

Anaphylactoid Reactions to Intravenous Solutions Used for Volume Substitution

Johannes Ring

*Universitäts haut Klinik und Allergie abterling, Universitäts Kraukenhaus
Eppendorf, Martinistr. 52, 2000 Hamburg 20, Germany*

INTRODUCTION

The shortage of donor blood and the risk of blood transfusion (3,50,53,83) have led to an increased use of iv volume substitutes in clinical medicine (20,50,67). The most commonly used solutions are either crystalloid (electrolyte and so on), or colloid in nature; the most commonly used colloid volume substitutes are plasma proteins, dextran, gelatin, and hydroxyethyl starch (HES). Work in progress includes other solutions, such as stroma-free hemoglobin or perfluorocarbons (49,82). Colloid solutions are not only used for volume displacement, but some of them—such as dextran—are also recommended for thromboprophylaxis as well as in the treatment of microcirculatory disorders. Every iv infusion goes along with a certain risk of possible local or systemic reaction (15,37,38,44,44a, 50,54,68,74,90–92,94) (Table 1). Transmission of infectious diseases does not seem to play a role in artificial colloid solutions and crystalloids, but has to be discussed for some plasma components, such as factor VIII. One of the most dramatic potential and life-threatening complications of iv volume substitution is the occurrence of an anaphylactoid reaction.

Table 1
General Risk of Intravenous Infusions

Trauma of venepuncture
Pain
Hematoma
Extravasation (inflammation, necrosis)
Air embolism
Pneumothorax
Catheter in wrong place
Fragmentation of catheter
Reactions to intravasal material
Phlebitis
Thrombosis
Embolism
Infused solution
Particulate matter (e.g., fibers, glass, rubber)
Infection
Chemical contamination
Adsorption to glass or plastic
Chemical or therapeutic incompatibility
Anaphylactoid reaction

CLASSIFICATION

In this context, the term “anaphylactoid” describes the clinical signs and symptoms of a reaction resembling a classical anaphylaxis (regardless of the pathomechanism involved) (67). This is a merely clinical term; it seems important to stress this fact, since the elucidation of the pathophysiology is often not possible or only successful after several weeks of laboratory studies have proven an immunological sensitization.

Anaphylactoid reactions can be graded according to their severity using a scale published previously (Table 2) (66). The clinical symptoms of anaphylactoid reactions to volume substitutes comprise a variety of symptoms ranging from skin manifestations only to major respiratory and cardiovascular problem (16,28,35,56,71,76,77,86,87), as shown for the symptomatology of 208 patients reacting to iv dextran (Table 3) (67).

Table 2
Classification of Anaphylactic/Anaphylactoid
Reactions According to Severity of Symptoms^a

Grade	Skin	Gastrointestinal	Respiratory	Cardiovascular
I	Urticaria, flush, and so on	—	—	—
II	Urticaria, flush, and so on	Nausea	Dyspnea	Tachycardia ($\Delta > 20/\text{min}$), hypotension, ($\Delta > 20 \text{ mm}$ Hg systolic)
III	Urticaria, flush, and so on	Vomiting defecation	Bronchospasm cyanosis	Shock
IV	Urticaria, flush, and so on	Vomiting defecation	Respiratory arrest	Cardiac arrest

^aAccording to Ring and Messmer (67).

Table 3
Symptomatology of 208 Patients Suffering
from Anaphylactoid Reactions to Dextran Infusions^a

Symptoms	Incidence, %
Skin	
Local irritation of vein	3
Urticaria and/or flush	61
Fever	6
Respiratory	
Dyspnea	38
Respiratory arrest	15
Gastrointestinal	
Nausea	29
Vomiting	12
Defecation	3
Cardiovascular	
Tachycardia	57
Hypotension	48
Hypertension	2
Shock	33
Cardiac arrest (died)	15(6)

^aAccording to 68.

Myocardial involvement in severe anaphylactoid reactions may be primary or secondary (20,57,67,81). Characteristic clinical features specific for single colloids will be discussed later.

FREQUENCY OF ANAPHYLACTOID REACTIONS TO VOLUME SUBSTITUTES

Anaphylactoid reactions can occur after all available volume substitutes. The frequency in comparison among the different agents is a continuing matter of controversy. Striking discrepancies have been observed between different studies regarding incidences reported between 0.0004% and an alarming 30.0% (67,70a,84) (Table 4). Generally, retrospective studies show lower frequencies than prospective studies, which seems to be almost a statistical law!

Results of a prospective multicenter trial performed in Bavaria, when anaphylactoid reactions were registered for the total of 200,906 infusion units, revealed a total incidence of 0.034% (66) (Table 5). There was no influence of geographic location, medical specialty, type of hospital, season of the year, age, or sex of the patients upon the incidence of anaphylactoid reactions to the colloids under study.

