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Reactions to Radiocontrast Material

Anaphylactoid Events in Radiology

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Contrast Agent Chemistry

The first relatively nontoxic, organic, iodinated contrast material (RCM) was created and successfully tested by Moses Swick, an intern from Mt. Sinai Hospital in New York City while on fellowship in Germany in 1929 *(1)*. He produced a monoiodinated pyridone ring from which commercially prepared di-iodinated pyridone rings were available for the next 20 years. Swick also helped in the development of the tri-iodinated, completely substituted six-carbon ring that has been the standard since the 1950s.

The first of these agents, whether as diatrizoate or iothalamate, was an ionic benzoate, iodinated at positions 2, 4, and 6 with substituted side chains at 3 and 5 to increase solubility (Fig. 1). With three iodines per molecule, it is fairly easy to reach a concentration of 300 mg I/mL which is necessary for most imaging. The cations of choice for these ionic compounds are sodium or the sugar, meglumine, or a combination of the two. These are relatively inexpensive compounds to produce, but the drawback is that for an ionic compound to achieve such a high concentration of iodine, it must be hypertonic relative to blood.

In fact, these iodinated, ionic, conventional contrast agents are about five times the osmolality of plasma, and this high osmolality results in significant problems. The problems include nausea and vomiting on injection, pain at the injection site, skin sloughing from inadvertent sc injection, and endothelial irritation and occasional

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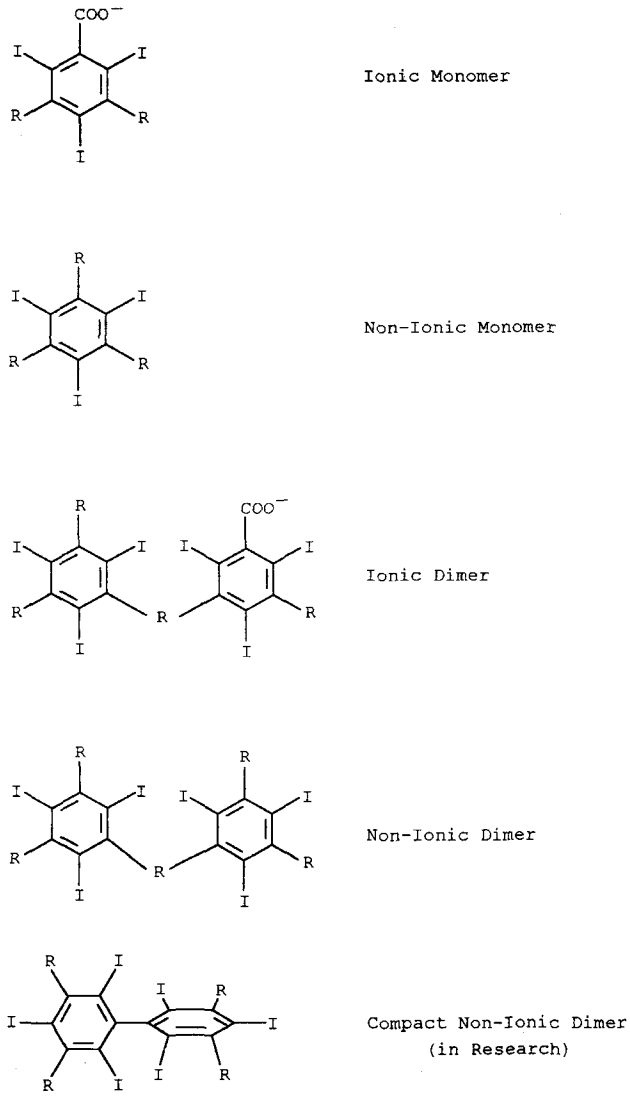

Fig. 1. Chemical structures of radiocontrast material.

thrombophlebitis. Intracoronary injections have negative inotropic and chronotropic effects as well as slowed conduction of electrical impulses.

A major advance in contrast material chemistry occurred two decades ago with the development of the first nonionic, iodinated contrast agent, metrizamide, by Torsten Almen, a Swedish radiologist. Metrizamide has been replaced in clinical practice by several similar agents that are easier to use, but all have the same basic configuration as the ionic monomer, except that the carboxyl is replaced by an

amide linkage that eliminates the ionization in solution (Fig. 1). As a result, the ratio of iodines to particles drops from 3 : 2 for the ionic agents to 3 : 1 for nonionic monomers. Consequently, the same concentration of iodine can be reached with roughly half the osmolality. The problems listed above, which are characteristic of ionic contrast agents, are markedly diminished with the nonionic monomers.

Shortly after the development of the nonionic monomers came the first iodinated dimer, ioxaglate. These are two benzene rings joined at the 3,5 side chains along with one ionic carboxyl and one nonionic linkage at the 1 positions (Fig. 1). The result is an agent with a ratio of 6 : 2 iodine atoms to particles. Thus, the ionic dimer is similar to the nonionic monomers both in osmolality and diminished side effects.

The most recent class of compounds to be introduced for clinical use is the nonionic dimer, iodixanol (Fig. 1), with a ratio of 6 : 1 iodines to particles resulting in an osmolality below that of plasma at 300 mg I/mL. Salts are added to bring the clinical products to iso-osmolality. The incidence of side effects is very low as would be predicted for an iso-osmolal agent. The agent is relatively viscous, however, because of the long chain (five carbon) connecting the two tri-iodo benzine rings resulting in a nonglobular, large-volume molecule. Current research is focusing on development of conformational changes in the molecule to shorten the bridge and create a more globular molecule (Fig. 1) *(2)*.

Scope of the Problem

All iodinated contrast materials, ionic or nonionic, small or large, viscous or nonviscous, cause quasiallergic adverse reactions. These reactions can cause dermal effects, they may cause respiratory distress, or they may result in cardiovascular collapse. The original ionic monomers have the highest rates of such adverse idiosyncratic reactions. The frequency of reactions to RCM in the United States has declined significantly since the introduction of lower osmolar agents approx 10 yr ago.

Reaction rates to hyperosmolar agents for all types of reactions are reported to range from 4.17 to 12.66% *(3–28)*. Because of the lack of standardized reporting criteria, it is impossible to discern the exact incidence of anaphylactoid reactions contained within these reports. However, it is believed that anaphylactoid reactions occur in approx 1% or less of patients receiving hyperosmolar RCM.

