapid absorption of the drug. If serious manifestations of anaphylaxis persist or the reaction progresses during the first 10 minutes following S.C. epinephrine administration, a second 300 μg to 500 μg dose is given S.C. If a serious reaction continues, an infusion of epinephrine is begun. Initial therapy with intravenous epinephrine

TABLE XXVI

An Outline of the Management of Anaphylaxis

General Therapeutic Measures

- Epinephrine (see text for details of therapy)
- Diphenhydramine
  - Diphenhydramine plus cimetidine

Specific Interventions

- Upper airway obstruction
  - Oropharyngeal airway
  - Endotracheal intubation
  - Cricothyrotomy
- Lower airway obstruction
  - Supplemental inspired oxygen
  - Intravenous aminophylline
  - Endotracheal intubation and assisted ventilation.
- Hypotension
  - Intravenous isotonic sodium chloride
  - Norepinepherine infusion
  - Isoproterenol infusion
  - Diphenhydramine plus cimetidine
- Cardiac dysrhythmias
  - Conventional therapy of dysrhythmias

Suppression of persistent or recurrent reactions

- Continued monitoring for at least 12 hours with specific interventions as indicated above
- Systemic glucocorticoids
  - One dose after initial reaction is controlled and a second dose 6 hours later

Formulation of a plan to avoid or immediately suppress future episodes

---

TABLE XXVII

Causes of Death From Anaphylaxis

Direct Causes

* Upper airway obstruction
* Bronchial dysfunction
* Hypotension secondary to cardiac dysfunction
* Hypotension secondary to loss of peripheral vascular tone

Indirect Causes

* Myocardial infarction
* Cerebral injury from hypotension or hypoxia
* Other ischemic or hypoxic injuries
* Epinephrine induced cardiac disorders
* Failure to use epinephrine

TABLE XXVIII

Treatment of Reactions

	Intermediate Reactions	Severe Reactions	Fatal Reactions
None	28		
Posture	24	21	
Oxygen	16	28	3
Epinephrine	6	14	
Steroid	93	35	1
Antihistamine	238	22	2
Aminophylline	15	6	
Intravenous drip	6	22	
Vasopressors	1	3	
Cardiac massage		7	1
Other	21	10	1

* This table from reference 13 summarizes the treatment of patients who experienced RCM reactions. Notably absent from the care of fatal reactions is the use of epinephrine.

probably should be reserved for instances of profound hypotension (systolic pressure less than 60 mm Hg), rapidly progressive severe reactions, and immediately life-endangering airway obstruction. Epinephrine for intravenous use is diluted to 2 µg/ml in D_5W (1 mg of epinephrine - 1 ml of 1:1000 or 10 ml of 1:10,000 - is diluted in 500 ml of D_5W). The initial infusion rate usually is 2 µg/minute (1 ml/minute) with adjustments (usually 0.5 to 5 µg/minute) based on the clinical response or the appearance of a cardiac dysrhythmia.

Many physicians unaccustomed to treating anaphylaxis, fear using epinephrine in patients with cardiac disease, hypertension or a litany of other conditions. These fears arise primarily from experiences such as those described below, reported or observed, in which concentrated intravenous doses or inappropriately high doses of epinephrine were given. If the experience of our Allergy Division is any index, failure to use epinephrine is a common cause of referral and of protracted anaphylaxis. Failure to treat patients with epinephrine promptly and vigorously is likely to contribute significantly to the morbidity and mortality of anaphylaxis (Table XXVIII).

Recently we had the opportunity to continuously monitor the electrocardiograms of two patients experiencing penicillin-induced anaphylaxis (116). The cardiac disturbances that occurred immediately after intravenous administration of epinephrine are described below.

Case 1. - A 34 year old woman ingested two tables from a bottle labeled "acetaminophen" for treatment of dysmenorrhea. The bottle contained 250 mg penicillin V potassium tablets rather than acetaminophen; the patient's daughter had switched the contents for her own use without the patient's knowledge. Within 30 minutes she noted the onset of vomiting, generalized pruritus, periorbital and labial angioedema, stridor, wheezing and dyspnea. An Emergency Medical Technician (EMT) team, controlled from the Parkland Memorial Hospital Emergency Room through continuous radio contact, arrived approximately 10 minutes after the onset of the systemic reaction. Vital signs on arrival were BP 120/78, respirations 32, and pulse 68. Telemetry ECG indicated sinus rhythm. Angioedema, respiratory distress, stridor and wheezing were noted. The hospital-based physician controlling the EMT ordered 5 ml of 1:10,000 epinephrine (500 µg) administered by slow intravenous push. Within seconds after the injection ventricular premature beats occurred following seconds later by an apparent accelerated ideoventricular rhythm (Figure 12). While an absolute diagnosis is difficult with a single lead ECG tracing, accelerated ideoventricular rhythm appeared to be present. Intravenous administration of 100 mg of lidocaine restored sinus rhythm. The systemic allergic reaction resolved without additional complications over the next 2 hours and did not recur. This patient had experienced generalized urticaria during penicillin V potassium treatment for pharyngitis 6 months before her anaphylactic incident. She had no other known allergic or systemic diseases and was taking no medications. Skin tests the day after admission demonstrated positive immediate wheal and flare reactions to prick tests using penicilloyl-polylysine (60 µM), to intradermal tests with cephalothin (10 mM), and to prick tests with a histamine control. No reaction

