



The Gell–Coombs classification of hypersensitivity reactions: a re-interpretation

T.V. Rajan

Department of Pathology, Room L-1037, 263 Farmington Avenue, Farmington, CT 06030-3105, USA

Gell and Coombs classified hypersensitivity reactions into four ‘types’. I suggest that the premise that these reactions represent ‘hypersensitivity’ manifestations is limiting and that they represent four major strategies that the body uses to combat infectious agents. I further propose that there is a fifth strategy that was not envisioned in the Gell and Coombs classification.

The word ‘allergy’ was first used by von Pirquet, to denote both host-protective and potentially host-injurious immune responses [1]. In a similar vein, the word ‘hypersensitivity’ was first described as denoting the status of a mammalian organism after exposure to an infectious agent. The mammal is then ‘hypersensitive’ to this agent and therefore able to deal with it effectively on second exposure. Over the past century, however, these two terms have acquired the connotation of deleterious responses. It is in the context of this deleterious connotation that Gell and Coombs developed their widely accepted classification of hypersensitivity reactions [2]. This classification has bewildered countless generations of medical students, who have found it difficult to pigeon-hole ‘immune disorders’ into this classification. Part of the confusion could be owing to the focus on ‘antigens’. It is increasingly clear that the immune system is designed to combat infections. It recognizes invasive organisms by detecting the presence of molecules that are structurally foreign. The immunological response to these ‘antigens’ is a byproduct of the recognition of invasive organisms and not the primary evolutionary drive for its existence. It is perhaps a reflection on the confusing nature of this scheme that recent editions of textbooks of medicine (for instance, Harrison’s Principles of Internal Medicine [3]) eschew this classification and instead describe diseases of immunopathological origin or overtones in terms of the putative mechanism of injury [4].

Despite the apparent disfavor to which the Gell and Coombs classification has fallen at least in some circles over the past few years, I would like to propose that it is useful in the original meaning of the term allergy. The four ‘types’ of hypersensitivity reactions can be viewed as describing broad strategies that the body uses in order to combat classes of infectious agents. I would further like to

propose that the mammalian organism uses a fifth strategy, another ‘hypersensitivity reaction’, which was not specifically conceived by Gell and Coombs.

Type I ‘hypersensitivity’ reaction

Of the four major hypersensitivity reactions, this has the most clear-cut immunopathological correlation. In the Gell–Coombs conception, disorders, such as hay fever or allergic asthma, are classic examples of Type I hypersensitivity. They implied that these disorders are driven predominantly by IgE bound to mast cells. On engagement of the cytophilic IgE with its appropriate antigen, mast-cell degranulation and subsequent release of histamine (causing an immediate reaction), leukotrienes (resulting in the more delayed symptoms) and other mediators, the classic symptoms of allergic airway disease result.

...disorders, such as hay fever or allergic asthma, are classic examples of Type I hypersensitivity.

Because immune reactions are more likely to have arisen for host protective reasons than purely for the discomfort of the host, I suggest that Type I hypersensitivity is a strategy designed to prevent multicellular, metazoan parasites from taking up residence in the respiratory and gastrointestinal systems. The result of mast-cell degranulation is not only vasodilatation and the outpouring of exudative fluid but also goblet-cell hyperplasia, synthesis of mucin of increased viscosity and increased peristaltic movement. It is clear that these strategies are used by the body to eliminate gastrointestinal pathogens. Indeed, the work of Carlisle *et al.* [5] has clearly demonstrated that parasitic nematodes can be successfully eliminated by the host by entrapment in mucin of such viscosity that the parasite does not successfully enter the epithelial cells lining the gut, the ecosystem in which it can further its morphogenesis. Thus, the viscous, inspissated mucus that is one of the troubling symptoms of asthmatic patients has a host-protective role in parasitic infection. Similarly, the longstanding work of Finkelman *et al.* [6] has shown that permutations of IgE, mast-cell and eosinophil degranulation, and

Corresponding author: T.V. Rajan (rajan@neuron.uchc.edu).

epithelial-, Paneth- and smooth muscle-cell activity are responsible for host protection in parasitic infections.

Type II hypersensitivity reactions

In the Gell–Coombs formulation, Type II hypersensitivity reactions are characterized by antigen–antibody interactions, resulting in the local production of anaphylotoxin (C5a), the recruitment of polymorphonuclear leukocytes (PMNs) and subsequent tissue injury due to the release of hydrolytic neutrophil enzymes after their autolysis. Classic examples of this kind of hypersensitivity reactions are the vasculitides.

...Type II hypersensitivity reactions are characterized by antigen–antibody interactions, resulting in the local production of ... C5a, ... recruitment of ... PMNs and subsequent tissue injury...