However, it became evident that the severity of the anaphylactoid symptoms increased with increasing age of the patients. Similar findings have been observed by other authors (25).

In the following, the specific characteristics and possible pathomechanisms of anaphylactoid reactions to the various types of infused solutions will be discussed.

CRYSTALLOID SOLUTIONS

Single cases of anaphylactoid reactions have been reported after infusion of crystalloid solutions and were mostly regarded to be caused by high-mol wt contaminants present in these infusions (60,67). The presence of small particles (10–30 μ), is common in crystalloid or colloid solutions. Some of these solutions also contain preservatives, such as benzyl alcohol or sulfites, which might elicit anaphylactoid reactions in susceptible individuals (22,39,55,78,80,85). Furthermore, the presence of chemical contami-

Table 4
Frequency of Anaphylactoid Reactions to Dextran
and Gelatin in Various Studies in the Literature

	Design of the study	Incidence referred to	n ^a	Total incidence, %	Reference ^d
Dextran					
Dx75	r ^b	Units	458.924	0.009	Beez and Dietl (1979)
Dx70	r	Units	488.748	0.025	Ljungström (1983)
Dx70	r	Patients	13.434	0.074	Bauer and Östling (1970)
Dx70	r	Patients	6.365	0.1	Adorján, Barna, and Hargitay (1978)
Dx (mol wt?)	r	Units(?)	6.980	0.1	Langrehr, Singbartl, and Neuhaus (1975)
Dx70	p ^c	Patients	1.993	1.1	Guber et al. (1980)
Dx70	r	Patients	603	0.83	Flaaten (1982)
Dx60	p	Patients	150	4.7	Schöning and Koch (1975)
Gelatin					
Modified fluid gelatin	r	Units	102.787	0.064	Lundsgaard-Hansen and Tschirren (1980)
Gelatin (specified?)	r	Units (?)	37.350	0.278	Langrehr, Singbartl, and Neuhaus (1975)
Oxypolygelatin	r	Patients (?)	31.110	1.3	Schmidt and Rieber (1980)
Urea-linked gelatin	p	Patients	1.147	0.78	Weis (1983)
Oxypolygelatin	p	Patients	707	8.2	Schmidt and Rieber (1980)
Urea-linked gelatin	p	Patients	150	30.0	Schöning and Koch (1975)
Oxypolygelatin	p	Patients	150	18.7	Schöning and Koch (1975)
Modified fluid gelatin	p	Patients	150	15.3	Schöning and Koch (1975)

^an = units of infusion or patients.

^br = retrospective study.

^cp = prospective study.

^d = quoted in 70a.

Table 5
Frequency of Anaphylactoid Reactions
Owing to Colloid Substitutes in Bavaria*

Colloid	Units infused	Anaphylactoid reactions	Incidence, %
Plasma protein			
Serum solutions	25,582	5	0.020
Human serum albumin	60,048	7	0.012
Dextran			
Dextran 60/75	34,621	24	0.069
Dextran 40	51,261	4	0.008
Gelatin			
Urea-linked gelatin	6,151	9	0.146
Oxypolygelatin	810	2	0.246
Modified fluid gelatin	6,028	4	0.066
Hydroxyethyl starch	16,405	14	0.085
Total	200,906	69	0.034

*Calculated per infusion units used (From 67).

nations by trace elements, such as chromate or nickel, could theoretically give rise to untoward reactions, e.g., hematogenous contact eczema in allergic individuals.

PLASMA PROTEIN SOLUTIONS

Anaphylactoid reactions (even fatalities), have been described after infusion of plasma protein derivatives, including human serum albumin, plasma factors, prothrombin, immunoglobulins, and so forth (5,7,15,30,36,53,63,64,66,69,69a,70a,72,75). The pathomechanisms of many of these reactions are not clear.

Allergic sensitization against protein determinants may play a role in some individuals, especially against xenogeneic proteins. In certain conditions, it was possible to induce immunological tolerance by pretreatment with highly purified monomeric xenogeneic proteins (8,65,67).

There are rare cases of true allergic reactions against allogeneic protein determinants (e.g., against IgA in patients with IgA deficiency) (40). However, long-term substitution with IgG containing small amounts of IgA did not lead to life-threatening complications in patients with selective IgA deficiency (89a).

Apart from IgA, allotypic antigens of the Gm type may be responsible for sensitization (17). Antialbumin autoantibodies have been described in various clinical conditions (21).

During the production, human serum albumin is heated for over 10 h at 60°C for inactivation of possible viruses (19,79). This process can lead to the formation of protein aggregates. In order to prevent this, stabilizing substances are added, most frequently caprylate and acetyltryptophan. In some individuals, an autoagglutination of red blood cells is found in the presence of caprylate-stabilized albumin. Others have found caprylate-dependent autoantibodies (quoted in 72). Patients with positive skin test reactions against caprylate-stabilized albumin suffering from anaphylactoid reactions after albumin infusion have been reported (68).

