



THE ROLE OF OXYGEN RADICALS IN IMMUNE COMPLEX INJURY

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Abstract—In this review we will summarize our current understanding of the mediation of immune complex induced tissue injury. Comparisons will be made between the mediation of IgG versus IgA immune complex injury with emphasis on the role that reactive oxygen products derived from leukocytic phagocytic cells play in the initiation of the tissue injury.

Keywords—Immune complexes, Immunoglobulin IgA, Immunoglobulin IgG, Oxygen radicals

I. INTRODUCTION

It has long been appreciated that immune complex formation serves an important protective function for the host by the complexing and elimination of infectious agents such as viruses or bacteria. In addition, it has been appreciated since the early part of this century that immune complexes could harm as well as protect the host.¹⁻² The subsequent development of a number

of experimental models of immune complex induced tissue injury, such as serum sickness, further strengthened this hypothesis. It is currently well accepted that certain human diseases, in particular autoimmune diseases such as systemic lupus erythematosus, appear to be triggered by immune complex formation and deposition in tissues.³⁻⁵

With the development of experimental models of immune complex induced tissue injury in the late 1950s and 1960s, many laboratories began to look for the mediators involved in this type of acute inflammation. It soon became apparent that the complement system was intimately involved. Studies using the technique of complement depletion were protective against the development of tissue injury in the Arthus vasculitis and anti-GBM nephritis models.⁶⁻⁸ The major mechanism by which complement appeared to initiate the tissue injury in these models was by the local generation of the chemotactic peptide C5a and the subsequent attraction of neutrophils into the site. Today we know that this is probably not the only mechanism by which complement is involved in these reactions. Immune adherence mechanisms dependent upon complement C3b receptors may also be important. There is also accumulating evidence that complement may directly injure the tissues via the generation of the terminal complement sequence C5b-C9, otherwise known as the "membrane attack complex" (MAC).⁹⁻¹⁰

Irrespective of the role of the complement system, phagocytic cell activation and migration into tissues are critical events leading to the development of immune complex tissue injury. Experimentally, neutro-

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phil or macrophage depletion is usually protective. Histologically, (Fig. 1), infiltrates of neutrophils or macrophages are characteristic at sites of immune complex deposition.¹¹⁻¹⁵

Because neutrophils and macrophages appear to play a pivotal role in the evolution of immune complex injury, attention has been focused upon the mediators generated by these cells and upon their relationship to the injury. As illustrated in Table 1, these cells produce an array of potent biological mediators including arachidonate products, proteases, cationic proteins and reactive oxygen products to name a few. Experimental evidence supports the concept that leukocytic reactive oxygen products play a pivotal role in the initiation of the tissue injury. In this review, we will summarize the experimental studies that support the concept of oxygen radical involvement in immune complex induced tissue injury. Specific attention will be directed at comparing IgG versus IgA induced injury. Recent studies suggest that the effector cells as well as the specific oxidant species implicated differ for these two classes of immune complex injury. Experimental evidence will also be presented on the interaction of other

inflammatory mediators, such as platelet adenine nucleotide products and macrophage cytokines, on oxygen radical generation by immune complex stimulated leukocytes. Finally, evidence will be presented that suggests not all immune complex induced tissue injury is oxygen radical mediated.

II. IgG IMMUNE COMPLEX INDUCED TISSUE INJURY

Because virtually all of the experimental work done on the pathogenesis of immune complex injury has been with IgG immune complexes, IgG induced tissue injury is often considered synonymous with the general topic of immune complex disease. This is probably appropriate in that IgG complexes are the predominant immunoglobulin in tissues in most immune complex diseases. However, it is important to remember that a number of human diseases have evidence of involvement of other immunoglobulin classes, in particular IgM or IgA. Recent experimental studies illustrate the importance of this distinction, in that the pathogenesis of immune complex induced injury appears to differ according to class.