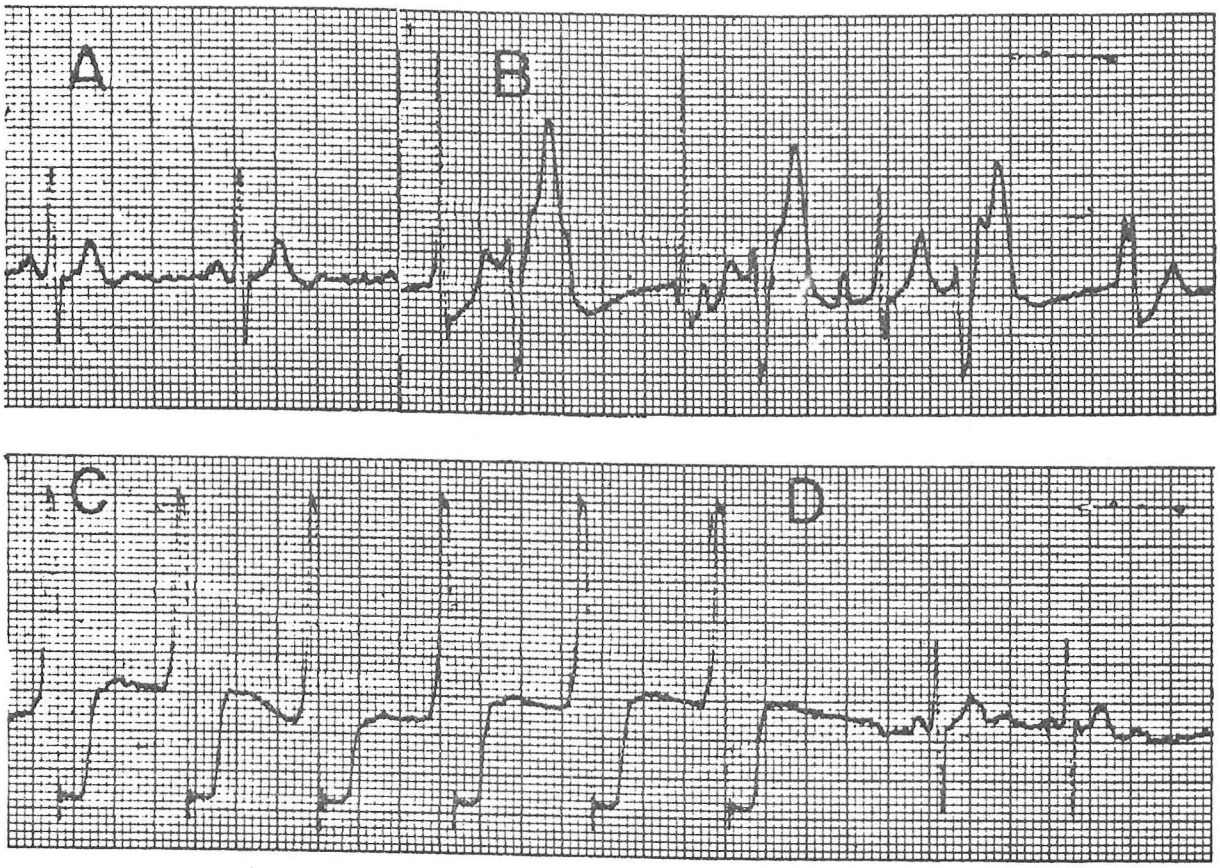


Figure 12

Electrocardiograpic record of the rhythm disturbance observed in a 34 year old woman who received intravenous epinephrine for treatment of anaphylaxis. A, rhythm before epinephrine injection; B, immediately after epinephrine injection; C, subsequent accelerated ideoventricular rhythm; D, reversion to sinus rhythm after lidocaine administration.

occurred at sites challenged with intradermal benzylpenicillin G (10 mM), penicilloic acid (10 mM) or a diluent control.

CASE 2. - A 24 year old man with streptococcal pharyngitis noted the onset of hoarseness 3 hours after ingesting the initial 250 mg penicillin V potassium tablet in his prescribed therapy. Thinking his pharyngitis was worsening the patient took another 250 mg tablet. Within 30 minutes after the second dose he experienced severe hoarseness, stridor, dyspnea, diaphoresis and a sense of impending death. Upon arrival of the EMT approximately 10 minutes after the severe systemic symptoms appeared, the patient's vital signs were BP 100/0, respirations 30, and pulse 120. Telementry ECG indicated sinus rhythm. Hoarseness, respiratory distress and stridor were observed by the EMT. On the orders of the hospital-based physician 5 ml of 1:10,000 epinephrine (500 µg) were administered by slow intravenous push. Within seconds after the injection a tachyarrhythmia occurred. Ventricular depolarization occurred over 0.15 seconds at a rate of approximately 150/minute with AV dissociation and one captured beat observed. Careful review of the tracing with cardiology consultants led to a tentative diagnosis of ventricular tachycardia, with the reservation that single lead electrocardiograms are not conclusive. The electrocardiographic record is not presented because of very poor preservation. Intravenous administration of 100 mg of lidocaine converted the patient's rhythm to a nodal and then a sinus rhythm. The stridor and hypotension improved rapidly, but severe laryngeal edema recurred approximately 1 hour later in the hospital. Endotracheal intubation was performed without incident and the patient ultimately recovered without permanent defects. Eighteen months earlier he had tolerated penicillin V potassium treatment for pharyngitis with no evidence of an allergic reaction. This individual had no known allergic or systemic diseases and was taking no medications. Skin tests the day after admission revealed positive immediate wheal and flare reactions to intradermal benzylpenicillin G (10 mM), peniciloic acid (10 mM), and cephalothin (10 mM) and to a prick test with histamine. No reactions were evoked by intradermal penicilloyl-polysine (60 µM) or a diluent control.

The two patients described above expressed IgE anti-penicillin antibodies as assessed by skin tests, developed systemic anaphylaxis after ingesting penicillin V potassium, and experienced ventricular dysrhythmias immediately after the intravenous administration of epinephrine. One of our patients probably was hypotensive and both were likely to have been hypoxic at the time the dysrhythmias appeared raising the possibility that the disorders were unrelated to epinephrine therapy. Mast cell mediators released into cardiac tissue during anaphylaxis do appear to render the myocardium prone to rhythm disturbances (42). The ability of epinephrine to provoke ventricular dysrhythmias even in normal cardiac tissue has been thoroughly documented, however. Abrupt intravenous introduction of epinephrine into subjects experiencing systemic anaphylaxis, who also may be hypotensive or hypoxic, would be expected to provoke dysrhythmias in a significant proportion of cases.

Continuous electrocardiographic monitoring of our patients revealed a close temporal relationship between the administration of epinephrine and the onset of dysrhythmias providing support for the concept that epinephrine played a casual role in our patients rhythm disturbances. A review of previous reports of cardiac disorders associated with anaphylaxis indicates that in many cases the first electrocardiographic assessments were made after the administration of intravenous or intramuscular epinephrine (58-63). The role of epinephrine in these alterations in cardiac function is unknown, but it is reasonable to speculate that the drug may have contributed to some of these disorders (115).

Epinephrine is widely regarded as the drug of choice for initial management of anaphylaxis (115). Subcutaneous administration of 250 to 500 μg usually is recommended for the first dose. The peripheral vasodilation frequently present during anaphylaxis apparently leads to rapid absorption from a subcutaneous site, usually resulting in prompt reversal of allergic reactions. Nevertheless, some authors recommend initial treatment with intravenous or intramuscular epinephrine in doses up to 2000 μg (117). The courses of the patients described above and published knowledge of the actions of epinephrine (115) are in accord with the notion that epinephrine given for treatment of anaphylaxis should be administered subcutaneously if possible or by slow infusion of diluted drug.

Continuous electrocardiographic monitoring of patients experiencing anaphylaxis, from the moment of arrival of the EMT team, led to the recognition of cardiac complications and documented their subsequent resolution. Our observations in combination with those of other investigators (58-63) suggest that cardiac monitoring should be employed (if possible) in the management of all cases of anaphylaxis. Physicians treating anaphylaxis should be aware of possible spontaneous or epinephrine-induced dysrhythmias and should be prepared to detect and manage such complications.