The incidence of reactions to lower osmolar agents is significantly less *(29–50)*. In one of the first large comparative studies, the overall reaction rate to hyperosmolar contrast was 12.66 vs 3.13% for the lower osmolar group. Severe reactions occurred in 0.22% of the

subjects receiving hyperosmolar media vs 0.04% of those receiving lower osmolar preparations. Urticaria occurred in 3.16% of patients given hyperosmolar contrast and in only 0.47% of those receiving a lower osmolar agent. Similar reductions were seen for flushing, sneezing, coughing, facial edema, a sudden drop in blood pressure, and itching. Reactions classified as severe occurred in 0.22% of subjects receiving hyperosmolar agents and in 0.04% of subjects receiving lower osmolar agents *(11)*. The data from this early study have been confirmed by a more recent analysis of the US Food and Drug Administration data by Lasser et al. *(49)*. The incidence of reactions to higher osmolar contrast media was compared with the incidence of reactions owing to lower osmolar contrast. The low osmolar media were divided into ionic and nonionic agents. The ionic lower osmolar agent was ioxaglate, and the nonionics were iopamidol, iohexol, and ioversol. The incidence of reactions per million examinations was highest for the higher osmolar agents. The total reaction rate for higher osmolar agents was 193.8 per million with a severe reaction rate of 37.4 and a fatality rate of 3.9 per million. For the nonionic lower osmolar media (iopamidol, iohexol, and ioversol), the total reaction rate was 44.4 per million with a severe reaction rate of 10.5 per million and 2.1 deaths per million. However, it is interesting to note that ioxaglate, the ionic lower osmolar agent, had a far higher incidence of reactions. The incidence rate for ioxaglate was 142.5 per million with a severe rate of 33.6 and a death rate of 6.4 per million. Of note is the fact that the ratio of deaths to total reactions was higher in the lower osmolar group both for nonionic and ionic agents. For the nonionic media, it was 23.7, and for the ionic ioxaglate, it was 23.6. For the ionic, higher osmolar media, it was 19.3. The authors postulated that the relatively higher incidence of fatalities to the lower osmolar agents was owing to the fact that they were given to the population at high risk. However, it is curious that other studies have noted no significant difference in fatality rates between subjects given high and lower osmolar agents *(11,31)*. This is in spite of the fact that there is clearly a reduction in the risk of severe reactions. For example the risk of severe reactions associated with high osmolarity media was 157/100,000 uses vs 126/100,000 uses for the low osmolar agents *(49)*. The reason for a failure to detect decreased mortality may be related to the small number of fatal reactions to these agents, which prohibits the detection of statistically significant differences in mortality.

Taken as a whole, both retrospective and prospective survey data clearly demonstrate a reduced reaction rate both for anaphylactoid and nonanaphylactoid events with the administration of lower osmolar agents. There may also be a difference between nonionic and ionic

lower osmolar agents that favors the use of nonionic preparations. However, there is no clear-cut documentation that the use of lower osmolar agents can reduce the incidence of fatal reactions, possibly because of the inability to demonstrate statistical significance owing to the low incidence of fatalities and the fact that lower osmolar agents are given preferentially to high-risk patients.

Nonetheless, these agents are far more expensive than hyperosmolar agents, and the difference in cost has prompted poignant debate regarding the cost–benefit ratio advantage of using lower osmolar agents and the attempt to establish criterion for their use *(50,51)*. The issue of cost has also prompted studies to see if the administration of corticosteroid pretreatment with a higher osmolar agent would offer protection similar to that afforded by the use of a lower osmolar agent alone *(40,45,52–54)*. These studies taken as a whole show that the use of a lower osmolar agent alone is equal to or more effective than a higher osmolar agent plus corticosteroid pretreatment in the prevention of reactions to RCM.

If everyone perceived to be at increased risk for a contrast reaction received low osmolal contrast material and everyone perceived to be at low risk received high osmolal contrast material, an unusual situation would arise. The low-risk group would have a higher incidence of adverse reactions than the high-risk group. This was first noted by Palmer in a study of 100,000 patients in Australia and New Zealand *(17)*, and he later referred to this as the "Australasian paradox."

Thus, on the one hand, there is the clear benefit to using low osmolal contrast agents selectively in high-risk patients, but on the other hand, such a strategy effectively places the low-risk patients at a relatively higher risk without ever changing their actual risk.

The simple solution would appear to be universal use of low osmolal contrast agents, but the simple solution has significant economic implications. When the nonionic agents were initially introduced, there was a 20-fold cost difference between them and conventional high osmolal, ionic agents. Early on, very few insurers were willing to reimburse for the higher-cost agents. As patents have expired, the cost of low osmolal agents has dropped to the point where there is now only a four- to fivefold cost difference. This closing of the gap in costs should have significantly alleviated the problem and facilitated the conversion to low osmolal agents, but the economics of the medical marketplace in the 1990s have driven down reimbursement rates and exaggerated small differences in costs. As the question of universal vs selective use of low osmolal contrast material has moved into the realm of cost–benefit analysis, there remains no simple answer *(55–57)*.

Epidemiology and Risk Factors

Reactions occur most commonly in subjects between 20 and 50 yr of age and are relatively rare in children *(22,58,59)*. Originally it was believed that reactions occurred with equal frequency in males and females *(19,20)*. However, recent data contest these observations and indicate that reactions are more common in females *(60–62)*. Lang et al. *(62)* evaluated the rate of anaphylactoid reactions according to gender in a sample of 5264 consecutive patients receiving radiocontrast for computed tomography (CT) scans. Of these subjects, 2642 were males and 2549 were females. Seventy-three anaphylactoid events occurred. Fifty-one of these were in females and 22 in males. The authors concluded that anaphylactoid reactions to radiocontrast were more common in females. This observation is in keeping with studies examining the overall incidence of anaphylaxis to multiple causes and episodes of idiopathic anaphylaxis *(63)*. In addition, it is consistent with the observations that anaphylactic and anaphylactoid reactions are more common in females to other specific agents, such as latex, aspirin, and iv muscle relaxants *(64)*.

Anaphylactic reactions to RCM occur both via iv and intra-arterial routes of administration *(61,65)*. There is debate regarding whether the incidence is equal by both routes of administration or whether reactions are more frequent when RCM is administered intra-arterially. Mikkonen et al. *(61)* found that the incidence of reactions was greater when RCM was administered intra-arterially (7.4 vs 1.2%), but attributed this difference to the fact that the administration of hyperosmolar agents occurred more frequently in the group receiving intra-arterial RCM. Other studies have found the incidences in intra-arterial and iv administration to be similar *(59)*. Reactions may be less common when RCM is administered intravenously via bolus injection vs slow-drip infusion *(65)*.