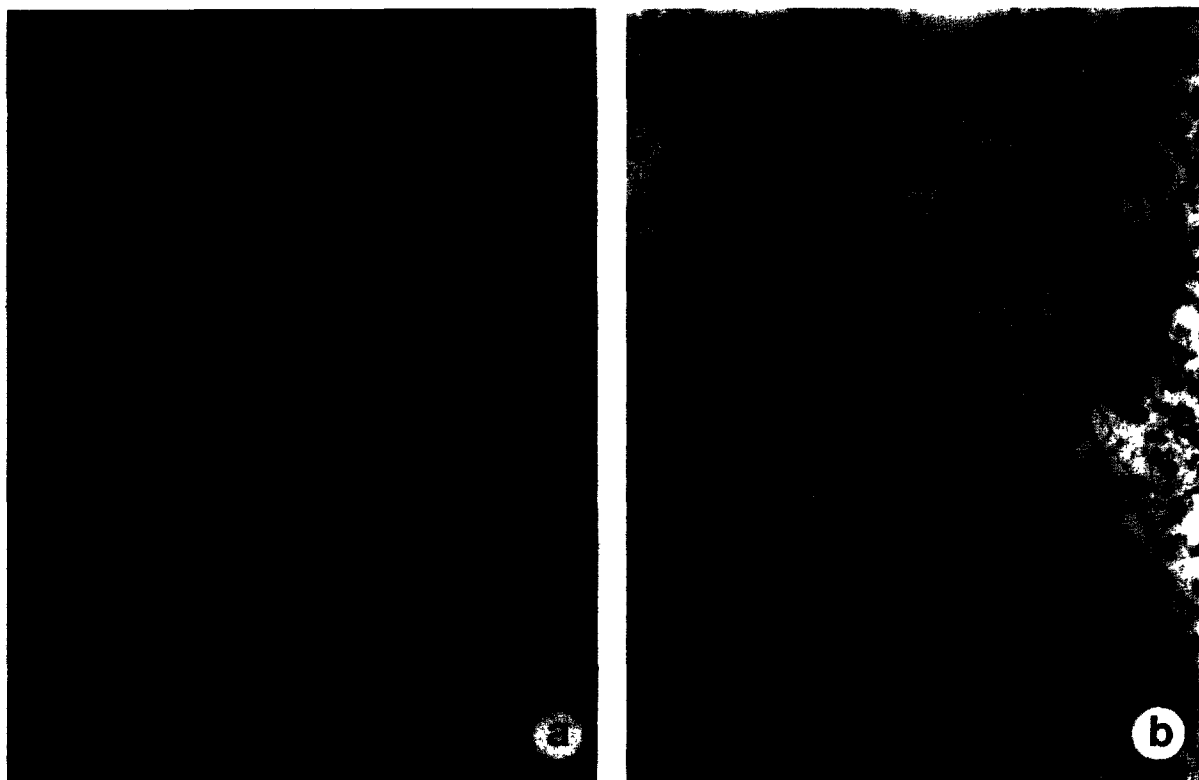


Fig. 1. Skin biopsy from a patient with a hypersensitivity vasculitis illustrating the acute inflammatory response triggered by the tissue deposition of immune complexes. (a) Direct immunofluorescence showing IgM deposition in the dermal blood vessels and (b) Light microscopy showing the resulting acute inflammation in the vessels with neutrophil infiltration and fibrinoid necrosis.

Table 1. Biologic mediators produced by neutrophils and macrophages

I. Neutrophil Products	
A. Oxygen Free Radicals (O_2^- , H_2O_2 ; etc.)	
B. Neutral Proteinases	
(1) Elastase	
(2) Cathepsin G	
(3) Proteinase 3	
(4) Collagenases	
C. Acid Hydrolases	
(1) B-Glycerophosphatase	
(2) N-Acetyl-B-Glucosaminidase	
(3) B-Glucuronidase	
(4) α -Mannosidase	
(5) Cathepsins, B and D	
D. Microbicidal Enzymes	
(1) Myeloperoxidase	
(2) Lysozyme	
E. Arachidonic Acid Metabolites (PGE, Thromboxanes, Leukotrienes, etc.)	
F. Other	
(1) Basic Proteins	
(2) Thrombin-Activating Material	
(3) Kininogenase	
(4) Surface Protease	
II. Macrophage Products	
A. Proteins	
(1) enzymes:	
(a) neutral proteinases (e.g. plasminogen activator, elastase, collagenases, etc.)	
(b) lysozyme	
(c) arginase	
(d) lipoprotein lipase	
(e) angiotension converting enzyme	
(f) acid hydrolases	
(2) plasma proteins:	
(a) coagulation proteins	
(b) complement components	
(c) α_2 -macroglobulin	
(d) fibronectin	
(3) monokines:	
(a) interleukin-1	
(b) tumor necrosis factor	
(c) interferon alpha	
(d) angiogenesis factor	
B. Reactive Oxygen Species	
(1) superoxide anion	
(2) hydrogen peroxide	
(3) hydroxyl radical	
C. Bioactive Lipids	
(1) prostaglandin E_2	
(2) prostacyclin I_2	
(3) thromboxane B_2	
(4) leukotriene B_4 , C_4 , D_4 , E_4	
(5) hydroxyicosatetraenoic acids	
D. Nucleotides	
(1) thymidine, uracil	
(2) cAMP	
(3) uric acid	

A. *In-vitro* studies on IgG immune complex stimulation of phagocytic cells

As mentioned previously, immune complex injury appears to be induced by the immune complex activation of neutrophils and macrophages and their release of potent biological mediators including reactive oxygen products. The most likely mechanism of this ac-

tivation is through immune complex attachment to the cell membrane via the Fc receptor. Attachment is followed by phagocytosis of the complex.¹⁶ *In vitro* studies have demonstrated that IgG immune complexes differ markedly in their ability to activate phagocytic cells in this fashion. The degree of activation depends upon physiochemical properties of the antigen-antibody complexes such as size and ratio of antigen to antibody. Relatively soluble IgG immune complexes (antigen-antibody ratio 1:2) maximally stimulate human neutrophils to produce superoxide anion, whereas large particulate immune complexes at equivalence (antigen-antibody ratio 1:5) are less effective neutrophil activators.¹⁷ Using rat neutrophils, maximal stimulation of superoxide production by IgG immune complexes occurs with complexes at an antigen:antibody weight ratio of 2:1.¹⁸ Thus, in the human, soluble immune complexes may be as important in the initiation of injury as the larger particulate complexes. Traditionally, the larger particulate complexes have been thought to be the most phlogistic because of their ability to maximally activate the complement system.¹⁸