A recent report by Feldschuh and Gambino indicated that commercial 1:10,000 epinephrine preparations were very acid, in some cases 10 ml (1 mg) of Abbott epinephrine was capable of neutralizing 33 mEq of sodium bicarbonate (118). This acid load was proposed as a major hazard associated with intravenous or intracardiac treatment with 1:10,000 epinephrine. No significant acid load was detected in 1:1000 preparations. We recently assessed this issue with two different lots of Abbott 1:10,000 epinephrine from the Parkland Memorial Hospital supply system (Table XXIX). We were able to confirm a very low pH, but titration revealed the presence of the acid equivalent of 2.0 and 1.7 mEq of bicarbonate. There may be substantial lot to lot variation. Until this problem is eleminated these observations suggest that when possible I.V. or intracardiac injections with epinephrine ought be made from diluted 1:1000 epinephrine rather than with 1:10,000 epinephrine.

Other measures. Occasionally anaphylaxis occurs in patients who have been receiving β-adrenergic blocking agents such as propranolol. Anaphylaxis in such patients may be unusually severe (48-50), and can be difficult to treat with epinephrine. Epinephrine often is of some

TABLE XXIX

Epinephrine Preparation	Total Epinephrine	Initial pH	$NaHCO_3$ (mEq) Required for neutralization to pH 7.40
Feldschuh and Gambino			
Abbott 1:10,000	1 mg	3.27	33.00
Bristol 1: 1,000	1 mg	3.65	4.02
Parke-Davis 1:1,000	1 mg	5.95	0.02
Stark and Sullivan			
Abbott 1:10,000	1 mg	3.78	2.00
	1 mg	3.80	1.70
Sinn 1:1,000	1 mg	5.08	> 0.02

TABLE XXX

Management of Upper Airway Obstruction

* Extension of the head
* Orpharyngeal airway
* Endotracheal intubation
* Surgical intervention

value, in accord with the concept that the β-adrenergic blockade usually is only partial even for endogenous epinephrine activation, and the blood levels of epinephrine achieved after therapy are comparatively quite high. In this situation other measures in addition to epinephrine should be introduced at the beginning of therapy. Diphenhydramine (100 mg IV in an adult) and cimetidine (300 mg IV over 5 minutes in an adult) to accomplish H_1 and H_2 receptor blockade may be useful as noted above, particularly when hypotension is present. The specific interventions described below are considered. An infusion of epinephrine or isoproterenol (1 μg/ml see below) with careful monitoring of the clinical response (especially blood pressure) and with continuous electrocardiographic monitoring can be considered. There are no proven guidelines for the upper limits for safe administration or the amounts needed to override β-adrenergic blockade.

Once assessment is completed, epinephrine has been administered and any necessary additional interventions completed, administration of antihistamines and glucocorticoids should be considered. Pruritic rashes can be treated according to the protocol in Table XXV. H_1 blockade alone does not appear to suppress the life-endangering aspects of anaphylaxis, but H_1-antihistamines usually are administered to suppress urticaria and angioedema and they are a logical adjunct to therapy. As noted above, combined H_1 and H_2 blockade may be useful for suppressing histamine effects on the cardiovascular system.

Systemic glucocorticoids do not appear to suppress the first phase of human anaphylaxis. Glucocorticoids play no role in the acute management of anaphylaxis since 2 to 4 hours are required to obtain a glucocorticoid effect.

Upper airway obstruction. Angioedema involving the larynx, oropharynx or tongue can occlude the airway, occasionally with very rapid progression. Symptoms such as a sensation of impending upper airway obstruction, hoarseness, or dyspnea should be monitored and carefully considered if present. The patient should be examined frequently with particular attention given to the appearance of hoarseness, stridor, use of accessory muscles of respiration, and retractions in the sternal notch or intercostal spaces. Vigilance is essential to maintaining airway patency. If the initial general measures to treat anapylaxis fail to reverse upper respiratory obstruction or if significant obstruction emerges, direct interventions must be made without hesitation. Proper positioning of the head, insertion of an oropharyngeal airway and assisted ventilation with a compressible bag should be considered, particularly if glossal or oropharyngeal edema is present. If this is not sufficient, endotracheal intubation should be performed. Occasionally only a small endotracheal tube can be inserted but even a number 6 or 7 endotracheal tube is sufficeint to ventillate an adult woman or man respectively (Table XXX).

If the obstruction is too advanced to permit intubation, cricothyrotomy should be considered. (The anatomy of the larynx is reviewed in Figures 13 and 14.) Effective ventillation can be re-established by cricothyrotomy or by tracheostomy (Table XXXI), but cricothyrotomy usually is the preferred procedure (119). The