The concomitant administration of other drugs can affect the risk of a reaction. β-blockers did not alter the risk in one study by Greenberger et al. *(66)*, but in a series evaluated by Lang et al., β-blockers were found to increase the frequency and the severity of reactions *(67,68)*. These authors retrospectively analyzed 34,371 RCM administrations during which there were 122 anaphylactoid events. The risk of wheeze, a severe reaction, and hospitalization was associated with the administration of β-blockers. They found that compared to nonasthmatic patients, those taking β-blockers were almost nine times more likely to be hospitalized during an acute event *(67,68)*. These studies also looked at any potential risks from the administration of angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers. No significant risks from these agents were seen *(66,67)*.

Perhaps more germane to the interest of allergists is the possible role of atopy and asthma (independent of atopy) as predisposing factors to RCM anaphylactoid reactions. The radiology literature is replete with references evaluating allergy and asthma as risk factors *(4,5,10,11,22,67–71)*. All but one of these *(69)*, a study that involved a small number of patients, cited allergy and/or asthma as risk factors, increasing the incidence of anaphylactoid reactions. However, it is difficult to evaluation the validity of these studies because in no instances were skin tests or in vitro tests performed to confirm the presence of atopic disease (all data were based on history alone), and much of the data were retrospective. In many of these studies, atopy was not strictly defined, and atopic diseases were included together with reactions owing to contact dermatitis and various forms of drug reactions under the generic rubric "allergy." However, in the more recent radiologic literature, stricter definitions of atopy were employed. For example, in one very large series, patients were classified under the categories of "atopic, asthma, and pollinosis" *(11)*. Individuals in these categories were more likely to experience a reaction to both hyperosmolar and lower osmolar agents. For example, 25.83% of "atopics," 19.68% of "asthmatics," and 25.9% of "pollinosis" patients experienced a reaction to the administration of a hyperosmolar agent. The administration of a lower osmolar agent to these groups produced reaction rates of 7.22% in the "atopic" population, 7.75% in the "asthmatics," and in 7.51% of the patients with "pollinosis." Severe reactions were also more common in these groups and reached a high of 1.88% in asthmatics given a hyperosmolar agent. These reaction rates differed significantly from the group as a whole. Similar results were obtained in a series by Wolf et al. *(28)* where asthma and hayfever were found to be independent variables enhancing the risk of a reaction. In the previously mentioned investigations by Lang et al. *(67,68)*, asthma was found to be a clear-cut risk factor. The greatest risk for a severe reaction was seen in patients with asthma receiving β-blocking agents. More recent studies in the radiologic literature have confirmed the relationship between allergy and/or asthma and increased predisposition to radiocontrast reactions *(61,70,71)*. In keeping with these observations is a more well-defined investigation that used not only historical data, but also skin tests and in vitro testing to assess the presence of atopic disease *(72)*. Sixty-eight percent of those patients reacting to RCM, compared with 30% of controls, had a positive history of atopic disease. Fifty-six percent of reactors, compared with 24% of controls, had positive immediate hypersensitivity skin tests.

These studies indicating that asthma and atopy are risk factors for radiocontrast reactions are consistent with findings regarding the

role of atopy as a risk factor for anaphylaxis to ingested antigens, exercise, and idiopathic anaphylaxis, and observations that the atopic population demonstrates the phenomena of basophil "hyperreleasability" *(64)*. They are also consistent with the observations by Littner et al. that the administration of radiocontrast material routinely results in small, usually clinically insignificant, reductions in airway caliber, which are exaggerated in the asthmatic *(73)*.

Thus, it appears as if both atopy and asthma (regardless of the presence of atopy) are risk factors for radiocontrast reactions. The increased risk for asthma is probably specific for the bronchospastic response.

Theories of Pathogenesis

Any classification of the theories of pathogenesis of reactions is by necessity artificial. However, for the purpose of discussion, such classifications are necessary. This article classifies theories of pathogenesis into four categories: direct histamine release, complement activation, antigen–antibody interactions, and multimediator recruitment.

Histamine Release from Mast Cells and Basophils

Numerous studies have documented the ability of radiocontrast to release histamine from mast cells and basophils *(74–107)*. The release process occurs in a dose-dependent fashion *(87)*. In basophil preparations, it does not cause cell death *(87)*, but in cultured mast cells (mast cell line RVL2H3), moderate cytotoxicity can occur *(103)*. In reactors, it can be specific for the RCM producing the anaphylactoid episode *(85,90)*. RCM histamine release is slower in time-course than that produced by antigen. It has a delayed onset, usually beginning 10 min after incubation, and is slow to peak, usually doing so 45 min after incubation *(88)*. This type of release resembles that induced by ionophore *(98)*. Contrast media can be an incomplete secretagog causing the release of preformed mediators (tryptase and histamine) from mast cells and basophils *(100,101)*, but not inducing release of mediators requiring *de novo* synthesis (leukotrienes and prostaglandins) *(100,101)*. In addition, RCM may be tissue-selective in that it can induce mediator release from mast cells obtained from lung and heart, but not from those obtained from skin *(101)*. Release is not enhanced by preincubation of basophils with either interleukin 2 (IL-2) or IL-3 *(100)*. RCM-induced histamine release is enhanced by serum, implying a role for anaphylatoxins in the release process *(87)*. Of note is the fact that iodine is not necessary for in vitro histamine release from basophils. Noniodinated diatrizoate is as effective as

iodinated diatrizoate in the release process *(97)*. Release occurs with both hyper- and lower osmolar agents *(76,87,100,101,103)*. It is unclear whether hyperosmolar agents are more efficient in the production of in vitro histamine release *(74,103)*. Lower osmolar agents have been shown to produce a unique biphasic release response *(76)*. Meglumine salts may be more effective releasing agents than sodium salts *(76)*. Release is optimal at 37°C and is calcium-dependent *(98,101)*. Atopic basophils appear to be more sensitive to RCM than those of nonatopics *(97)*. In addition, previous reactors appear to be more sensitive than patients who have received RCM without reaction in terms of in vitro release *(87)*.

An interesting aspect of histamine release was discovered by Younger et al. They found that diatrizoate can inhibit histamine release owing to other agents *(98)*. When diatrizoate is incubated with basophils under conditions that do not produce release (e.g., in the absence of calcium), subsequent incubation of these same cells with releasing agents, such as anti-IgE, F-met peptide, and calcium ionophore, fails to produce histamine release. This inhibitory or "desensitizing" property of diatrizoate is maximal at 37°C and is not related to cell death. It cannot be overcome by increasing calcium concentration, the addition of a nonspecific methyl donor, or the addition of heavy water (D_2O). It was postulated that diatrizoate produced these effects by binding with and inactivating cell-membrane enzymes necessary for degranulation *(98)*.