Enhancement of the oxygen radical burst by IgG immune complex stimulated neutrophils is seen when cytochalasin B is added to the system.¹⁹ The mechanism by which cytochalasin B causes this enhancement is not clear. Cytochalasin B exerts a variety of effects on cells. One of these, dissociation of microfilaments, induces cytoskeletal alterations, which allow stimuli such as immune complexes to activate the cells without having to undergo endocytosis. Cytochalasin B is also known to enhance calcium flux into cells.²⁰⁻²² Whatever the mechanisms involved, there are marked differences when cytochalasin B is added to macrophages rather than neutrophils. Instead of enhancing, cytochalasin B inhibits superoxide production by macrophages stimulated by IgG immune complexes.²³ This contrasting effect of cytochalasin B suggests that the mechanism of cell activation by IgG immune complexes is different in neutrophils and macrophages. This impression is strengthened by studies described in detail below where IgA immune complexes stimulate the macrophage but not the neutrophil respiratory burst.

Recent experimental studies have also shown that immune complex stimulation of phagocytic cells and oxygen radical formation can be potentiated by the addition of other inflammatory mediators. Van Epps originally showed that pretreatment of neutrophils with chemotactic peptides such as C5a would markedly increase neutrophil superoxide production when subsequently given a second stimulus such as zymosan.²⁴ This "potentiation" of oxidant burst activity was confirmed by Speer et. al. who found that pretreatment of

macrophages with proteases greatly enhanced the production of superoxide when the cells were subsequently stimulated with phorbol myristate acetate (PMA).²⁵ Studies in our laboratory have demonstrated similar potentiation of neutrophil and macrophage superoxide production by C5a when immune complexes were used as the second stimulus.²⁶ Thus, direct stimulation of phagocytic cells by complement products, in particular C5a, may be important in the pathogenesis of tissue injury. Whether the terminal complement activation peptide C5b-C9, otherwise known as the membrane attack complex (MAC), can "prime" phagocytic cells in a similar fashion as C5a is not known. It is clear, however, that the MAC can directly induce oxidant generation by these cells under certain conditions.²⁷

Other factors have also been described that enhance the respiratory burst of phagocytic cells when stimulated by IgG immune complexes. These include polyelectrolyte substances such as cationic histones (e.g., polyhistidine and polyarginine), and anionic substances (e.g., polyanetholsulfonate).²⁸⁻³⁰ The mechanisms by which these charged substances enhance oxygen radical formation by phagocytic cells is not known. However, biological relevance has been inferred from *in vivo* studies which show that the addition of these charged substances enhances immune complex mediated tissue injury.²⁸

Finally, in the last few years some very exciting observations have been forthcoming suggesting that inflammatory mediators produced by platelets and macrophages enhance oxygen radical production by IgG stimulated phagocytic cells. In terms of macrophage-derived cytokines, interleukin 1 (IL-1), and to a lesser degree, tumor necrosis factor (TNF), have been found to enhance superoxide generation by IgG stimulated macrophages. This effect is not seen in neutrophils.^{26,18} At the concentrations used, these cytokines alone had no direct stimulatory effect on macrophages although it has been reported that TNF can directly stimulate neutrophils to generate superoxide.³¹ Platelet factors have also been found to enhance the oxidant burst activity of IgG immune complex stimulated neutrophils. This platelet stimulatory factor appears to be a platelet derived adenine nucleotide (ATP, ADP).³²⁻³³

In conclusion, based on *in vitro* studies, we now know that many factors affect the ability of IgG immune complexes to activate phagocytic cells to produce oxygen radicals. The physiochemical characteristics of the immune complexes themselves appear important. Smaller, soluble immune complexes appear to be at least as efficient in stimulating the cells as the larger particulate complexes. There also appear to be complex relationships with other inflammatory mediators such as C5a, adenine nucleotides from platelets, and mac-

rophage cytokines such as IL-1 and TNF. These mediators appear to have the ability to prime immune complex stimulated phagocytic cells to augment their production of oxygen radicals (Table 2). These observations clearly point out the complexity of the phagocytic cell activation process, and also suggest a possible reason why *in vivo* studies have implicated many different inflammatory mediators in the development of tissue injury. Many of these mediators may in fact be exerting their primary effect by augmentation of the respiratory burst of the phagocytic cells.