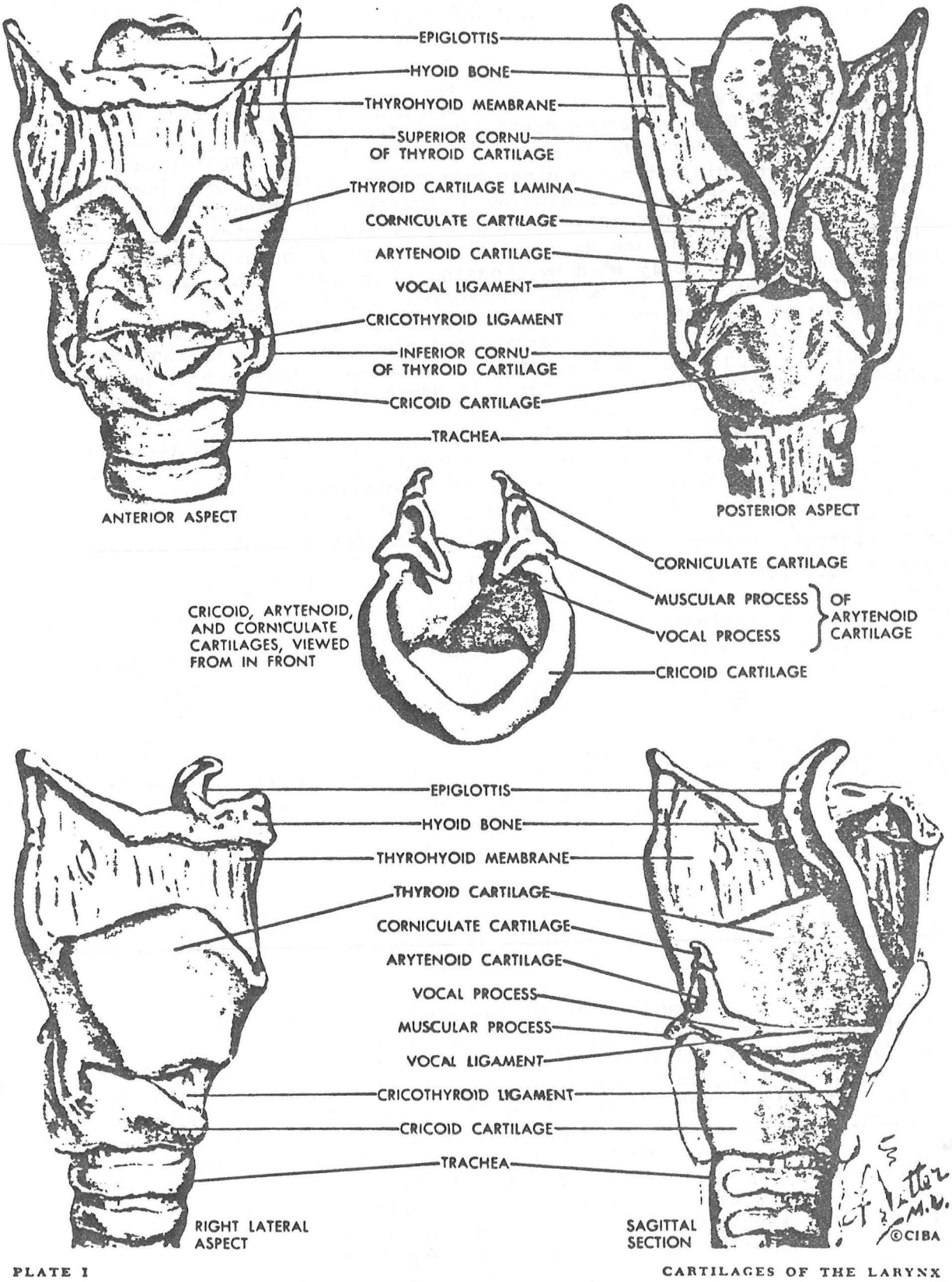

EPIGLOTTIS
HYOID BONE
THYROHYOID MEMBRANE
SUPERIOR CORNU OF THYROID CARTILAGE
THYROID CARTILAGE LAMINA
CORNICULATE CARTILAGE
ARYTENOID CARTILAGE
VOCAL LIGAMENT
CRICOTHYROID LIGAMENT
INFERIOR CORNU OF THYROID CARTILAGE
CRICOID CARTILAGE
TRACHEA
ANTERIOR ASPECT
POSTERIOR ASPECT
CRICOID, ARYTENOID, AND CORNICULATE CARTILAGES, VIEWED FROM IN FRONT
CORNICULATE CARTILAGE
MUSCULAR PROCESS
VOCAL PROCESS
OF ARYTENOID CARTILAGE
CRICOID CARTILAGE
EPIGLOTTIS
HYOID BONE
THYROHYOID MEMBRANE
THYROID CARTILAGE
CORNICULATE CARTILAGE
ARYTENOID CARTILAGE
VOCAL PROCESS
MUSCULAR PROCESS
VOCAL LIGAMENT
CRICOTHYROID LIGAMENT
CRICOID CARTILAGE
TRACHEA
RIGHT LATERAL ASPECT
SAGITTAL SECTION
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PLATE I
CARTILAGES OF THE LARYNX

Figure 13

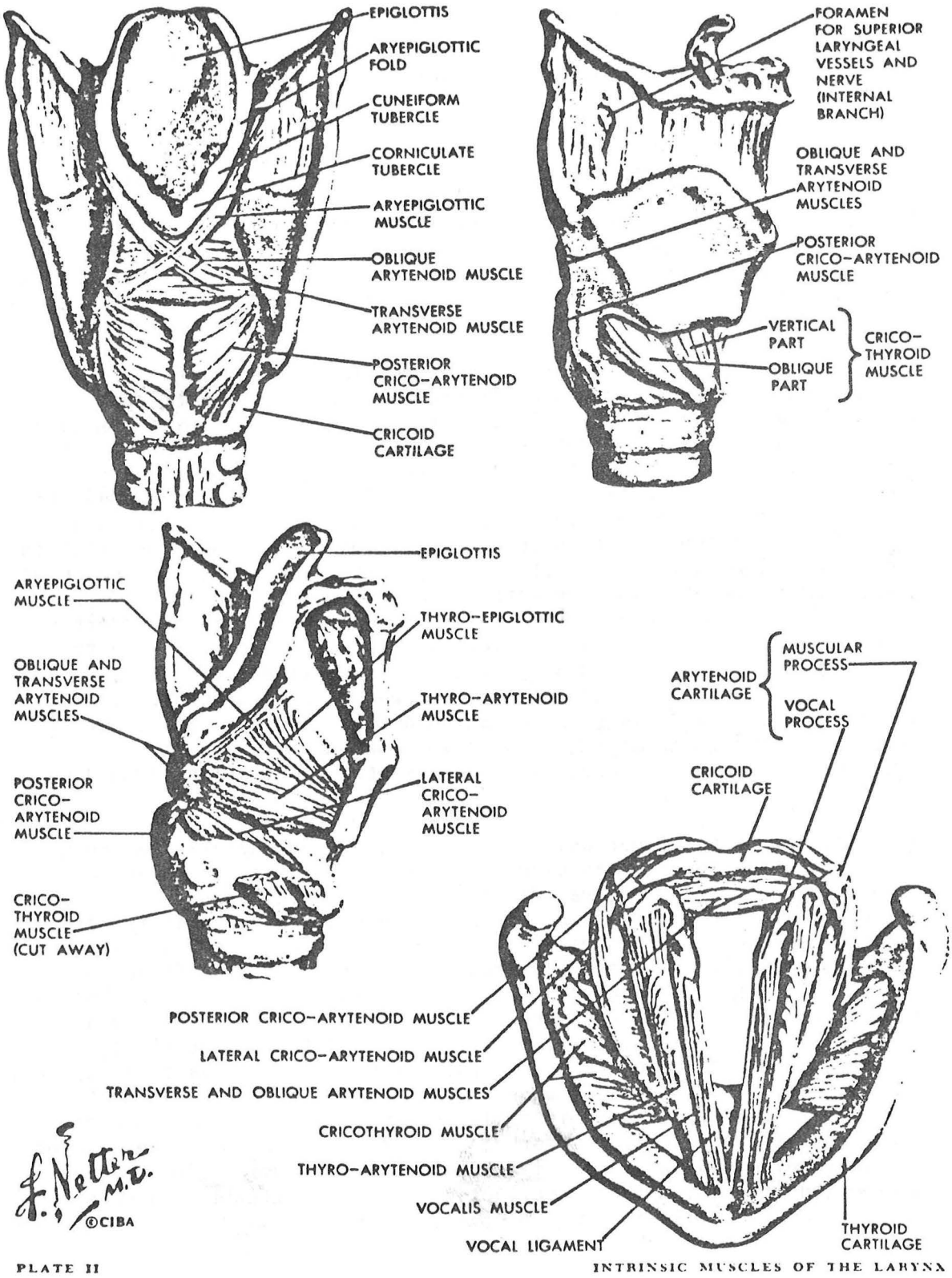
EPIGLOTTIS
ARYEPIGLOTTIC FOLD
CUNEIFORM TUBERCLE
CORNICULATE TUBERCLE
ARYEPIGLOTTIC MUSCLE
OBLIQUE ARYTENOID MUSCLE
TRANSVERSE ARYTENOID MUSCLE
POSTERIOR CRICO-ARYTENOID MUSCLE
CRICOID CARTILAGE
FORAMEN FOR SUPERIOR LARYNGEAL VESSELS AND NERVE (INTERNAL BRANCH)
OBLIQUE AND TRANSVERSE ARYTENOID MUSCLES
POSTERIOR CRICO-ARYTENOID MUSCLE
VERTICAL PART
OBLIQUE PART
CRICO-THYROID MUSCLE
EPIGLOTTIS
ARYEPIGLOTTIC MUSCLE
THYRO-EPIGLOTTIC MUSCLE
OBLIQUE AND TRANSVERSE ARYTENOID MUSCLES
THYRO-ARYTENOID MUSCLE
POSTERIOR CRICO-ARYTENOID MUSCLE
LATERAL CRICO-ARYTENOID MUSCLE
CRICO-THYROID MUSCLE (CUT AWAY)
ARYTENOID CARTILAGE
MUSCULAR PROCESS
VOCAL PROCESS
CRICOID CARTILAGE
POSTERIOR CRICO-ARYTENOID MUSCLE
LATERAL CRICO-ARYTENOID MUSCLE
TRANSVERSE AND OBLIQUE ARYTENOID MUSCLES
CRICOTHYROID MUSCLE
THYRO-ARYTENOID MUSCLE
VOCALIS MUSCLE
VOCAL LIGAMENT
THYROID CARTILAGE
F. Netter M.D.
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PLATE II
INTRINSIC MUSCLES OF THE LARYNX