I propose that this reaction is the strategy used by the mammalian organism to deal with small extracellular pathogens that can be successfully ingested and subsequently killed by PMNs. The two reactions that are seen as ‘deleterious’ are merely designed to perform two important host-protective actions. First, the interaction of antibodies with ‘antigens’ is designed to permit the opsonization of extracellular bacteria that might be resistant to phagocytosis. Second, the release of neutrophil chemoattractants (such as C5a) are designed to attract PMNs to the site of inflammation. Thus, as might be the case in the Type I hypersensitivity reactions, Type II hypersensitivity reactions would be host-destructive only when they occur inappropriately, more intensely than designed or as a result of a misperception of the presence of a foreign invader, even although there is no real threat.

Type III hypersensitivity reaction

In the Gell–Coombs system, Type III hypersensitivity reactions occur when antibody reactions occur in the blood, resulting in the formation of antigen–antibody complexes, which are deposited in the glomerular and/or pulmonary basement membranes. Here, the very presence of these complexes, in addition to the PMNs attracted by complement activation, results in tissue injury and compromised function.

...Type III hypersensitivity reactions occur when antibody reactions occur ..., resulting in the formation of antigen–antibody complexes...

I propose that the evolutionary drive for this reaction is to handle circulating viral particles. In nature, the

antigen–antibody reactions occurring in the bloodstream during the viremic phase would prevent the virus from reaching potential target cells and causing further damage. The potential deleterious outcome of these reactions is the one visualized by Gell and Coombs in their formulation. However, under most physiological circumstances, the outcome is probably more favorable to the host. Early in the development of immunology as a discipline, Heidelberger found that the amount of complement per complexed antibody molecule decreased as the amount of fresh serum was increased [7]. The solution to this counter-intuitive observation came from the work of Miller and Nussenzweig who first showed that the binding of complement to antigen–antibody complexes has an unexpected result [8]. Although the mechanisms are not yet fully understood, the binding of excess complement (primarily C3) to preformed antigen–antibody complexes results in their disaggregation into smaller entities that no longer bind more complement. Takahashi *et al.* [9] further showed that these complexes do not activate the lytic components of complement and do not release anaphylotoxins. They also showed that these smaller complexes can be ingested by the reticulo-endothelial system (RES; the complex of littoral macrophages in the spleen and liver) and eliminated. Thus, this reaction, the formation of antigen–antibody complexes has, in fact, a host protective response and is perhaps the ideal one to eliminate circulating viral particles. In this context, it is interesting to note that clinicians have long noted that renal disease in systemic lupus erythematosus (SLE) is inversely related to complement levels [8]. It is tempting to suggest that the mechanism delineated by the work of Nussenzweig and Takahashi does not take place when C3 falls below critical levels, resulting in the failure to degrade antigen–antibody complexes into small, soluble fragments, and permitting their deposition in areas that are inimical to the host. Thus, as with other ‘hypersensitivity reactions’, it appears highly likely that the ‘Type III hypersensitivity reaction’ was evolutionarily designed for protection and becomes deleterious when the demands exceed the capacity of the system.

Type IV hypersensitivity reactions or cell-mediated reactions

Gell and Coombs conceived several organ-specific autoimmune disorders as falling into the Type IV hypersensitivity reactions. One example would be insulinitis, seen in the early phases of insulin-dependent diabetes mellitus. Here, the islets of Langerhans are infiltrated by a mixed cellular population comprising T cells, macrophages, natural killer (NK) cells and other leukocytes. Destruction of host cells ensues, by a combination of apoptotic death and cytotoxicity.

...several organ-specific autoimmune disorders [are] Type IV hypersensitivity reactions.

As for the other cases of ‘hypersensitivity’, this reaction is clearly an aberration of a well orchestrated cellular

response to pathogens. Viral infections are best dealt with by the mobilization of cytotoxic T cells, which can delete infected cells before they can produce more viral progeny. The relationship of the Type IV cell-mediated response to both host protection and injury is quite clear. Using the paradigm of insulin dependent diabetes mellitus, it is not surprising that there appears to be a relationship between antecedent viral infection, susceptible MHC class II alleles and the onset of insulinitis [10]. The mechanisms that underlie host protection (control of cell proliferation and metabolism by cytokines; induction of apoptosis of target cells by Fas–FasL interactions or by perforin-granzyme mediated apoptosis) are similar to those that cause deleterious effects to the host.

Type V hypersensitivity?