However, in the majority of the cases, pseudoallergic mechanisms seem to elicit the clinical symptoms. Protein aggregates present in almost all of these solutions in varying amounts have been demonstrated to produce anaphylactoid reactions in nonsensitized dogs (67). These protein aggregates can either contain IgG or IgM, or can only reflect a polymerized albumin.

Some authors stressed the role of kallikrein-kinin-like substances, which have been found in some plasma protein solutions (2,26,31,48). A rather rare event can be seen in severe anaphylaxis occurring after plasma or blood transfusion from donors with IgE-mediated allergy and later following allergen application in the host, e.g., foods such as fish or drugs such as penicillin (12).

There is a remarkable difference among several albumin batches. Therefore, some solutions produced by the classic cold ethanol technique have been found to induce histamine release from peripheral leukocytes (73).

DEXTRAN

Clinically used dextran solutions are produced by the bacterium *leuconostoc mesenteroides* (strain NRRL B 512), and contain about 95% α -1-6 glycosyl linkages with a mol wt range between 40,000–75,000, which has been found to be nonimmunogenic in most experimental models and clinical settings studied (62). It has to be stressed that, under clinical conditions, a tremendous amount (up to 100 g), of dextran is given intravenously, most likely produc-

ing immunological unresponsiveness in the sense of a "high-zone tolerance."

As a typical polysaccharide with repetitive structure, dextran induces a thymus-independent antibody response most prominently of the IgM class and has been found to be a polyclonal B-cell activator. By coupling to a protein, dextran can be converted to a thymus-dependent antigen, giving rise to IgG antibodies (62,58). Clinical dextran does not induce mitogenic effects in human lymphocyte cultures *in vitro* (67).

Although anaphylactoid reactions to dextran have been regarded for a long time as typical examples of pseudo-allergic reactions on the basis of animal experiments, where dextran has been found to be a direct histamine liberator and inducer of anaphylactoid reactions in certain rat strains (23), today severe DIAR is classified as "immune complex anaphylaxis" resulting from a high titer of dextran-reactive antibodies in individual patients (25,62,67). There was a direct positive correlation between the antibody titer and the intensity of the clinical symptoms (24,61,67). Patients suffering from severe reactions showed significantly higher DRA titers than normal individuals. The relevant antibodies were shown to belong to the IgG class and, most likely, to the IgG2 subclass (29,41). There was no evidence for involvement of IgE-mediated reactions in extensive serologic and PCA studies (25,29,62).

Complement studies in the sera of patients with severe DIAR indicated activation via the classical pathway (24,25). Autopsy findings revealed prominent occlusion of pulmonary vessels similar to changes in severe immune-complex anaphylaxis in monkeys (57,81).

The origin of dextran-reactive antibodies in humans is not yet clearly known. The infusion of clinically used soluble dextran obviously does not play a role (67). It is more likely that crossreactivity with bacterial wall antigens is crucial.

Based on these immunopathological findings, hapten inhibition was used in an attempt to prevent these reactions; promising results had been reported *in vitro* (33,34), and in several animal experiments in guinea pigs and in dogs (8,59,61,63). In extensive clinical trials in several European countries, it was shown that the frequency and intensity of anaphylactoid reactions were decreased significantly by prior administration of low-mol-wt dextran (dextran 1000), as a hapten (42,43,52,63a; Table 6). By applying the

Table 6
Results of Experimental Clinical Studies Using Hapten Inhibition
for Prophylaxis of Dextran-Induced Anaphylactoid Reactions^d

Species	Study	Immune reaction, type ^b	Hapten administration	Effect reaction ^a /total
Guinea pig	Hoene et al., 1961 (31)	III (passive)	Pretreatment	1/10
	Richter, 1971 (64)	I (active)	Pretreatment	2/12
Dog	Seemann et al., 1978 (84)	III (active)	Pretreatment	1/27
		III (active)	Admixture	2/18
(awake)	Schwarz et al., 1981	III (active)	Pretreatment	1/10
		III (active)	Admixture	5/7
Humans	Laubenthal et al., 1981 (41)	III	Pretreatment, 10 mL	2/5,920
		III	Pretreatment, 20 mL	2/24,513
	Ljungstrom, 1983 (43)	III	Pretreatment, 10 mL	7/29,252
		III	Pretreatment, 20 mL	0/6,121
		III	Admixture, 20 mL	2/5,939
	Gruber et al., 1982 (20)	III	Pretreatment, 20 mL (10 mL)	0/701
	Watzek et al., 1981 (93)	III	Pretreatment, 20 mL (10 mL)	1 ^c /531

^aSevere reactions (grades III and IV).