Figure 14

cricothyroid membrane is directly under the skin. A minimum of equipment, dissection, and time are needed to perform cricothyrotomy in distinct contrast to the usual tracheotomy. The speed of the cricothyrotomy procedure is an important feature when dealing with imminent asphyxiation. A small endotracheal tube can be inserted, permitting assisted ventillation if necessary.

The cricothyrotomy procedure described in Table XXXII apparently minimizes the risk of hemorrhage from the cricothyroid arteries (119). The risks of perichondritis of the cricoid, conus elasticies injury or laryngeal stenosis apparently are small and are minimized when the cricothyrotomy is closed within 24 hours (119).

Insertion of large needles into the airway usually does not provide adequate ventillation, unless several are used, and do not significantly facilitate assisted ventillation.

Bronchial dysfunction. If general measures fail to reverse lower airway dysfunction, aminophylline is administered. In subjects not on theophylline therapy an initial dose of 6 mg/kg of body weight is given I.V. over 20 minutes, followed by an infusion of 0.9 mg/kg/hour. If theophylline blood level measurements are available, the concentration should be maintained between 10 and 20 µg/ml of plasma. The appearance of nausea, vomiting or cardiac rhythm disturbances may indicate that toxic levels of theopylline have been achieved. Aminophylline infusions should be halted until signs of toxicity remit. Patients who are being treated with theophylline for asthma should receive lower doses during anaphylaxis. Blood levels of theophylline are an especially important adjunct to selecting the rate of infusion in these patients. In the absence of this information 3 mg/kg of aminophylline I.V. over 20 minutes usually can be administered followed by 0.9 mg/kg/hr. If general measures and intravenous aminophylline are not sufficient to reverse bronchoconstriction, aggressive management as status asthmaticus, including intubation and assisted ventilation, should be instituted.

Hypotension. Loss of perfusion pressure during anaphylaxis can result from loss of peripheral vascular resistance, diminished cardiac return resulting from peripheral vasodilation, shift of intravascular fluid to the extravascular space through increased vascular permeability, and cardiac dysfunction (see below). If general treatment of anaphylaxis does not promptly restore blood pressure, salt-containing fluid such as normal saline should be given rapidly up to 100 ml/minute to a limit of 3 liters. If the blood pressure becomes normal, the rate of fluid administration may be reduced. A decision to deliver more fluid, rapidly, should be governed by the patient's age, cardiovascular status, and urine output. A pressor agent may be needed if fluid administration fails or if the hypotension is profound. Fluids should be given in parallel with the use of pressors in this situation. Dopamine has been ineffective in several cases of anaphylaxis. This may reflect unexpected effects on the anaphylactic process - Dopamine enhances mast cell mediator release in some species (120) and has not yet been examined in man. Norepinephrine has repeatedly proven effective in anaphylaxis,

TABLE XXXI

Cricothyrotomy

Potential Advantages

* Cricothyroid membrane is directly under the skin.
* A minimum of equipment and dissection is needed.
* Considerably faster than tracheotomy.
* Ventillation through endotracheal tube feasible.

Potential Complications

* Hemorrhage from cricothyroid arteries.
* Perichondritis of cricoid.
* Laryngeal stenosis.
* Damage to the conus elasticus with permanent voice changes.

TABLE XXXII

Cricothyrotomy Procedure

1. Extend the head.
2. Locate cricoid cartilage.
3. Make a small transverse incision in the skin in the anterior one-third of the cricothyroid space just above the upper border of the cricoid cartilage.
4. Puncture the cricothyroid membrane in the midline.
5. Enlarge the opening laterally with blunt dissection.
6. Insert a no. 6 (adult women) or a no. 7 (adult men) endotreacheal tube.

when hypotension responds to pressor agents, and appears to be the pressor of choice. This agent should be diluted to 4 µg/ml (4 ml of a 1 mg/ml solution in 1000 ml of D_5W). The initial dose for adults is 8 to 12 µg/minute (2 to 3 ml/minute) by intravenous infusion. The infusion rate should be adjusted to sustain a systolic blood pressure of 80-100 mm Hg. Previously hypertensive subjects may require higher pressures, but the systolic pressure should be 40 mm Hg or more below the patient's usual systolic pressure. Infusion rates of 2 to 4 µg/minute usually will be appropriate. Conventional precautions should be taken to avoid or to treat extravasation of the drug.