In addition to the in vitro observations noted above, in vivo histamine release has been demonstrated both in animal models *(103)* and in humans *(86,95)*. It occurs after both iv and intra-arterial administration *(77,95)*. In in vivo animal models, release can be consistently correlated with the production of pathophysiologic events *(79)*. In humans, however, such a correlation cannot be consistently demonstrated. In three studies *(76,105,106)*, reactors could not be distinguished from nonreactors by the measurement of intravascular histamine. However, in another study *(82)*, which measured urinary histamine, reactors experienced significantly elevated levels of urinary histamine compared with a nonreactor group. The levels of urinary histamine in the reactor group were similar to those found in patients having anaphylactic episodes produced by allergen immunotherapy.

The mechanism by which histamine release occurs has not been elucidated. Five theories have been advanced:

1. A direct effect on mast cells and basophils via interaction with a cell-membrane receptor.
2. Release owing to hyperosmolarity.
3. Release owing to the generation of anaphylatoxins.
4. Release owing to IgE antigen interaction.

5. Release owing to the direct association of aggregates of RCM with the FC portion of IgE.

The most plausible of these theories appears to be the postulated interaction between RCM and a cell-membrane receptor. Evidence favoring this theory can be summarized as follows:

1. In vitro release may be specific for the RCM producing a reaction in a given individual *(85,90)*. This suggests a stoichiometric relationship between the putative cell receptor and a prosthetic group of the RCM.
2. In vitro release resembles ionophore-induced release *(88)*.
3. Release occurs with washed basophils, thus demonstrating serum factors, such as complement, are not necessary for degranulation *(88)*. However attempts to define specific stoichiometric relationships or to detect direct evidence for RCM binding to the membrane have not been successful *(87)*.

The hypothesis that the hypertonicity of RCM is responsible for histamine release is supported by several observations. Mast cells can be degranulated by hyperosmolar agents *(103)*, and as noted, radiocontrast agents are hyperosmolar. In addition, the rate of reactions to hyperosmolar agents is greater than that owing to lower osmolar agents as previously discussed. On the contrary, hypertonic agents (not RCM) administered intravenously to rabbits failed to produce the same adverse effects as those caused by RCM of equal osmolarity *(89)*. In addition, in vitro histamine release is produced both by lower osmolar and hyperosmolar agents *(101)*. Finally, the characteristics of in vitro release owing to hyperosmolar agents differs from the characteristics of release induced by RCM. These differences exist in regard to the time-course of release, calcium dependency, and the optimum temperature for release *(98)*. Thus, it would appear that hyperosmolarity alone cannot explain all aspects of reactions to radiocontrast.

The most recent hypothesis offered to explain the ability of RCM to produce histamine release is based on the observation that RCM tends to aggregate, and that the aggregates can bind to IgG and inhibit the ability of IgG to agglutinate red blood cells. This binding appears to take place at the FC portion of the IgG molecule. It was theorized that similar binding could occur at the FC portion of IgE and thus cause mast cell/basophil degranulation by linking two cell-surface IgE molecules *(107)*.

The above observations clearly demonstrate that RCM can induce histamine release, although the exact mechanism through which the release occurs has not been established. Table 1 lists the characteristics of RCM-induced histamine release.

Table 1
Characteristics of RCM-Induced Histamine Release from Basophils and Mast Cells

Occurs in vivo and in vitro
Calcium-dependent
Dose-dependent
Optimal at 37°C
Not cytotoxic
Delayed in onset, slow to peak
May be specific for a given RCM
Enhanced by serum
Iodine not necessary
RCM appears to be an incomplete secretagog, releasing preformed mediators only
Release may be tissue-specific
Occurs in vitro with hyper- and lower osmolar agents
Atopic basophils more sensitive to RCM in vitro (release at lower dose)
Previous reactors basophils more sensitive to RCM in vitro (release at lower dose)
There is no consistently demonstrated relationship between histamine release and the anaphylactoid event

Complement Activation

RCM clearly activates the complement cascade. This has been demonstrated both in vitro and in vivo *(108–126)*. Significant decreases in serum complement occur in large percentages of subjects receiving RCM for diagnostic studies *(108,109,112,116,120)*. In vivo reductions occur within 90 s of iv infusion *(111)*. They are usually short-lived, with serum complement returning to normal after 30 min *(111)*.

Nonetheless, decreases in complement do not consistently correlate with the presence of anaphylactoid reactions. Nonreactors cannot be uniformly distinguished from reactors on the basis of complement changes *(106,109,111)*. However, baseline levels of serum complement (CH50) have been shown to be reduced in a group of reactors, compared with controls *(116,119)*. Reactors have also been found to have depressed C1-esterase inhibitor levels in both baseline and post-infusion serum samples *(116)*. On the basis of these observations, it has been hypothesized that reactions occur in patients with ongoing complement use *(116,118)*. For example, patients with systemic lupus erythematosus might be more subject to reactions. This has not been confirmed, however, by prospective analysis. A prospective study of subjects experiencing reactions does not support this contention in that there is no apparent predilection for reactions to occur in patients with diseases involving complement activation *(19)*.

Several investigators have attempted to define the mechanisms by which RCM induces complement activation. However, in spite of intense attempts to elucidate these mechanisms, no one mechanism has been found to explain this activation.

RCM can induce activation through unique interactions not involving the classic or alternative pathways. Activation occurs in serum depleted of C4 *(120)* and C2 *(114)*, and in agammaglobulinemic serum *(114)*. Activation can also occur in the presence of ethylenediamine tetra-acetic acid (EDTA) or ethylene glycol tetra-acetic acid (EGTA) *(113,114,120,122)*. Another unusual feature of complement activation by RCM is that it can be nonsequential, that is, there is simultaneous utilization of components of both the alternative and classic pathways, and this utilization is nonsequential *(120)*. Finally, RCM-induced complement activation can produce a cleavage product of C3 that is not identical to that produced by activation of either the classic or the alternative pathways *(113)*. The exact mechanism by which nonsequential activation occurs is unknown. There is evidence, however, to support the contention that activation occurs indirectly through the induction of a lytic enzyme system. This putative enzyme system cleaves several complement components simultaneously (nonsequentially) *(113,114,120)*. In support of this postulation is that C3 cleavage occurs only in the presence of serum, and that the cleavage product, as noted above, is distinct from that produced by the alternative and classic pathway. It has been suggested that this lytic enzyme system is the plasminogen activator-plasmin system *(120)*. Recruitment of this system is consistent with the fact that a consumptive coagulopathy can occur during RCM-induced anaphylactoid reactions *(117)* and that subjects with depressed complement levels can also have fibrin-split products in their serum *(106)*.