^bIII = immune complex reaction: I=IgE-mediated reaction.

^cOccurred after pretreatment with 10 mL of hapten dextran.

^dQuoted in (70a).

principle of hapten prophylaxis, it was found that the risk of a severe DIAR was lowered by 15–45×, depending on the study involved (42,43,63a).

Meanwhile, more than 2,000,000 persons have been treated with dextran and hapten prophylaxis. There have been cases of DIAR in spite of hapten inhibition. In all of these cases, extremely elevated titers of dextran-specific IgG were found in the serum samples (62). One patient undergoing sepsis died from dextran anaphylaxis with a specific IgG antibody titer of 1:1,600,000 (corresponding to 2.4 mg specific IgG per mL serum (63a). It may be speculated that in these

rare cases with extremely high grades of sensitization, the amount of monovalent hapten is simply not enough to exert the prophylactic inhibitory effect. When comparing the risks and benefits of dextran and hapten prophylaxis, one should have in mind that, by the beneficial effect of thromboprophylaxis, in Sweden in a 2-yr period, some 200 patients probably were protected from fatal lung embolism (63a).

In many European countries, the application of dextran without hapten prophylaxis is no longer in use. It is recommended that, at least 2 min prior to each first infusion of dextran, 20 mL of monovalent hapten dextran (15%), have to be given. If the patient receives several infusions of dextran on the same day or on subsequent days, a renewed hapten prophylaxis is not necessary. However, when the interval between two dextran infusions exceeds 48 h, a new preinjection of hapten dextran is recommended (43).

The concept of immune-complex anaphylaxis and its prophylaxis by hapten inhibition holds true only for the severe (Grade II–IV) types of reactions. There are some mild anaphylactoid reactions (flush, subjective symptoms, and so on), with no antibody involvement, where pseudoallergic reactions might play a role (62,67).

GELATIN

Clinically used gelatin solutions are produced by hydrolysis of collagen and chemical modification in mainly three ways, succinylation (modified fluid gelatin), by crosslinking with glyoxal and subsequent degradation by oxidation and heating (oxypolygelatin), or by crosslinking with hexamethylene diisocyanate (urea-linked gelatin). Urticaria is the most frequent symptom of gelatin-induced anaphylactoid reactions. In some studies with careful observation, an incidence of up to 30% was observed (45,67). The differences in preparation may play a role regarding the pathophysiology of anaphylactoid reactions resulting from gelatin.

Urea-linked gelatin has been shown to be a direct histamine releaser (51). These results were confirmed in many clinical studies, where increased plasma histamine concentrations after rapid infusion of gelatin were measured (45). This effect seems to be batch-

dependent and may be connected with an excess of diisocyanate in some of the solutions (13,47). With improved purification procedures, the amount of free diisocyanate in gelatin (hemacel), was reduced considerably; in parallel, the frequency of anaphylactoid reactions to this new polygeline solution decreased considerably (93). Furthermore, the possibility of immunologic sensitization against isocyanates has been discussed, since IgE-mediated reaction against isocyanates can be measured in people working with this substance (4).

Anticollagen antibodies have also been described in human sera, especially in patients with rheumatic diseases (1). The presence of these antibodies, however, does not seem to correlate with the occurrence of anaphylactoid reactions to gelatin. However, in single observations, a decrease of an elevated titer of antigelatin antibodies parallel to a clinical incompatibility reaction has been reported (68).

Positive *in vitro* histamine-release reactions after incubation of peripheral basophiles with modified fluid gelatin have been reported and argued for an immunologically mediated mechanism (88). The same authors also reported positive skin tests with a 1:1000 solution of modified fluid gelatin.

Gelatin can also be used as an alternative macromolecular agent for centrifugal leukapheresis; here, a slightly higher reaction rate (mild urticarial symptoms, sneezing, and rhinitis), was observed compared to HES (27). Since histamine has been shown to be the predominant mediator of gelatin-induced reactions (13,45,51), prophylactic pretreatment with histamine antagonists has been recommended. By using a combination of H_1 and H_2 antagonists, the reaction rate was significantly reduced in several studies (46,47,47a).

Of special interest is a case report of an anaphylactoid reaction after gelatin infusion in an individual with another episode of anaphylaxis after having eaten a gummy bear made out of gelatin. Here, specific IgE antibodies against gelatin were detected (89). However, in several other patients with severe anaphylactoid reactions to gelatin infusions, no specific IgE against gelatin was detected (cooperation with R. Wahl, unpublished).