When fluids, pressors, and positive inotropic agents (see below) fail to restore blood pressure, administration of an H_1 antihistamine (100 mg of diphenhydramine IV in an adult) and the H_2 blocking agent cimetidine (300 mg I.V. over 5 minutes in an adult) should be considered. Concurrent blockade of H_1 and H_2 receptors appears to be necessary for optimal reversal of the effects of histamine on blood vessels. These agents also may block deleterious effects of histamine within the myocardium.

Cardiac dysfunction. Dysrhythmias and diminished force of cardiac contraction may appear during anaphylaxis (See above). Rhythm disturbances may arise from the effects of intracardiac mediator release, actions of intravascular mediators, hypoxia, hypotension, or the effects of epinephrine or other drugs. Electrocardiographic monitoring will reveal such disturbances. Conventional therapy for ventricular dysrhythmias can be instituted in concert with general measures to suppress anaphylaxis. Occasionally the hypotension appearing during anaphylaxis does not respond to the administration of fluids or vasopressors, but does respond to treatment with positive inotropic agents: epinephrine infusion (as described above) or isoproterenol infusion (1 mg in 500 ml of D_5W -2 µg/ml- infused at 0.5 to 5 µg/minute for adults). Refractory hypotension may reflect myocardial infarction occurring as a complication of anaphylaxis.

Management of anaphylaxis after the life-endangering phase is controlled. A second phase of drug-induced anaphylaxis, a resurgence of the reaction 4 to 10 hours after the initial reaction, is detectable in a substantial number of patients. Patients should be observed at least 12 hours after the onset of the reaction. Since glucocorticoids can suppress the second phase of experimental immediate hypersensitivity reactions in the human lung, skin and nose, these agents are given in an attempt to suppress recurrent anaphylaxis. Intravenous methylprednisolone (80 mg in an adult) or its equivalent should be administered when the initial reaction is controlled. A second and final dose, 60 mg of oral prednisone or its equivalent, should be given 6 hours after the first corticosteroid dose.
Once the acute manifestations have been suppressed as noted above, additional medication usually is not needed.

Patients who have been severely hypotensive or hypoxic should be evaluated for possible myocardial, renal or central nervous system complications.

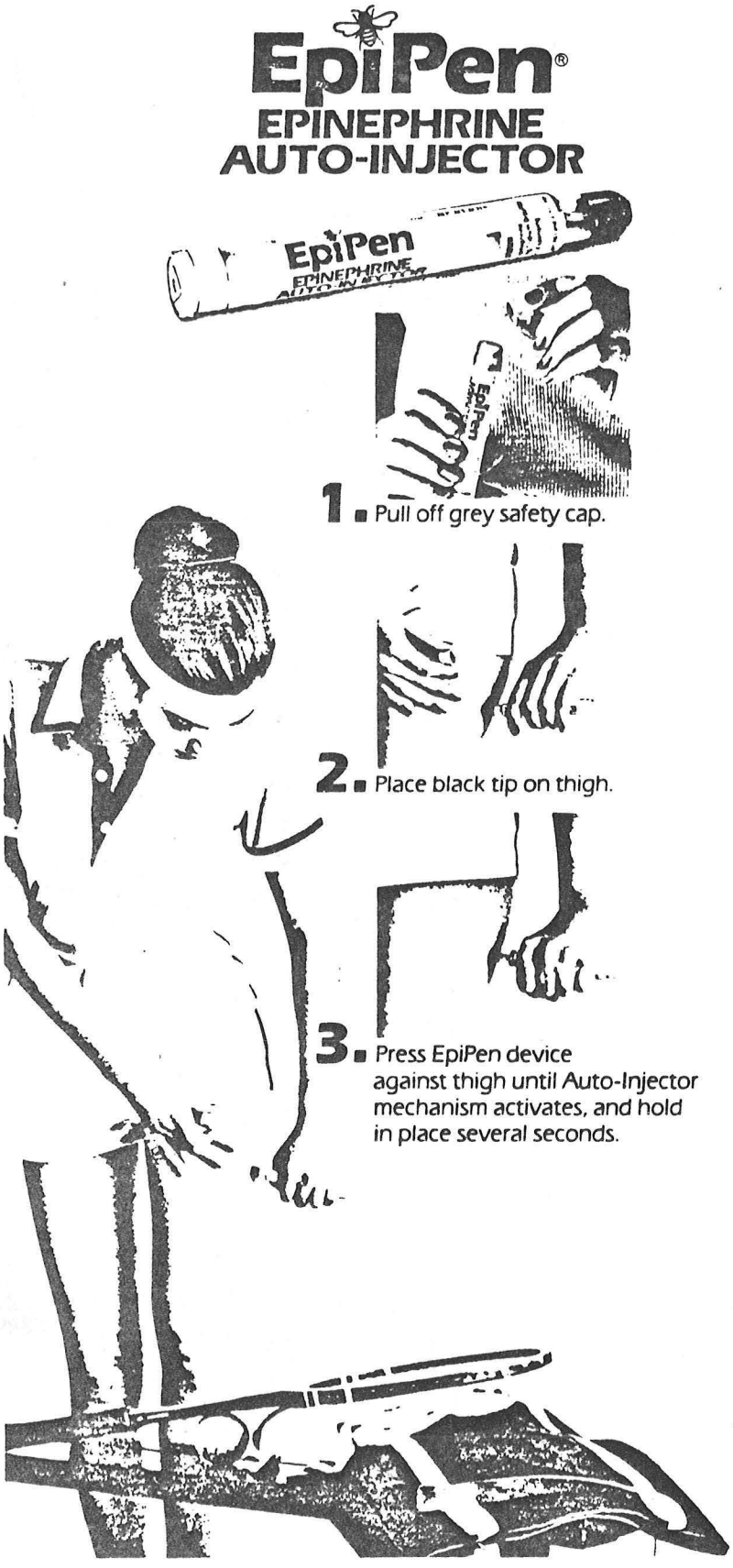
AVOIDANCE OR CONTROL OF ADDITIONAL EPISODES OF ANAPHYLAXIS

- General Measures -

Patients should be evaluated thoroughly to determine the cause of an episode of anaphylaxis. As noted above, plans should be formulated to avoid or minimize future reactions with specific maneuvers being selected on the basis of the apparent cause of the anaphylaxis. When recurrent anaphylaxis is possible outside of a hospital setting (insect stings, food, exercise, mastocytosis, etc.), the patient should be equipped with 1.) self-injectable epinephrine and with 2.) some form of medic alert device.