B. *In vivo* studies on IgG immune complex tissue injury

The classic experimental models of immune complex induced tissue injury are almost exclusively models of IgG induced injury. The best known examples include serum sickness, anti-GBM or nephrotoxic nephritis and the Arthus reaction. In the rat anti-GBM nephritis model, recent studies have provided strong evidence that reactive oxygen products from neutrophils are primarily responsible for the early glomerular injury.³⁴ Treatment of animals with catalase is markedly protective with virtually 100% suppression of the proteinuria. Morphologically, as illustrated in Fig. 2, the glomeruli of the catalase treated animals appear normal even though large numbers of neutrophils are present. This suggests that catalase is exerting its protective effect by its conversion of hydrogen peroxide rather than by interfering with neutrophil recruitment.

Further studies have implicated the myeloperoxidase halide products of H₂O₂ as the cause of the glomerular injury. Halogenation products are present in the glomeruli of animals that have an immune complex glomerulonephritis. Furthermore, the infusion of myeloperoxidase accentuates glomerular injury.³⁵⁻³⁶ Of in-

Table 2. Factors which enhance the respiratory burst of immune complex stimulated leukocytes

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1. Chemotactic peptides (C5a), Formyl Peptides (FMLP).
 2. Proteases
 3. Cytochalasin B (neutrophils only).
 4. Polyelectrolyte substances
 - (a) histones
 - (b) polyhistidine
 - (c) polyarginine
 - (d) polyanethosulfonate
 5. Macrophage derived cytokines (macrophages only).
 - (a) interleukin-I (IL-1)
 - (b) tumor necrosis factor (TNF)
 6. Platelet adenine nucleotides (neutrophils only).
 - (a) ATP
 - (b) ADP
 7. Endotoxin
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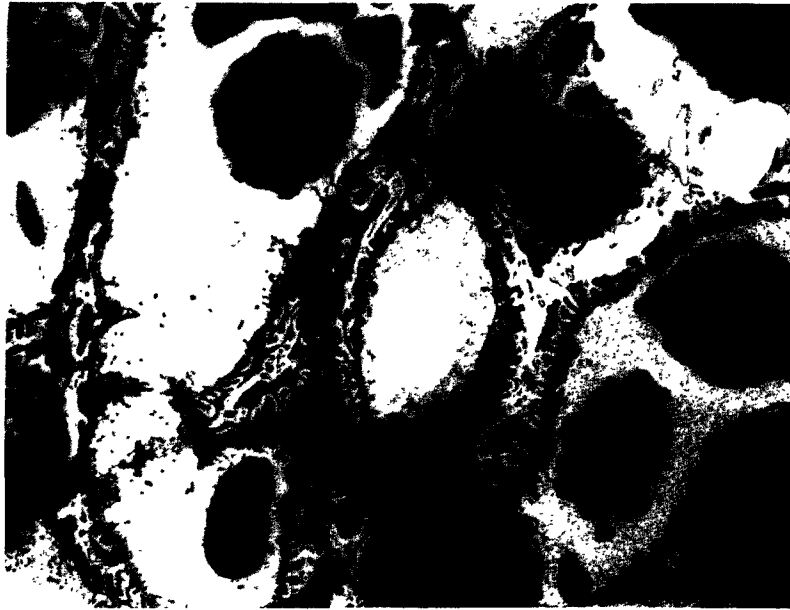


Fig. 2. Illustration of the protective effects of catalase in the heterologous anti-GBM nephritis model. Neutrophils are present in the glomerular capillaries but there is no evidence of injury.

terest is the fact that therapeutic interventions designed to either prevent the formation of the hydroxyl radical ($\cdot\text{OH}$), or to scavenge it, have been ineffective in preventing experimental glomerular injury. This also suggests that the myeloperoxidase halide products of hydrogen peroxide, such as hypochlorous acid (HOCl^-), may be more important in the pathogenesis of neutrophil dependent glomerular injury than the hydroxyl radical. However, it must be stressed that these studies are preliminary and further studies are necessary to definitively resolve this question.

Several models of IgG immune complex induced acute lung injury have been developed that are clearly oxygen radical dependent. Several years ago, our laboratory developed a model of passive immune complex lung injury where the IgG antibody is instilled into the lungs with the antigen given intravenously. Within 3–4 hours an intense inflammatory reaction develops in the lung secondary to the *in situ* formation of immune complexes in the alveolar septae.³⁷ This model gives rapid and reproducible acute lung injury. Both complement and neutrophils are required for its development. In terms of neutrophil mediators, reactive oxygen products appear most directly responsible for the initiation of the lung injury.^{38–39} The administration of superoxide dismutase results in a partial protective effect, which is overcome in time. The mechanism of this partial protection appears to be that of delaying the recruitment of neutrophils into the site. A much more prominent and long lasting suppressive effect is seen if the animals are treated with catalase, either

native or conjugated to polyethylene glycol. This protection is not overcome with time. Morphologically, (Fig. 3), neutrophils are present in the catalase treated animals, but, as was also true in the glomerulonephritis model, no tissue injury is present. More recent studies have incriminated the iron dependent formation of the hydroxyl radical as the most critical oxidant species generated in this model. Treatment with iron chelating agents such as deferoxamine are markedly protective. This protective effect is overcome if iron saturated deferoxamine is used or exogenous iron is administered.⁴⁰ Therefore, the data strongly implicates the hydroxyl radical as the cause of the tissue injury in this model. This is consistent with other models of acute lung injury developed in our laboratory. IgA immune complex injury as well as other types of non-immune complex initiated lung injury also appear to be mediated by the iron dependent formation of the hydroxyl radical.^{41–42} Therefore, this model of IgG immune complex lung injury provides a good example of the phlogistic potential of oxygen free radicals and specifically the hydroxyl radical.