HYDROXYETHYL STARCH (HES)

Severe anaphylactoid reactions have been observed after HES infusion (65). The pathomechanism of these reactions is by no means clear. Some of the authors described decreases in complement factors that, however, were similarly detected in people tolerating the HES infusion (68). Antibodies against HES have been produced in animals (60), and detected in the sera of normal human subjects. The relevance of these anti-HES antibodies is not clear. In one patient with a fatal HES reaction, no antibodies were detected (68).

There are several problems rather specific for HES: sometimes during infusion, an intense local irritation along the infused vein occurs, which sometimes mimics thrombophlebitis (68). Occasionally, in a patient, the clinical course of the reaction may be very prolonged with a slow onset and a long-lasting bronchospasm. These observations have raised speculations about the involvement of eicosanoids (11,14,16,78).

The infusion of HES leads to an increased concentration of serum amylase, which is generally without clinical relevance, but might give rise to differential diagnostic considerations, if not known (32). Maybe the greatest problem with HES is its prolonged intravascular persistence, and possible storage in the liver and reticuloendothelial system, especially after repeated infusions when, for instance, used for leukopheresis or granulocyte collection (70).

After a 10-d course of HES therapy, some people exhibit an intense pruritus sine materia. We tested three patients with this condition with HES (prick and intradermal), together with serum antibody determination, with negative results.

STROMA-FREE HEMOGLOBIN SOLUTIONS

An elegant way of producing an ideal blood substitute would be to use oxygen carriers, such as hemoglobin. The major problem consists of the presence of stroma, which may give rise to severe disturbances of kidney function and blood coagulation as well as porphyria-like symptoms (82).

Therefore, an attempt was made to couple a colloid to the hemoglobin moiety, which was done successfully with HES (10). However, up to now, the stroma-free hemoglobin solutions are still in a state of research and cannot be recommended for clinical routine.

PERFLUOROCARBONS AS OXYGEN-TRANSPORT FLUIDS

Synthetic perfluorochemicals are organic compounds that dissolve comparatively large amounts of oxygen. It was found in animal studies that these solutions caused arteriolar constriction, vessel wall damage, and blood cell aggregation in the microcirculation (18). Other effects include complement activation via the alternate pathway and cytotoxicity to macrophages (9). In rats, peritoneal mast cell degranulation and histamine release have been observed by perfluorocarbons (49). This author has observed similar results (cooperation with B. Endrich and M. Intaglietta, unpublished).

A clinical trial of perfluorocarbons in 200 human subjects (many of whom were Jehovah's witnesses), revealed a significant improvement in tissue oxygenation owing to an enhancement of oxygen distribution within the microcirculation. In the same study, hypotension and pulmonary complications were observed together with intravascular complement activation. By treatment with corticosteroids, these symptoms were diminished (52a).

Similar to HES, perfluorocarbon emulsions tend to accumulate in the body, namely in lymphoid tissues. Transient depression of the immune system and decreased resistance to bacterial endotoxin have been described (9,49). The mechanism of these perfluorocarbon effects is most likely of a toxic nature; however, this has not yet been clearly established.

PROPHYLAXIS AND TREATMENT

The possible prophylaxis by hapten inhibition for dextran (63a) or by pretreatment with H_1 and H_2 antagonists for gelatin-induced anaphylactoid reactions has been discussed in detail

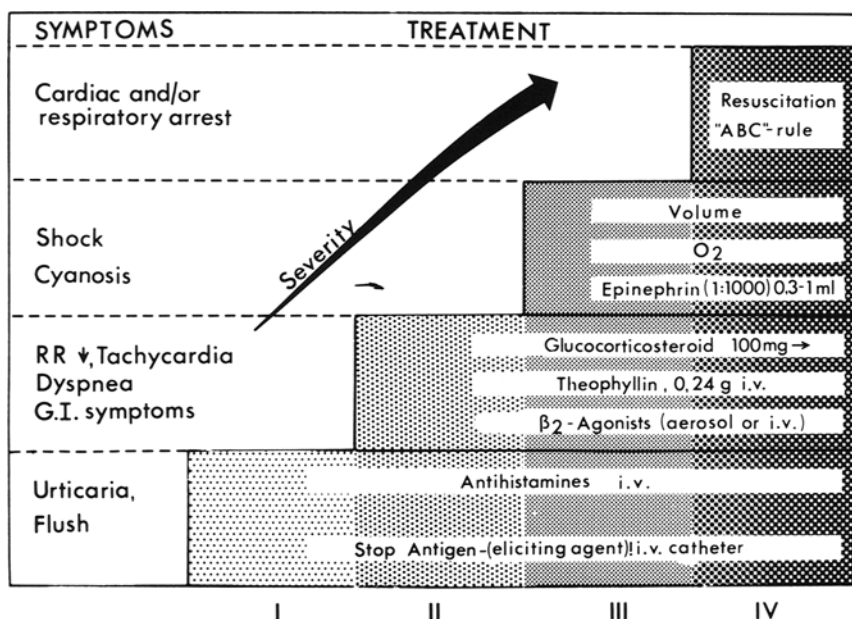


Fig. 1. Therapeutic regimen for treating anaphylactoid reactions with regard to increasing severity (Ring, 71).