Several forms of self-injectable epinephrine are available. At Parkland Memorial Hospital Epi Pens are available (Figure 15). This device is ultimately simple to use and will inject through most clothing. In order to contend with a possible need for a second injection before reaching a medical facility, two Epi Pens usually are prescribed. Treatment with Medihaler-Epi does not achieve satisfactory systemic levels of epinephrine and probably should be avoided for this reason. Other kits, such as the Ana-Kit, are available that require self-injection without a spring loaded assist, a handicap, but that do permit injection of a second dose of epinephrine. The patients should be carefully educated about the steps to be taken in the event of anaphylaxis, the indications for epinephrine, and methods of administration. Teaching Epi Pens are available and patients can be taught to make subcutaneous injections with syringes if self injection is selected. The patient should not have to read directions at the time an injection is required.

A prominent card or piece of paper carried in a wallet or purse stating the nature of the anaphylactic sensitivity can be lifesaving. Formal methods for alerting medical personnel or others to the existence of anaphylactic sensitivity are depicted in Figures 16 and 17. A relatively inexpensive form of emergency medical identification and the more thorough Medic Alert systems are presented. These or similar approaches should be taken to alert medical personel to the nature of a problem or to avert a problem when a patient can not provide a history.


EpiPen®
EPINEPHRINE
AUTO-INJECTOR
EpiPen
EPINEPHRINE
1. Pull off grey safety cap.
2. Place black tip on thigh.
3. Press EpiPen device against thigh until Auto-Injector mechanism activates, and hold in place several seconds.

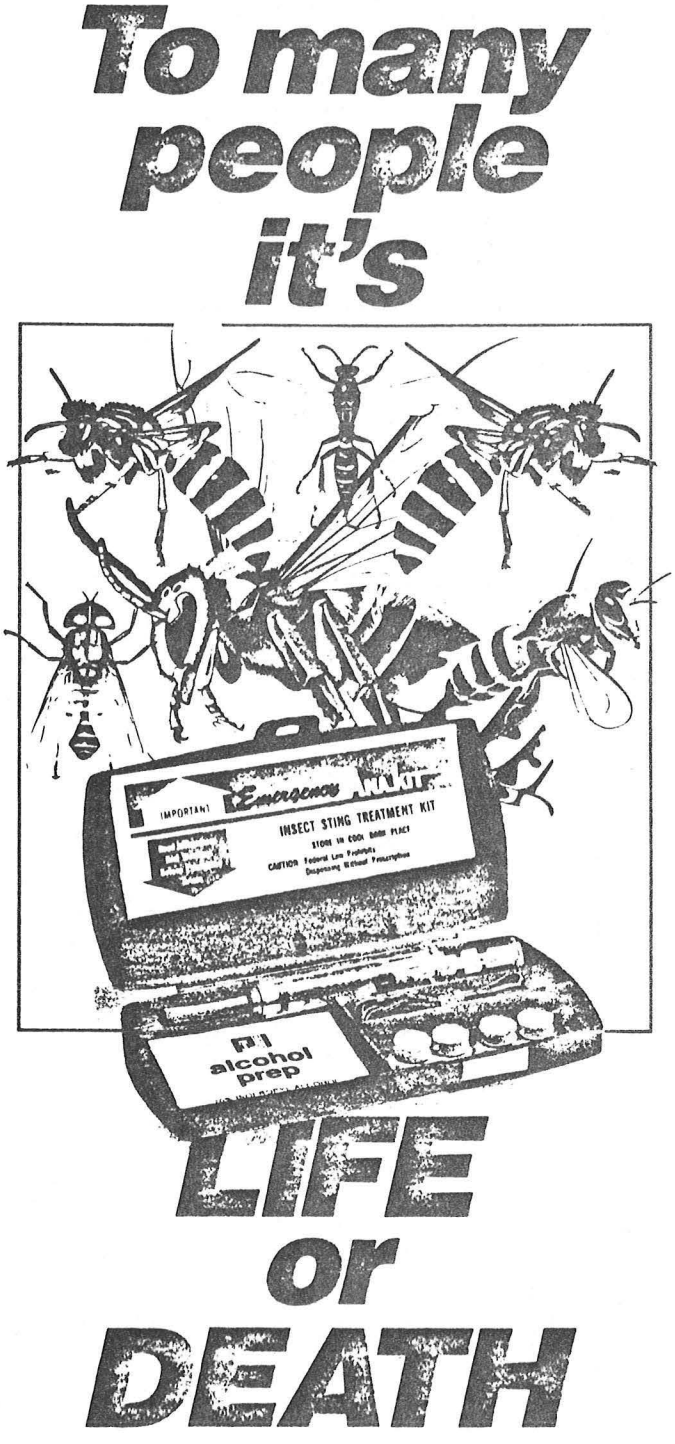

To many people it's
IMPORTANT
INSECT STING TREATMENT KIT
#1 alcohol prep
LIFE or DEATH

Figure 15

Medic Alert Enrollment Form

Print or type clearly. If you have any questions about this form, call Medic Alert: 1-800-344-3226. In California: 1-209-668-3333.

Figure 16

Are you already a Medic Alert member? ☐Yes ☐No
If yes, enter your membership number:

Last Name First Middle

Mailing Address

City State Zip

Street Address If Different

Telephone Area( )- Birth Date

Social Security Number ☐ Male ☐ Female

Relative or Person to Notify in Emergency

Street Address

City State Zip

Telephone Area( )-

Physician's Name

Street Address

City State Zip

Telephone Area( )-

Medical Conditions to be Engraved on Emblem

Engraving space is limited by size and type of emblem. Small bracelet: limit 60 spaces. Standard bracelet: limit 90 spaces. Necklace: limit 95 spaces. Always leave one space between each word. Blood type, religion and desire to be an organ donor may also be engraved in these spaces. Additional information will follow regarding arrangements to ensure that organ donor wishes are carried out. It may be necessary for Medic Alert to restructure information to fit on the emblem and to use standard medical terminology and abbreviations.

Check Style and Metal of Emblem Needed

If no style is requested, we send standard bracelet. Fee includes Lifetime Membership. Gold and silver prices guaranteed to 12-31-82.

Standard Bracelet ☐ Small Bracelet ☐
Necklace (with 26" chain ☐
Size of wrist to nearest ¼ inch_____
Stainless Steel $15.00 ☐ Sterling Silver $30.00 ☐
Heavy Gold Plated $38.00 ☐

(1) (10) (20)
(30) (40) (50)
(60) (70)
(80) (90) (95)

Other Emergency Information (additional medical conditions, medications, other doctor, other person to notify, etc.)

Important: The member agrees not to wear the emblem or carry the wallet card until the emergency record has been carefully reviewed to ensure it is correct. The member agrees to inform Medic Alert in writing of any error. The member authorizes Medic Alert to relay this information in response to emergency telephone calls requesting medical information.