Even though the IgG induced acute glomerulonephritis and lung injury models are both oxygen radical mediated, the critical oxidant species incriminated differs in the two systems. In the lung, most evidence suggests that the hydroxyl radical is responsible for the injury. In the glomerulonephritis models, on the other hand, we have been unsuccessful in documenting a role for the hydroxyl radical. Rather, there is preliminary evidence for the involvement of the myelope-

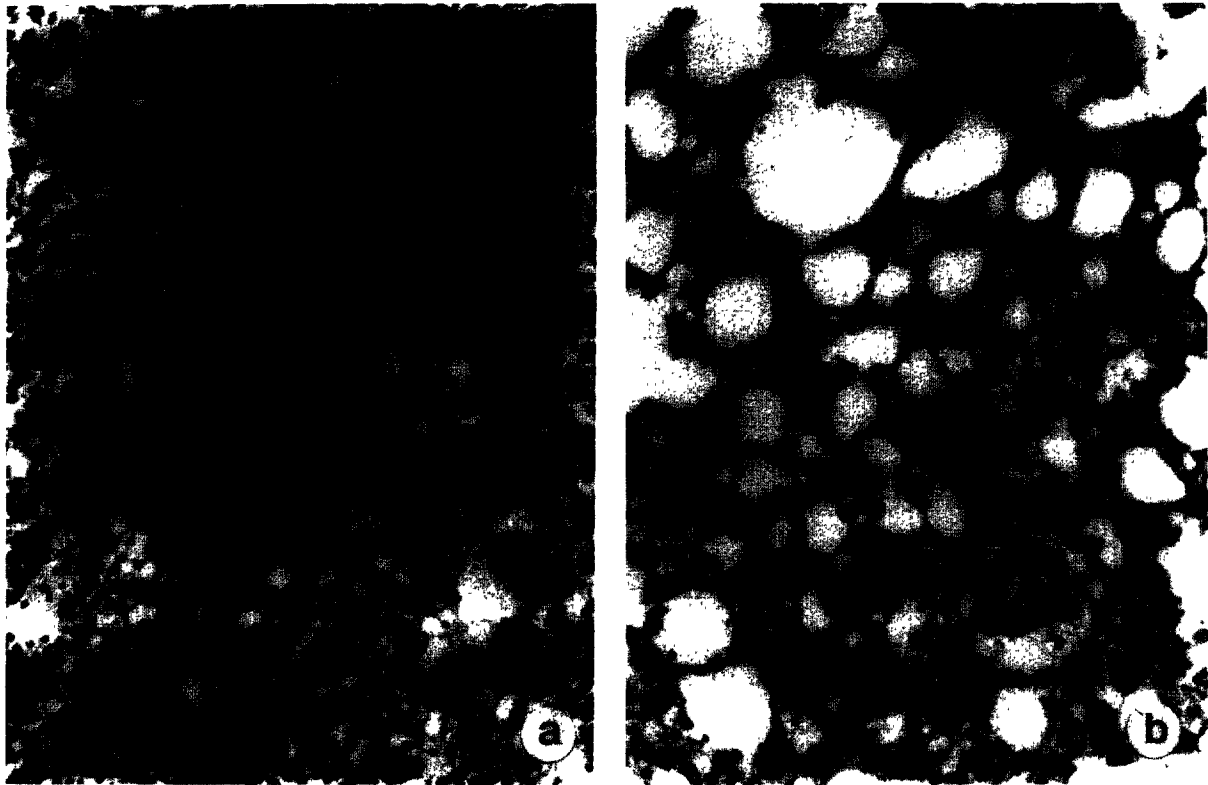


Fig. 3. Illustration of experimental IgG immune complex induced lung injury and the protective effects of catalase. (a) Pulmonary histology of an animal given IgG immune complexes. There is intense acute inflammation and hemorrhage. (b) Pulmonary histology of an animal given catalase in addition to the IgG immune complexes. Neutrophilic infiltrates are present in the interstitium but little cellular injury or hemorrhage is present.

oxidase products of hydrogen peroxide metabolism such as hypochlorous acid. Obviously, further research needs to be done before any definitive statements can be made, but it does point out that immune complex induced, oxygen radical mediated tissue injury is not identical in every organ system.