(47a). The treatment of anaphylactoid reactions to volume substitutes follows the general principles of antianaphylactic treatment according to the intensity of the reaction (Fig. 1) (71,74).

By early diagnosis, prophylaxis, and treatment, the prognosis of anaphylactoid reactions in general is good, if there are no other risk factors present. "The earlier the treatment, the better the outcome."

REFERENCES

1. Adlmann, B. and Schöning, B. (1980), *Klin. Wochenschr.* **58**, 625-629.
2. Alving, B. M., Johim, Y., and Pisano, J. J. (1978), *N. Eng. J. Med.* **299**, 66-70.
3. Avoy, D. R. (1981), *Vox Sanguinis* **41**, 329-245.
4. Baur, X. (1983), *J. Allergy Clin. Immunol.* **71**, 197-205.
5. Bland, J. H. L., Laver, M. B., and Lowenstein, E. (1972), *JAMA* **224**, 1721-1724.
6. Bleeder, W. K., Agterberg, J., Rigter, G., de Vries-van Rossen, A., and Bakker, J. C. (1987), *Vox Sang.* **52**, 281-290.

7. Brehm, G. (1982), *Eur. J. Clin. Invest.* **13**, 233 (abstract)
8. Brendel, W., Seifert, J., and Ring, J. (1975), *Münch. Med. Wochenschr.* **117**, 1363.
9. Bucala, R., Kawakami, M., and Cerami, A. (1983), *Science* **220**, 965–967.
10. Cerny, L. C., Cerny, E. L., Robach, J., Reath, M., and Pontero, L. (1984), *Appl. Biochem. and Biotechn.* **10**, 151–153.
11. Czarnetzki, B. M. (1983), *Int. Archs. Allergy Appl. Immunol.* **70**, 78–82.
12. Davey, R. J. and Rosen, S. (1981), *Transfusion* **21**, 621–624.
13. Doenicke, A. and Koenig, U. D. (eds.) (1983), *Immunologie in Anaesthesie und Intensivmedizin*. Sertürner Workshops Einbek, Springer, Berlin.
14. Dorsch, W. and Frey, L. (1981), *Arch. Pharmacol.* **317**, 351–356.
15. Dukes, M. N. G. (ed.), (1984), *Meylers Side Effects of Drugs*, 10th ed., Excerpta Medica, Amsterdam.
16. Dukor, P., Kallos, P., Schlumberger, H. D., and West, G. B. (eds.) (1980), *Pseudo-Allergic Reactions I. Genetic Aspects and Anaphylactoid Reactions*, Karger, Basel.
17. Economidou, J. et al. (1971), *Vox Sang.* **20**, 252.
18. Endrich, B., Greenburg, A. G., Intaglietta, M., and Peskin, G. W. (1979), *J. Surg. Res.* **26**, 185–198.
19. Pinlayson, J. S. (1980), *Seminars Thromb. Hemostasis* **6**, 85.
20. Fisher, M. (ed.) (1984), *Clinics in Anaesthesiology. Adverse Reactions*. Saunders.
21. Gregor, I., Iberg, N., Berger, W., and Flückiger, R. (1986), *Diabetologia* **29**, 481–484.
22. Grant, J. A., Bilodeau, P. A., Guernsey, B. G., and Gardner, F. H. (1982), *N. Engl. J. Med.* **306**, 108.
23. Halpern, B. N. and Briot, M. (1952), *Comptes Rendus Société de Biologie (Paris)*, **146**, 1552–1560.
24. Hedin, H., Richter, W., and Ring, J. (1976), *Int. Arch. Allergy Appl. Immunol.* **52**, 145–152.
25. Hedin, H. and Richter, W. (1982), *Int. Arch. Alergy Appl. Immunol.* **52**, 122–126.
26. Heinonen, J., Peltola, K., Himberg, J. J., and Suomela, H. (1981), *Develop. Biol. Standard* **48**, 129, 130.
27. Hester, J. P. (1982), *Cytapheresis and Plasma Exchange, Clinical Indications* (Vogler, W. R., ed.), Liss, New York, pp. 115–124.
28. Hoigné, R. (1962), *Acta Allergol.* **17**, 521.
29. Illievich, U. M., Scheiner, O., Laubenthal, H., Hedin, H., Richter, W., Ring, J., and Kraft, D. (1989), *Allergologie* **8**, 326–331.
30. Isbister, J. P. and Fisher, M. (1980), *Anaesth. Intensi. Care* **8**, 145–151.
31. Izaka, K., Tsutui, E., Mima, Y., and Hasegawa, E. (1974), *Transfusion* **14**, 242–248.
32. Jesch, F., Hubner, G., and Zumtobel, V. (1979), *Infusionstherapie* **6**, 112–117.
33. Kabat, E. A. (1960), *J. Immunol.* **84**, 82–85.
34. Kabat, E. A., Turino, G. M., Tarrow, A. B., and Maurer, P. H. (1957), *Ann. NY. Acad. Sci.* **55**, 471–476.