Ionic and nonionic RCM may activate complement through different mechanisms *(123)*. Ionic RCM has been shown to exert a direct effect on C3 and C4 not involving the enlistment of a lytic enzyme system. Ionic RCM can cause a conformational change in C3 and C4 leading to products resembling activated C3 and C4. These "activated products" are antigenically related to C3b and C4b and are able to assemble fluid-phase C3 convertases, but are hemolytically inactive. The formation of these products is not inhibited by EDTA. These "C3b-like" and "C4b-like" molecules are similar to those produced through the action of nitrogen nucleophiles and chaotropes on complement. It was shown that ionic RCM cleaved native C3 and C4 molecules at their internal thiolester bonds to produce these unique C3b-like and C4b-like molecules. Hepatatrophic ionic RCM was more effective than nephrotrophic ionic RCM in causing these changes *(123)*.

In contrast to ionic RCM, a nonionic preparation, metrizamide, did not react with the internal thiolester bonds of C3 and C4, but activated complement through two other pathways. The C3b molecule produced by metrizamide-induced complement activation was identical to that produced by the activation of the alternative complement pathway, and metrizamide failed to exert an effect on C4. Metrizamide-induced activation was inhibited by EDTA. Furthermore, metrizamide effectively prevented the action of the alternative pathway inhibitory system (factors H and I). Thus, it was suggested that metrizamide's action on complement was the result of the inhibition of factors H and I, allowing for unrestricted alternative complement pathway activity *(123)*.

Metrizamide also had a less important effect on C2. Although C3 consumption in metrizamide-treated sera did not occur when EDTA was added (thus preventing alternative pathway activation), total hemolytic activity was reduced in the presence of EDTA. This reduction paralleled decreases in C2, whereas C1 and C4 were not affected. The mechanism of C2 "activation" was not elucidated *(123)*.

Regardless of the mechanism of complement activation used by RCM, the cleavage products so produced are biologically active. In vitro activation produces anaphylotoxic and chemotactic cleavage components *(122)*. In vivo injection during coronary angiography generates C3a levels between 4- and 10-fold normal. Seven of 11 patients undergoing angiography demonstrated C3a formation. However, only one patient developed symptoms, and these were mild, not requiring therapy *(124)*. In another study, it was postulated that complement activation was responsible for the death of a patient undergoing an iv pyelogram with diatrizoate *(121)*. In this patient, pathology findings were similar to those found in the adult respiratory tract distress syndrome. Granulocytic aggregates were impacted in microscopic pulmonary arteries and capillaries. It was suggested that these aggregates were owing to complement activation with formation of anaphylatoxins. Such anaphylatoxin generation was demonstrated in vitro by incubation of diatrizoate with serum *(121)*.

It should be noted that not every investigation has confirmed the observation that RCM is capable of activating complement. In two investigations *(113,125)*, only iodipamide, and no other agent, was capable of activating complement. In one of these investigations *(125)*, no actual cleavage components were found. There was an illusion of activation with the formation of cleavage products produced by direct binding of RCM to complement components. This nonspecific binding produced an artificial reduction in the concentration of complement components when these components were measured antigenically *(125)*. In another investigation *(126)*, the administration of RCM failed

to produce evidence of true complement activation as assessed by measurement of C3d. Changes in CH50 were observed in some patients, however. The authors attributed these changes to a nonspecific interaction between complement molecules and RCM because of the lack of C3d formation, rather than true activation of the complement cascade.

Nonetheless, the weight of evidence, based on the aforementioned studies, supports the contention that RCM is capable of activating complement both in vitro and in vivo. There appear to be multiple activation pathways. Ionic agents may activate complement in a nonsequential fashion. They appear to do so either through the recruitment of a lytic enzyme system or by a direct action on internal thiolester bonds of C3 and C4. Nonionic agents may work through different means, the most important of which may involve the inactivation of factors H and I. The role of complement in the production of the anaphylactoid event remains speculative, however. Changes in complement titers cannot be consistently correlated with the induction of anaphylactoid events. Table 2 lists the characteristics of RCM-induced complement activation.

Antigen–Antibody Histamine and Complement

Because of the clinical similarity between the RCM-induced anaphylactoid reaction and classical anaphylaxis, it has been postulated that RCM reactions are IgE-mediated. Based on this supposition, a number of studies have attempted to document the fact that RCM can be immunogenic *(97,127–136)*. The earliest studies in this regard were by Brasch and Caldwell who found anti-RCM antibodies in sera of patients who had experienced a radiocontrast reaction *(127,128,136)*. They found RCM, conjugated to Keyhole-limpet hemocyanin, bovine serum albumin, or bovine γ globulin could act as a hapten. Immunization with RCM and the above-noted carrier proteins induced the synthesis of IgG and/or IgE antibodies dependent on the immunization method *(136)*. Other authors *(97,131)* have confirmed the immunogenicity of RCM. In addition, isolated case reports *(130,134)* have demonstrated the presence of antibodies against RCM. In the most recent instance *(134)*, anti-RCM was incriminated as the responsible hemolytic antibody in a patient with an acute hemolytic reaction. In this instance, the anti-RCM also reacted with group I antigen on adult red blood cells. Anti-RCM was also demonstrated in a patient with acute renal failure occurring after iv urography *(130)*. More pertinent to the anaphylactoid response, Sweeney and Klotz demonstrated IgE antibody to radiocontrast *(132)*, and Wakkers-Garritsen et al. *(133)* reported a case of an anaphylactoid event where a positive intradermal reaction to RCM was demonstrated. The skin test reactivity