Finally, there is evidence that some experimental models of IgG immune complex tissue injury are not oxygen radical dependent. The best example of this is the Arthus dermal vasculitis model where superoxide dismutase provides a partial protective effect due to the apparent inhibition of neutrophil migration into the site.⁴³ However, this inhibition is transient, so that by the time of the maximal injury response, SOD treated animals show as severe a vasculitis as the nontreated controls. Furthermore, catalase, hydroxyl radical scavengers, and iron chelators have no protective effect in this model. Therefore, it appears that this model of immune complex injury is not oxygen radical dependent. Thus, it is clear that oxidants are not responsible for all types of immune complex induced tissue injury. Rather, other mediators such as neutrophil derived proteases or cationic proteins may be involved.⁴⁴⁻⁴⁶ All of this serves to point out the complexity of the mediation of IgG immune complex induced injury.

III. IgA IMMUNE COMPLEX INDUCED TISSUE INJURY

Recently it has become clear that IgA immune complexes initiate some human diseases. For example, the most common type of idiopathic glomerulonephritis biopsied today is associated with a predominance of IgA immune complexes in the glomeruli.⁴⁷ Figure 4 illustrates IgA immune complex deposition in the glomerulus of a patient with Berger's IgA glomerulonephritis. IgA immune complexes are also prominent in such diseases as dermatitis herpetiformis and Henoch-Schonlein purpura.⁴⁸ Until recently, we knew virtually nothing about the pathogenesis of IgA induced injury except that it appeared to differ from IgG induced injury in terms of involvement of the complement system. Systemic complement activation appears not to occur in IgA mediated diseases, although immunofluorescence studies do show localized complement deposition at the site of immune complex deposition. Additionally, corticosteroid therapy is not effective in suppressing IgA mediated injury, whereas it is often protective in IgG induced injury. In the following discussion we will summarize experimental work illustrating the different pathogenic mechanisms



Fig. 4. Direct immunofluorescence of a renal biopsy from a patient with IgA induced glomerulonephritis showing intense IgA immune deposits in the mesangial regions of the glomeruli.

involved in IgA and IgG immune complex tissue injury. However, as we shall see, both types of injury share an identical final pathway; the formation of reactive products of oxygen associated with tissue injury.

A. *In vitro* studies on IgA immune complex stimulation of phagocytic cells

In vitro experimental studies using IgA immune complexes have found striking differences in their ability to activate phagocytic cells when compared to IgG. As shown in Table 3, IgA immune complexes activate alveolar macrophages to produce reactive oxygen products at a level comparable to that of IgG immune complex stimulation.⁴⁹ However, IgA complexes, unlike those containing IgG, do not activate neutrophils appreciably.²⁶ The reason for this selective ability of IgA immune complexes to activate macrophages but not neutrophils is not understood. However, it may be due to the fact that IgA Fc receptors are present on macrophages.⁵⁰ As detailed later, this selective macrophage activation is consistent with observations made *in vivo* that IgA immune complex injury models require macrophages rather than neutrophils to mediate the tissue injury.

IgA immune complex stimulation of macrophages can be enhanced by the addition of other inflammatory mediators. C5a augments superoxide anion production by IgA immune complex stimulated macrophages.¹⁸ Furthermore, the addition of the macrophage cyto-

kines, TNF and IL-1 also enhances superoxide production by IgA stimulated macrophages.^{26,18} (See Table 2). Therefore, similar to IgG immune complexes, these inflammatory mediators prime phagocytic cells to generate more oxidants than if IgA immune complexes alone are present. The obvious difference is that this priming effect is seen with both neutrophils and macrophages in the IgG system, whereas in IgA it occurs only with macrophages. These studies again support the *in vivo* observations detailed below that IgA immune complex injury is macrophage mediated.

B. *In vivo* studies of IgA immune complex injury

Recently it has been possible to demonstrate that IgA immune complexes induce reproducible acute tis-

Table 3. Comparison of IgA versus IgG immune complex activation of rat phagocytic cells

Cell Type	Stimulus	O ₂ ⁻ (nmol/30 min)
Neutrophils (2 × 10 ⁶)	PMA*	9.3 ± 0.8
	IgA immune complex**	1.7 ± 0.4
	IgG immune complex**	9.1 ± 0.9
	IgA alone	0.4 ± 0.7
	IgG alone	0.6 ± 0.8
Alveolar Macrophages (5 × 10 ⁵)	PMA*	9.9 ± 0.5
	IgA immune complex**	8.4 ± 0.5
	IgG immune complex**	9.8 ± 0.8
	IgA alone	0.7 ± 1.0
	IgG alone	0.9 ± 0.9

*-100 ng.

**-30 ug

sue injury in the absence of involvement of other immunoglobulins such as IgG or IgM. Although this now seems clear, there was at one time a considerable controversy over the phlogistic potential of IgA in the absence of these other immunoglobulins.