35. Kallos, P. and Kallos, L. (1980), *Pseudo-allergic Reactions: Involvement of Drugs and Chemicals* (Dukor, P., Kallos, P., Schlumberger, H. D. and West, G. B. eds.), Karger, Basel, p. 28.
36. Kernoff, P. B. A., Durrant, I. J., and Rizza, C. R. (1972), *Br. J. Haematol.* **23**, 777–783.
37. Kimura, E. T., Darby, T. D., Krause, R. A., and Brondyk, H. D. (1971), *Tox. Appl. Pharmacol.* **18**, 60–68.
38. Klaschka, F. (1982), *Allergologie* **5**, 199–207.
39. Kleinhans, D. and Galinsky, T. (1982), *Allergologie* **4**, 120, 121.
40. Koistinen, I., Heikkilä, M., and Leikola, J. (1978), *Br. Med. J.* **2**, 923.
41. Kraft, D., Hedin, H., and Richter, W. (1982), *Allergy* **37**, 481–489.
42. Laubenthal, H., Peter, K., and Richter, W. (1983), *Diagnostik Intensivtherapie* **8**, 4–14.
43. Laubenthal, H. (1986), *Dextrananaphylaxie. Pathomechanismus und Prophylaxe*, Springer, Berlin.
44. Laxenaire, M. C., Moneret-Vautrin, D. A., Boileau, S., and Moeller, R. (1982), *Klin. Wochenschr.* **60**, 1006–1009.
- 44a. Laxenaire, M. C. and Moneret-Vautrin, D. A. (eds.) (1990), *Le Risque Allergique en Anesthésie-Réanimation*, Masson, Paris.
45. Lorenz, W. and Doenicke, A. (1978), *Mount Sinai J. Med.* **45**, 356–386.
46. Lorenz, W., Doenicke, A., and Dittmann, I. (1977), *Anaesthesist* **26**, 644–668.
47. Lorenz, W. and Doenicke, A. (1985), *Allergy* **6**, 37–57.
- 47a. Lorenz, W., Ennis, M., Doenicke, A., and Dick, W. (1990), *J. Clin. Anesth.* **2**, 345–360.
48. Luben, G., Quast, V., and Geiger, H. (1981), *Dev. Biological Standardization* **48**, 123–170.
49. Lowe, K. C. (1987), *Comp. Biochem. Physiol.* **4**, 825–838.
50. Lutz, H. (1975), *Plasmaersatzmittel*. Thieme Verlag, Stuttgart.
51. Messmer, K., Lorenz, W., Sunder-Plassmann, L., Klöveborn, W. P., and Hutzler, M. (1970), *Arch. Path. Pharm.* **267**, 433–439.
52. Messmer, K., Ljungström, K. G., Gruber, U. F., Richter, W., and Hedin, H. (1980), *Lancet* **1**, 975.
- 52a. Mitsuno, T., Ohyanagi, H., and Naito, R. (1982), *Ann. Surg.* **195**, 60–69.
53. Myhre, B. A. (1980), *J. Med. Ass.* **12**, 1333.
54. Parker, C. W. (1975), *N. Engl. J. Med.* **292**, 511.
55. Przybilla, B. and Ring, J. (1983), *Lancet* **I**, 483.
56. Przybilla, B., Ring, J., and Harle, R. (1984), *J. Allergy Clin. Immunol.* **73**, 164.
57. Reimann, H. J. (1981), *New Trends in Allergy* (Ring, J. and Burg, G. eds.), Springer, Berlin, pp. 50–57.
58. Revenäs, B. (1979), *Acta Universitatis Upsaliensis* **320**, I–IV, 16.
59. Richter, W. (1971), *Int. Arch. Allergy Immunol.* **46**, 438–447.
60. Richter, W. and De Belder, A. N. (1976), *Int. Arch. Allergy Immunol.* **52**, 307–314.
61. Richter, W., Granath, K., and Östling, G. (1976), *Int. Arch. Immunol.* **50**, 606–612.