Table 2
Characteristics of RCM-Induced Complement Activation

Occurs in vitro and in vivo
Is dose-dependent
Biologically active cleavage products are formed
May occur through activation of a lytic enzyme system
Activation may be nonsequential for ionic agents
Nonionic agents may inhibit factors H and I
Decreases in complement occur rapidly and are short-lived
Iodine not necessary
There is no consistently documented relationship between decreases in complement and the anaphylactoid event

could be passively transferred by serum from the patient, and the ability to transfer the reaction was abolished by preheating the serum to 56°C. A similar case was more recently reported by Kanny et al. *(135)*. In this instance, a patient had experienced two separate anaphylactoid reactions to the administration of radiocontrast. On one occasion, he reacted to sodium and meglumine ioxytalamate, and on the other, to sodium and meglumine diatrizoate. The second reaction occurred in spite of pretreatment with hydroxyzine and tranexamic acid. The patient was skin tested to meglumine and sodium ioxytalamate, meglumine diatrizoate, meglumine and sodium diatrizoate, meglumine and sodium ioxaglate, and iopamidol. The human basophil degranulation test was also employed using these RCMs. The patient was not atopic and did not have elevated serum IgE. However, he did demonstrate a positive skin test to meglumine sodium diatrizoate, and basophil degranulation occurred to meglumine diatrizoate, sodium and meglumine diatrizoate, and meglumine and sodium ioxytalamate. The preheating of sera prior to the performance of the basophil degranulation test (basophils were incubated with sera prior to the addition of RCM) abolished the previously noted degranulation. Based on these results, the patient was administered iopamidol. He did not experience a reaction to this agent. The authors concluded that this case may have been an example of a rare instance of true IgE-mediated hypersensitivity to RCM. Nonetheless, the characteristics of in vitro RCM-induced histamine release differ from those of antigen-induced release *(98)*, and the weight of evidence does not support the thesis that the majority of reactions are caused by an immunologic event.

Multiple Mediator Recruitment and Miscellaneous Biological Effects

RCM can induce serotonin release from platelets *(89)* and can exert profound effects on the clotting system *(137)*. Disseminated

intravascular coagulation has been demonstrated in patients experiencing reactions to RCM *(138,139)*. Disseminated intravascular coagulation can occur after the administration of both lower and hyperosmolar agents *(139)*. Fibrin-split products can be found in the sera of both reactors and nonreactors receiving RCM *(106)*. RCM binds nonspecifically to serum proteins *(140–142)* and clotting factors *(122)*. This binding seems to inhibit a number of different enzyme systems, including urokinase, streptokinase, collagenase, tissue plasminogen activator, lysozyme, and acetylcholinesterase *(142–144)*. This inhibition occurs both with hyper- and lower osmolar agents *(142)*. There appears to be no correlation between the hydrophilicity or the osmolality of various RCMs regarding the inhibition of enzyme activity *(142)*. RCM infusion alters myocardial contractility *(145)*, and infusion of RCM can induce hypocalcemia *(111)*. Red blood cell structure and flow can be significantly altered *(146)*, and administration of radiocontrast can produce the sickling of erythrocytes in vitro and in vivo in patients with sickle cell disease *(147)*. This can cause severe sickle cell crisis with intravascular hemolysis and pulmonary infiltrates *(147)*. RCM also has effects on granulocytes, and infusion can produce granulocytosis perhaps by reducing granulocyte adherence to vascular endothelium *(126)*. During anaphylactoid reactions neutrophilia can occur, and there can be elevated levels of neutrophil enzymes, including elastase and lactoferrin *(148)*. The administration of radiocontrast disrupts vascular endothelium *(149)*. This disruption can activate factor 12, thus initiating clotting, clot lysis, and kinin formation *(150)*. The mechanism of production of endothelial injury is unknown, but it may be owing to a combination of the effects of hyperosmolarity *(151)*, direct toxicity *(152)*, and perhaps high injection pressures *(152)*. Mikkonen et al. *(153)* investigated the possible clinical importance of disruption of endothelium resulting in the activation of factor 12 by assaying plasma levels of prekallikrein, α II microglobulin, and C1-esterase inhibitor in patients with urticarial reactions to contrast media. They found differences in these measurements between patients with previous urticarial reactions compared to a group of nonreacting age- and sex-matched controls. However, they concluded that although high plasma prekallikrein activity, high plasma α 2 macroglobulin activity, and low C1 inhibitor activity were associated with urticarial reactions to contrast, the value of these measurements in terms of predicting reactions was limited *(153)*.

Even if these diverse effects are not related to the anaphylactoid event, it is possible that they are playing a role in the production of other untoward reactions, such as the adult respiratory tract distress syndrome *(58)* and disseminated intravascular coagulation *(138)*, that

Table 3
Miscellaneous Biologic Effects of RCM

Inhibition of platelet activity
Serotonin release from platelets
Activation of the clotting-clot lysis systems
Inactivation of numerous enzyme systems
Activation of prekallikrein-kallikrein system
Hypocalcemia
Alterations in myocardial conduction and contraction
Aggregation and sludging of red blood cells and leukocytes
Vascular endothelial disruption

occur after the administration of radiocontrast. Table 3 lists several of the various biological effects of RCM.

Approach to the Patient at Risk of an Anaphylactoid Reaction

It can be seen from the above discussion that, in spite of intensive efforts to uncover the mechanism of production of anaphylactoid reactions, the pathogenesis of these events remains unclear. Fortunately, however, in spite of our inability to uncover the origin of these events, we are able to deal effectively with the most salient clinical problem, the patient who must receive radiocontrast in spite of the increased risk of an anaphylactoid event.

Patients who have experienced a previous reaction are clearly at risk of a repeat reaction. The exact recurrence rate is unknown, but with ionic hypertonic agents, it probably ranges between 16 and 30% and may be as high as 44% *(11,154–168)*. Faced with the dilemma created by the necessity to re-administer radiocontrast to such patients, several clinical investigators have devised pretreatment regimens to reduce the incidence of recurrence. All of these have been evaluated through clinical trials, and each has been successful to some extent. Regimens include those of an H1 antagonist alone *(154)*, prednisone or methylprednisolone alone *(167–170)*, prednisone plus an H1 antagonist *(158)*, prednisone, an H1 antagonist plus ephedrine *(156)*, the combination of an H1 and H2 antagonist *(163)*, prednisone plus an H1 antagonist, an H2 antagonist and ephedrine *(161)*. It appears that all of these regimens are effective in reducing the frequency as well as the severity of recurrent reactions. The recurrence rate using these regimens plus a hyperosmolar agent ranges from 6 to 9% *(171)* and can be even further reduced (to 1% or less) when a lower osmolar agent is used in addition to the preferred medication pretreatment regimen. This preferred regimen consists of prednisone, 50 mg by

mouth, 13, 7, and 1 h before the procedure; diphenhydramine, 50 mg intramuscularly 1 h before the procedure; and ephedrine, 25 mg by mouth 1 h before the procedure *(172)*. This pretreatment protocol has been developed by Greenberger and Patterson at Northwestern University. Through a series of studies involving several hundred patients, it has proven to be highly effective not only in the prevention of mild to moderate reactions, but also in the prevention of life-threatening reactions. Administered in 19 procedures to patients who had previously experienced life-threatening shock or respiratory arrest, it prevented the recurrence of symptoms in all but two re-administrations. Reactions in these two were minimal. In 256 patients pretreated in this fashion, the incidence of recurrence was <1% *(172)*.