In humans, the renal glomerulus is a primary target of IgA immune complexes. The ability of IgA immune complexes to induce acute glomerular injury was initially assessed in animal experiments. Oral immunization of mice by antigens such as bovine gamma globulin results in the formation of an IgA antibody to this foreign antigen.⁵¹ These IgA immune complexes then deposit in the glomeruli, although they apparently do not cause renal dysfunction. This gut immunization model may be relevant to the study of human IgA immune complex diseases in that we know that some IgA diseases appear to be initiated by mucosal immunity. In other experimental studies, investigators found that preformed IgA immune complexes would deposit in the glomeruli of animals and result in transient hematuria.⁵² However, these models all result in relatively minor glomerular injury, making mediator studies difficult.

Several years ago our laboratory developed a model

of reproducible acute lung injury secondary to the formation of IgA immune complexes in the lung.⁴⁹ This lung injury is maximal at 3–4 hours and there are increased numbers of macrophages in the lungs of these animals, but virtually no neutrophils. Mediator studies have demonstrated that complement is required for the injury to occur and that neutrophil depletion has no effect. These depletion studies support the morphological observations that neutrophils are not responsible for IgA immune complex injury.

Even though neutrophils are not required for the development of IgA lung injury, experimental studies clearly show that oxygen radicals are responsible for the development of the injury. As illustrated in Fig. 5, treatment of the animals with superoxide dismutase, catalase, dimethylsulfoxide (DMSO) and deferoxamine are all markedly protective, while iron saturated deferoxamine is not.⁵³ It cannot be determined precisely which oxygen radical is most responsible for the injury. However, the strong protective effect of the iron chelator deferoxamine, plus the inhibitory effect of DMSO, provide good evidence that the formation of the hydroxyl radical is most critical to the evolution of the injury.

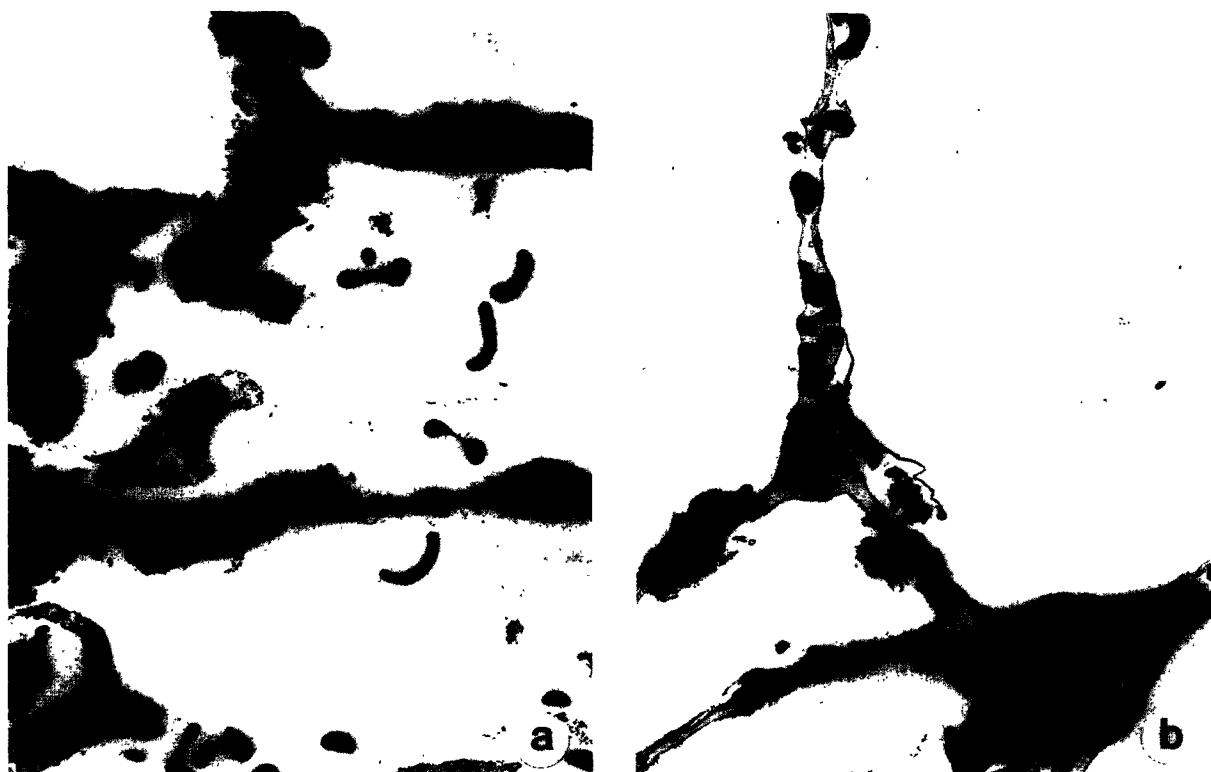


Fig. 5. Experimental IgA immune complex induced lung injury. (a) An IgA immune complex treated animal with pulmonary macrophage accumulation and intraalveolar hemorrhage. (b) The protective effects of antioxidants and iron chelators in this model as illustrated by an animal given the iron chelator deferoxamine in addition to the IgA immune complexes. Histologically, the lung appears normal.