Signature of Enrollee or Parent/Guardian

Physician's signature (optional)

Sponsor Code 643

Total Fee (tax deductible medical expense).... $_____

Contribution (tax deductible)..... $_____

Total Amount Enclosed..... $_____

☐ check ☐ money order

CHARGE CARD
VISA ☐ MASTERCHARGE ☐

Credit Card Account Number_____

Expiration Date_____

Normal delivery time is four weeks. Send check or money order to: Medic Alert, P.O. Box 1009, Turlock, CA 95381-1009.

Mail to **Health Enterprises, Inc.** Dept. 2.
15 Spruce Street, North Attleboro, MA 02760
Toll Free 1-800-225-2148 (Mass res. 695-0727)

Date Mailed _____ Amount Sent $ _____
Normal Delivery is 10 Days No Telephone Orders
I D Ordered Bracelet ☐ Chain ☐ Expansion or ☐ Necklace

YOUR RECEIPT DETACH AND RETAIN

ORDER FORM
Emergency Medical I.D.

- **Beautifully Polished Stainless Steel ID's with Raised Red Alert Symbol**
- **Jewelry Quality Engraving**
- **FREE Plastic Medical History Wallet Card with Each ID ($1.59 Value)**

WHEN AN EMERGENCY STRIKES,
YOUR MEDIC WARNING™ ID
WILL COME INTO ACTION ON THE SCENE
PROVIDING MEDICAL FACTS

EXAMPLE OF MEDICAL DATA

Heart Patient Diabetic On Anticoagulant Contact Lens Penicillin Algy Epilepsy

LIST YOUR MEDICAL PROBLEM TO BE ENGRAVED
Medications — Doctor Name, Telephone Number

ENGRAVING $1.00 PER LINE

INFORMATION TO BE ENGRAVED ON ID

(ENGRAVING — 5 LINES MAXIMUM) Include (area code) in Phone No.

CHECK ONE

$ ☐ Necklace ☐ Fine Chain Bracelet ☐ Heavy Chain Bracelet **$4.95**

Deluxe Expansion Wrist Bracelets

		*Wrist Size	
$	☐ Long	7" - 8½"	**$7.95**
	☐ Regular	6¼" - 7"	
	☐ Short	5¾" - 6¼"	

$ ____ Lines Engraving @ $1.00 Per Line

$ _____ Total

Mail Check or Money Order payable to Health Enterprises

YOUR NAME _____

ADDRESS _____

CITY _____ ZIP _____

*Circle wrist with string and measure Normal Delivery is 10 Days

Figure 17

The best emergency medical identification system in the world.

63

Only Medic Alert offers complete lifetime protection.

Tragic or fatal mistakes can be made during emergency medical treatment if hidden medical conditions are not recognized. Of the more than 200 common conditions, severe allergies, diabetes, heart trouble, hypertension and epilepsy are just a few. If you, or someone you know, has such a condition - then Medic Alert can help.

Medic Alert signals 3 ways.

1. The Medic Alert emblem, worn as a bracelet or necklace, is engraved on the back with your special medical condition. It identifies you immediately in an emergency and speaks for you -- if you can't. Emergency and health care personnel are trained to look for this emblem.
2. Also engraved on the emblem is a special "call collect" number that provides instant access to your emergency medical records and the names of physicians or relatives to be contacted. This 24-hour emergency answering service is on call 365 days a year.
3. Medic Alert members also carry a wallet identification card that contains additional personal and medical information. This card is re-issued annually.

$15 for a lifetime of protection.

Medic Alert membership costs just $15 for life (there is a nominal charge if records need updating or for emblem replacement). This one-time charge includes the cost of your Medic Alert emblem - plus 24-hour protection for the rest of your life. This $15 could be the most important investment you ever make.

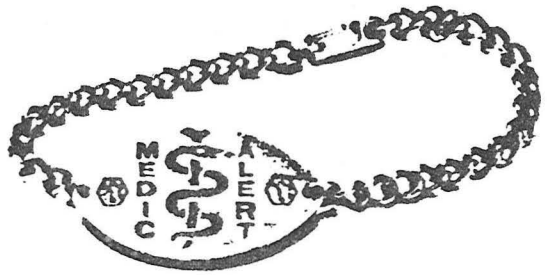
Non-medical reasons for Medic Alert protection.

Many people wear a Medic Alert emblem and carry the Medic Alert wallet card if they're frequent travelers, joggers or scuba divers. They are worn by organ donors, people who encounter hazardous situations in their jobs, live alone, or have any other special condition that should be known in an emergency.

Medic Alert protection is especially important when you're away from home - or in a foreign country where you may not speak the language. The Medic Alert emblem bears the symbol of the medical profession and is recognized all over the world. Just one collect phone call can put a medical person in touch with people and physicians who know you -- anytime, and from anywhere in the world.

Your membership is confidential.

Medical conditions, no matter how common, still remain a personal and very private matter - between you and your physician. That's why all information in your Medic Alert file is kept strictly confidential -- and is released only in an emergency when your membership number is given.



The Medic Alert emblem instantly conveys the member's special message.

20 good reasons for joining Medic Alert

Allergic to codeine	Heart condition
Allergic to insect stings	Hypertension
Allergic to morphine	Hypoglycemia
Allergic to penicillin	Implanted pacemaker
Arthritis	Mental retardation
Asthma	Neck breather
Diabetes	On hemodialysis
Emphysema	Organ donor
Epilepsy	Takes anticoagulants
Glaucoma	Wears contact lenses

How to become a member.

To start receiving Medic Alert protection, first select a Medic Alert emblem (examples shown below). Then fill out the enrollment form on the reverse side of this pamphlet.

Selecting an emblem: The Medic Alert emblem may be worn as a bracelet or necklace. Medic Alert recommends the bracelet as the more effective alerting device. Your $15-membership fee includes the cost of a stainless steel emblem. Emblems are also available for additional cost in sterling silver and gold-filled with 23 karat heavy gold plate.

Standard Bracelet (actual size)

Small Bracelet

Necklace with 26" chain

Engraved on the reverse of the emblem are your medical conditions and the Medic Alert 24-hour collect phone number.

SUMMARY

Systematic studies of experimental anaphylaxis led to the identification of the IgE class of antibody, to the recognition of the role of mast cells, to the recognition of the mediators of immediate hypersensitivity, and to a realization that massive mast cell mediator release causes the bulk of what is called clinical anaphylaxis. More recently diverse non-immunologic causes of anaphylaxis have been defined. We are on the threshold of having an array of mediator assays available to supplement clinical parameters in the assessment of mast cell activity and the impact of therapeutic strategies. Use of existing knowledge of avoidance and treatment would markedly reduce the morbidity and mortality of anaphylaxis. As knowledge of IgE and mast cell mediator release reactions progresses we should one day be able to regard anaphylaxis as an historical curiosity, as it began.

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