Unexpectedly, the Northwestern group found that the addition of an H2 antagonist to this regimen added no protection and may have reduced the efficacy of the pretreatment protocol *(159)*. Other investigators studying patients at less risk found the combination of H1 and H2 antagonists to be superior to an H1 antagonist alone *(163)*. In one study, there was no difference between patients treated with a combination of an H1 and H2 antagonist and those treated with an H1 antagonist alone *(161)*. Thus, it can be seen that controlled trials of the combination of an H1 and H2 antagonist in the prevention of radiocontrast reactions have created some confusion. Furthering this confusion are the observations that the combination of an H1 and an H2 antagonist is more effective than an H1 antagonist alone in preventing anaphylactic and anaphylactoid reactions to other agents *(173–176)*. In addition, there are individual case reports citing the beneficial effect of the addition of an H2 antagonist (compared to an H1 antagonist alone) in the treatment of anaphylaxis in general *(177)* and for the prevention of a potentially serious anaphylactoid reaction to the re-administration of RCM during cardiac catheterization *(178)*. Finally, there are the observations that histamine is active through both H1 and H2 receptors in the production of the manifestations of anaphylaxis *(173,174)*. Thus, based on the above observations, use of an H2 antagonist remains an option to be used at the discretion of the physician ordering the pretreatment protocol.

As noted, the addition of a lower osmolar agent has greatly increased the efficacy of the pretreatment protocol *(179)*. In fact, the use of a lower osmolar agent (iohexol) alone has been shown to decrease the recurrent reaction rate to 5.5% *(96)*. This observation plus the fact that other side effects occur less frequently with lower osmolar agents *(180–185)* mandates the use of lower osmolar agents in previous reactors. However, it should be clearly noted that anaphylactoid reactions can occur owing to the administration of lower osmolar agents *(186–189)*.

Based on the above observations, therefore, the pretreatment regimen of choice would in most cases consist of the administration of prednisone, an H1 antagonist, ephedrine, and a lower osmolar agent with an H2 antagonist used at the discretion of the physician. In addition, the necessity of the study should be documented, the potential risks explained to the patient, and their consent obtained.

Another issue that must be dealt with relates to drugs the patient may be taking at the time of the re-administration of the radiocontrast. Many patients requiring RCM intravascular studies are taking β-adrenergic blocking agents and ACE inhibitors. As previously noted, there is evidence in the literature pertaining to RCM reactions indicating that the frequency and severity of reactions in patients taking β-blockers may be increased *(67,68)*. In addition, although there is no evidence to incriminate ACE inhibitors in this regard, based on other observations involving hymenoptera anaphylaxis, ACE inhibitors or ACE blockers may have similar effects *(190)*. Thus, in spite of the lack of clear-cut evidence that ACE inhibitors and ACE blockers place a patient at increased risk, the authors prefer their discontinuation (as well as the discontinuation of β-blockers) prior to the re-administration of radiocontrast to patients at risk.

Occasionally, a high-risk patient must undergo an emergency radiographic procedure when there is no time to use the standard pretreatment regimen, which requires 13 h. For this purpose, an emergency pretreatment protocol has been established by Greenberger et al. *(191)*. This procedure consists of the administration of hydrocortisone, 200 mg intravenously, immediately and every 4 h until the procedure is performed. Diphenhydramine, 50 mg intramuscularly, is also given 1 h before the procedure. Although there are no published data to validate the addition of ephedrine in this situation, it is likely that it would be helpful. A lower osmolar agent should of course be used. The use of an H2 antagonist remains an option to be used at the discretion of the physician.

A graded provocative challenge has also been proposed for the management of the previous reactor high-risk patient *(192,193)*. Such provocation dosage regimens were originally abandoned because of the observation that reactions could occur at very low doses given as "test doses" *(78)*. However, when RCM is highly diluted and administered using a gradually increasing dosage regimen, successful administration to previous reactors has been accomplished. This method entails the administration of progressively stronger concentrations at 10- to 15-min intervals until full-strength RCM is given. At the conclusion of the uneventful graded administration, the RCM study is performed. This procedure has been effective in preventing serious reactions by producing minor reactions during provocative

testing, thereby allowing the physician to abort the procedure before the advent of severe symptoms *(161)*. The procedure probably works based on the fact that RCM reactions are, like other drug reactions, dose-dependent.

There are obvious disadvantages to this provocative testing procedure. These include the time required (about 1.5 h) to complete the procedure and the necessity for a physician's presence during the course of administration. Furthermore, because pretreatment medication and lower osmolar agents have been so successful in reducing the incidence and severity of recurrent episodes, the provocative testing procedure has been abandoned. However, when the previous reaction has been life-threatening, the physician may opt to use a combination of pretreatment, a lower osmolar agent, and the provocative dosage regimen.

It is important to note that the pretreatment protocol noted above is not effective in preventing *nonanaphylactoid*, life-threatening reactions. Of particular importance in this regard is the occurrence of the acute adult respiratory tract distress syndrome (noncardiogenic pulmonary edema) owing to the administration of RCM. It is therefore incumbent on the physician to determine the nature of the previous reaction. Although the adult respiratory tract distress syndrome (noncardiac pulmonary edema or shock lung) is rare owing to the administration of RCM, a significant number of cases has been reported *(194–198)*. These reactions can occur to both high and lower osmolar agents *(196)*. They can occur even though the patient exhibited no previous reaction to the administration of radiocontrast *(195)*, and they do not respond to the standard pretreatment regimen *(194,197,199)*. Thus, in instances in which the initial reaction was consistent with noncardiogenic pulmonary edema, the pretreatment protocol cannot be trusted to prevent a recurrence.

It is important to note that anaphylactoid reactions to RCM can occur when these agents are administered via nonvascular routes. For example, reactions have occurred during histosalpingograms *(200,201)*, myelograms *(202)*, and retrograde pyelograms *(203,204)*. Thus, previous reactors undergoing these procedures should be pretreated. Table 4 summarizes the approach to pretreatment of patients who have had a previous anaphylactoid reaction and who must have another radiocontrast study.