As mentioned above, histologic evidence suggests that macrophages are the critical effector cells in this model. This is corroborated by recent studies demonstrating that they appear to be the source of oxygen free radicals.⁵³ Markedly increased numbers of macrophages are present in the lungs of the IgA immune complex injured animals as assessed by the technique of bronchoalveolar lavage. There is also evidence of *in vivo* activation of these macrophages by the IgA immune complexes. Macrophages lavaged from the lungs of the IgA immune complex injured animals produce high levels of superoxide and hydrogen peroxide spontaneously without *in vitro* stimulation. Furthermore, these macrophages appear to be primed by *in vivo* contact with the IgA immune complexes, in that a second stimulus *in vitro* such as phorbol myristate acetate, markedly increases the formation of reactive oxygen products when compared to control alveolar macrophages.⁵³ Thus it seems clear that macrophages are the source of the oxygen radicals in this type of immune complex injury. This is not unexpected given that macrophages, being phagocytic cells, have a membrane associated NADPH oxidase system and therefore can produce and export high levels of reactive oxygen products. Furthermore, we have described another *in vivo* model of acute lung injury that is not triggered by immune complexes where oxygen radicals derived from macrophages appear to be responsible for the injury.⁴⁰

In summary, IgA immune complex injury, at least that which occurs in the lung, is similar to IgG immune complex injury in that reactive oxygen products appear important in its evolution. However, unlike IgG complex injury, IgA induced injury seems to be mediated by the macrophage rather than the neutrophil. Thus, macrophages appear to be important in the initiation

of some types of immune complex triggered acute tissue injury via their production and release of reactive oxygen products. This has important implications in our understanding of the pathogenesis of human immune complex diseases particularly those associated with the deposition of IgA.

IV. SUMMARY

Historically, many human diseases have been thought to be mediated by the formation and deposition of immune complexes in the affected tissues. With the development of the classic experimental models of immune complex induced injury such as serum sickness and anti-GBM nephritis, this hypothesis was strengthened. These models clearly showed that circulating antibody complexed to antigens in the blood or formed against tissue antigens *in situ* would initiate an inflammatory response in the tissues.

Our understanding of mediators involved in the pathogenesis of immune complex induced injury has progressed markedly in the last few years. The complement system appears to be involved in many of these reactions, both by the generation of the chemotactic peptide C5a, as well as their ability to prime phagocytic cells when presented with a second stimulus. Under very specialized circumstances, complement can also directly induce injury by the generation of the terminal membrane attack complex (MAC). However, immune complex induced tissue injury is usually triggered by the activation of either neutrophils or macrophages by the immune complexes. Reactive oxygen products produced by these cells appear to be central to the development of the tissue injury.

While these statements are generally true, the latest evidence suggests that the precise mechanism of im-

Table 4. Mediation of experimental immune complex induced tissue injury in various organ systems

Organ System	Complement Dependency	Neutrophil Dependency	Macrophage Dependency	Reactive Oxygen Species Implicated		
				O ₂ ⁻	H ₂ O ₂	·OH
I. Lung						
(A) IgG immune complex injury	yes	yes	no	no	yes	yes
(B) IgA immune complex injury	yes	no	yes	yes	yes	yes
II. Skin						
IgG immune complex injury (Arthus Reaction)	yes	yes	no	no	no	no
III. Kidney						
(A) IgG immune complex glomerulonephritis						
1. Anti GBM nephritis heterologous phase	yes	yes	no	no	yes	no
2. Anti GBM nephritis autologous phase	no	no	yes	unknown	no	unknown

immune complex injury varies in different organ systems. As summarized in Table 4, IgG and IgA immune complex induced experimental lung injury involves oxygen radicals, specifically the hydroxyl radical ($\cdot\text{OH}$). However, neutrophils appear to be the source of the oxidants in IgG induced injury, whereas macrophages appear to be the source in IgA induced injury. In the kidney, some experimental models of glomerulonephritis are neutrophil mediated, whereas most appear to be macrophage dependent. In the neutrophil dependent models, such as anti-GBM nephritis, reactive oxygen products initiate the injury. Hydrogen peroxide and perhaps the myeloperoxidase halide products of hydrogen peroxide are most strongly implicated. Studies to date in these latter models have not implicated the hydroxyl radical.

Finally, some models of immune complex injury appear not to be primarily mediated by oxygen radical formation. In macrophage dependent immune complex models of glomerulonephritis, preliminary studies have so far failed to incriminate oxygen radicals in the evolution of the glomerular injury. Also, in the Arthus reaction, recent studies have not found a prolonged protective effect for oxygen radical inhibitors or for iron chelators. This suggests again that oxidants are not primarily responsible for the vascular injury in this model. In fact, proteases and/or cationic proteins may be more important in this system.

Thus, when describing the mediation of immune complex injury, it is important to remember the differences and the complexities. It emphasizes the danger of extrapolating information on immune complex injury not only from species to species, but also from one organ system to another. Hopefully, further studies will provide more of a unifying hypothesis on the pathogenesis of immune complex induced tissue injury.

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