62. Richter, W., Hedin, H., Ring, J., Kraft, D., and Messmer, K. (1980), *Allergologie* **3**, 51–58.
63. Richter, A. W. and Hedin, H. I. (1982), *Immunology Today* **5**, 132–138.
- 63a. Richter, W. (1986) *New Trends in Allergy II*, (J. Ring and G. Berg, eds.) Springer, Berlin, 272–283.
64. Ring, J., Seifert, J., and Lob, G. (1974), *Klin. Wochenschr.* **52**, 595–598.
65. Ring, J., Seifert, J., Messmer, K., and Brendel, W. (1976), *Eur. Surg. Res.* **8**, 398,399.
66. Ring, J., Seiler, F., and Brendel, W. (1976), *Int. Arch. Allergy Immunol.* **52**, 227–233.
67. Ring, J. and Messmer, K. (1977), *Lancet* **1**, 466–469.
68. Ring, J. (1978), *Anaphylaktoide Reaktionen nach Infusion natürlicher und künstlicher Kolloide*. Springer, Berlin.
69. Ring, J., Stephan, W., and Brendel, W. (1979), *Clin. Allergy* **9**, 89–99.
- 69a. Ring, J. (1982), *Allergologie* **5**, 216–220.
70. Ring, J., Shasrkoff, D., and Richter, W. (1980), *Vox Sang.* **39**, 181–185.
- 70a. Ring, J. (1985), *Int. Anesthesiol. Clinics* **23**, 67–69.
71. Ring, J. (1988), *Angewandte Allergologie*, 2nd Ed. MMV-Vieweg, München.
72. Ring, J. and Rother, K. (1985), *Plasmatherapie* (Lutz, H. and Rother, K., eds.), *Med. Verlagsgesellschaft*, Marburg, pp. 401–418.
73. Ring, J. (1984), *Int. Archs. Allergy Appl. Immunol.* **74**, 71–75.
74. Ring, J. (1987), *Surgical Research, Recent Concepts and Results* (Baethmann, A. and Messmer, K., eds.), Springer-Verlag, Berlin, 210–221.
75. Ring, J. and Thomas, P. (1988), *Clin. All.* **18**, 510–512.
76. Ring, J. (1982), *Allergy: Theory and Practice* (Korenblat, P. and Wedner, J., eds.), Grune and Stratton, Orlando, in press.
77. Schlumberger, H. D. (1982), *Allergologie* **5**, 183–189.
78. Schmutzler, W., Rämisch, K. D., van Wersch, J., and Lüttgens, M. (1982), *Allergologie* **5**, 208–215.
79. Schröder, D., Seifert, J., and Mangelsen, P. (1984), *Fortschr. Med.* **20**, 557–562.
80. Simon, R. A. (1984), *J. Allergy Clin. Immunol.* **74**, 623.
81. Smedegard, G. (1980), (thesis). *Acta Universitatis Upsaliensis* **548**, I–V, 18.
82. Sunder-Plassmann, L., Dieterle, R., Seifert, J., Jesch, F., and Messmer, K. (1975), *Eur. J. Intens. Care Med.* **1**, 37–42.
83. Tabor, E. (1982), *Infectious Complications of Blood Transfusion*. Academic, New York.
84. Tschirren, B., Bucher, U., and Lündsgaard-Hansen, P. (1979), *Vox Sang.* **36**, 39–49.
85. Twarog, F. J. and Leung, D. Y. (1982), *JAMA* **248**, 2030–2032.
86. van Arsdel, P. P. (1978), *Allergy, Principles, and Practice*, (Mittleton, E. C., Ellis, E., and Reed, E., eds.), vol. 2, C.V. Mosby, St. Louis, p. 1133.
87. Vervloet, D. L., Arnaud, A., Vellieux, P., Kaplanski, S., and Charpin, J. (1979), *J. Allergy Clin. Immunol.* **63**, 348–353.

- 88. Vervloet, D. L., Dugue, P. Ch., and Asrnaud, A. G. (1983), *J. Allergy Clin. Immunol.* **71**, 283.
- 89. Wahl, R. and Kleinhans, D. (1989), *Clin. Exp. Aller.* **19**, 77–80.
- 89a. Wadsworth, C. and Hanson, L. A. (1976), *Scand. J. Immunol.* **5**, 15.
- 90. Watkins, J. and Ward, A. M. (1978), *Adverse Response to Intravenous Drugs*. Academic, London.
- 91. De Weck, A. L. (1971), *Immunological Diseases* (Samter, M., ed.), Little, Brown, Boston, p. 415.
- 92. De Weck, A. L. and Bundgaard, M. (eds.) (1984), *Allergic Reactions to Drugs, Handbook Exp. Pharmacol.* vol. 63, Springer, Berlin.
- 93. Weis, K. H. (1983), *Anaesthesist* **32**, 488–493.
- 94. Wüthrich, B. (1983), *Schweiz. Rundschau Med. (PRAXIS)* **72**, 691–699.