Miscellaneous Observations Regarding Reactions to Radiocontrast Material

Clearly, the anaphylactoid event and its prevention are the most important aspects of radiocontrast reactions for the allergist/immunologist. However, recently other observations regarding adverse

Table 4
Management of Patients Who Have Had a Previous Anaphylactoid Reaction to RCM Who Must Have Another Radiocontrast Study

Document the necessity of the study
Determine that the previous reaction was not owing to noncardiogenic pulmonary edema[a]
Explain the potential risk to the patient and obtain consent for readministration
Pretreat as follows
Benadryl 50 mg im 1 h before the procedure
Prednisone 50 mg orally 13, 7, and 1 h before the procedure
Ephedrine 25 mg orally 1 h before the procedure (when not contraindicated)
Use a lower osmolar agent
If patient taking β-adrenergic blocker, ACE inhibitor, or ACE blocker, discontinue this drug if possible[a]
A provocative dosage regimen can be used (at the discretion of the physician) if the previous reaction was life-threatening[a]
The use of an H2 antagonist is controversial and is employed at the discretion of the physician[a]

[a]*See text.*

reactions to radiocontrast have been made that are at least of peripheral interest to our specialty. They are more difficult to classify and therefore are included in this section dealing with miscellaneous observations.

One of these observations regards studies of reactions to gadopentetate dimeglumine. Gadopentetate dimeglumine is used as an imaging contrast media for magnetic resonance imaging. It is associated with relatively few adverse reactions compared with radiopaque contrast media. However, reactions, including anaphylaxis, have been noted *(37,205,206)*. The role of pretreatment in prevention of reactions to gadolinium-based contrast agents has not been evaluated.

Anaphylactoid reactions to gastrointestinally administered contrast media are owing to different types of reactions than those discussed previously for radiocontrast administered by other routes. It has been estimated that the incidence of severe anaphylactoid reactions to gastrointestinally administered agents is approx 1 in 2.5 million *(207)*. The causes of the majority of these reactions remain unknown. However, they appear to be heterogeneous in nature. Documented etiologic agents include latex *(208)*, glucagon *(208)*, carrageenan *(209)*, and carboxymethylcellulose *(210)*. In addition, diatrizoate *(211)*, a hyperosmolar radiocontrast also used for iv studies, has produced an anaphylactoid reaction when administered by mouth. In this instance, the re-administration of this drug on a second occasion caused a second, more severe episode.

Thus, agents administered through the gastrointestinal tract including barium sulfate as well as triodinated benzene ring radiopaque

agents, such as diatrizoate, can produce anaphylactoid and anaphylactic reactions through various mechanisms. To date there are no pretreatment protocols established for these types of reactions. Also there are no well-defined risk factors.

Delayed and recurrent reactions to radiocontrast *(212–217)* of an anaphylactoid *(213)* and nonanaphylactoid nature *(212,214–217)* have been reported. These "allergy-like" reactions occur to ionic and nonionic agents, occur after both iv and intra-arterial administration, and are infrequent *(217)*. Of interest is a case described by Wedner of a 22-yr-old female with asthma who experienced an anaphylactoid reaction to an arthrogram. The patient experienced symptoms repeatedly over a 62-h period. Exacerbations were interrupted by asymptomatic interludes. The first episode occurred within 5 min of the injection and each required hospitalization *(213)*. In addition, a late urticarial reaction (12 h after the administration of iohexol) was reported to occur in a 67-yr-old man after an excretory urogram intravenous pyelogram (IVP). Five days later, the patient developed a diffuse, erythematous macular papular rash. A similar widespread erythema and edema occurred 6 h after the administration of RCM administered during a CT examination. Biopsy revealed focal spongiosis of the epidermis and a perivascular infiltrate of small, round cells, a few neutrophils, and eosinophils in the dermis *(214)*.

Also of interest is the adverse reaction to iv contrast associated with the administration of IL-2 *(218–222)*. The administration of IL-2 seems to predispose patients to unusual reactions owing to RCM. These reactions usually occur 1–4 h after the radiocontrast has been administered. They appear more commonly after hyperosmolar than lower osmolar agents. They are not anaphylactoid in nature, but are characterized by hypotension. The most common symptoms are nausea, vomiting, diarrhea, edema, renal failure, rash, fever, chills, and hypotension. Occasionally, the hypotension is severe and requires pressor treatment. There is question regarding whether or not steroid pretreatment prevents the reaction. In one series *(218)*, it did not. In this series, 70 patients were given RCM before and then 2, 6, and 10 wk after IL-2 administration. Both hyperosmolar and lower osmolar agents were employed. No reactions occurred before the administration of IL-2, but after the administration of IL-2, reactions occurred in nine subjects. Reactions were more frequent after hypertonic agents. All patients fully recovered. Six patients who had reacted to contrast 2 wk after IL-2 therapy received contrast again 4 wk later. Five had no reaction, and only one experienced a recurrence. The cause of the IL-2-related reactions to RCM is unknown. These reactions, however, mimic those owing to IL-2 itself.

Finally, it is worthwhile to note two of the common misconceptions about reactions to RCM. One of these involves iodine allergy and the other shellfish. It should be noted that contact dermatitis to iodine has no relationship to anaphylactoid events owing to radiocontrast and vice versa. The anaphylactoid reaction is not related to the iodine molecule *per se*, and as has been noted, histamine release occurs in vitro to radiocontrast materials stripped of iodine *(97)*. Thus, patients who have had an anaphylactoid reaction to radiocontrast are not at risk for the administration of potassium iodide, radioactive iodine, or contact reactions to iodine. In addition, patients who have had contact dermatitis to topical iodine preparations or nonanaphylactoid reactions to iodine administered orally are not at increased risk of an anaphylactoid reaction to the administration of radiocontrast.

It is curious to note that the older radiologic literature states that patients who have had anaphylactic reactions to shellfish are at increased risk of anaphylactoid reactions to the administration of radiocontrast material. The irony of this observation is that it may be correct, but for the wrong reason. The original rationale for this observation appears to be based on the fact that shellfish contain high quantities of iodine. It was thus assumed that individuals allergic to shellfish would be at risk for an RCM reaction. We now know that neither shellfish allergy nor RCM reactions are owing to iodine, and thus, the original rationale was faulty. However, since it has been shown that atopy *per se* is a risk factor, the association between previous anaphylactic reactions to shellfish and a possible predisposition to a radiocontrast reaction may be valid.

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