In this context, I would like to raise the possibility that there is another strategy that is used by the body to deal with a class of infectious agents, for which there is perhaps a deleterious ('hypersensitive') outcome as well. This paradigm is phylogenetically ancient, and appears to be used by many metazoan genera (even phyla) to deal with large, metazoan extracellular parasites. Strand and Pech [11] and Christensen and Fortan [12] have independently documented the response of insects to the presence of nematode larvae within them. In many of these instances, resistant strains or species of insects ensheath invading organisms with pseudo-coelomic hemocytes, followed (often) by a series of reactions resulting in the deposition of melanin. This ensheathment and melanization results in the death of the parasite. The latter of these reactions (melanization) does not appear to be used by mammalian cells but the process of ensheathment of indigestible foreign material is used and is referred to as granuloma formation. In contrast to invertebrate organisms, in which the reaction is mediated entirely by what would be called the innate immune defense, some mammalian granulomas

are orchestrated by the adaptive immune system, particularly T cells. Granulomas are clearly effective in mediating host protection and are widely used in dealing with both inanimate foreign objects (foreign body granulomas) as well as diverse infectious agents, including mycobacteria, fungi and perhaps metazoan extracellular parasites. There are at least three distinct forms of the granulomatous response. The first of these has been called the non-immune or 'foreign body' granuloma by pathologists. This seems to take place in the absence of adaptive immunity and might be evolutionarily closest to the ensheathment reaction of insects. In the pathology literature, all other granulomas are 'immune' and are typified by the formation of epithelioid cells (modified macrophages). Characterization of cytokine responses has shown that there are at least two different 'immune' granulomas. One is typified by a Type 1 cytokine milieu and is seen in response to pathogens, such as *Mycobacterium tuberculosis*. The second is characterized by a Type 2 milieu and is seen in response to extracellular, multi-cellular metazoan parasites, such as the Schistosomes.

...possibility ... there is another strategy that is used by the body to deal with a class of infectious agents, ... [with] perhaps a ... 'hypersensitive' outcome as well.

Conceivably, the 'hypersensitivity' counterpart to this is sarcoidosis. Sarcoidosis has long been known as a disease characterized by the formation of disseminated granulomas, with no known etiological agent despite the best efforts of countless researchers. Granuloma formation

Table 1. Infection-centric view of immune responses

Pathogen	Gell–Coombs scheme	Effector mechanism	Possible untoward consequences
Gastrointestinal or respiratory tract multicellular, metazoan parasites	Type I	Orchestrated by Th2 cells. Effectors include IgE antibody (+ IgE1 in mouse), mast cells, Paneth cells, mucosal glands, smooth muscle cells	Anaphylaxis, hay fever, asthma
Extracellular microorganisms (staphylococci, streptococci)	Type II	Antibodies to surface antigens of microorganisms, C5a release, chemotaxis of polymorphonuclear leukocytes (PMNs) to site of infection	Certain drug reactions; the vasculitides such as polyarteritis nodosa; Graves disease (agonist antibody to thyroid stimulating); myasthenia gravis (antagonist antibody to acetylcholine receptor)
Circulating viral particles, such as in viremia	Type III	Antibodies complexing with and inactivating circulating viral particles; subsequent solubilization by C'. CD4 and CD8 cells recognizing MHC antigens presenting viral peptides	Immune complex disease, such as in systemic lupus erythematosus (SLE)
Viral or intracellular bacterial infection	Type IV		Insulin dependent diabetes; Hashimoto's thyroiditis
Extracellular, indigestible agents, such as <i>Mycobacterium tuberculosis</i> , Schistosome eggs	Not included	Formation of granulomas that encapsulate and isolate the pathogen. Driven by innate immunity ('foreign body') or type 1 (<i>M. tuberculosis</i> infections) or type 2 (Schistosome eggs) cytokines	Sarcoidosis?

often proceeds to the point that deleterious consequences ensue. Is it possible, consistent with the other 'hypersensitivity' reactions, that sarcoidosis is merely another instance of the host response to an imagined insult or an over-reaction to a real but as yet undiscovered infectious agent? If this were so, we should add a 'Type V' category to the Gell–Coombs classification.

In summary, the classical work of Gell and Coombs in classifying hypersensitivity reactions has not stood the test of time very well (Table 1). In part this appears to be because the classification has focused on the deleterious consequences to the host, without necessarily paying attention to their evolutionary drive. Perhaps it is useful to consider these reactions not only from the deleterious aspect but perhaps from the host protective aspect as well.

Acknowledgements

This work was made possible by grants AI 39705 and AI 42362 to T.V.R. I would like to thank Robert Clark, Thiru Ramalingam, Leo Aguila and Bhargavi Rajan for critical review of this manuscript.

References

- 1 Bendiner, E. (1981) Baron von Pirquet: the aristocrat who discovered and defined allergy. *Hosp. Pract.* 16, 137–144
- 2 Gell, P.G.H. and Coombs, R.R.A. (1963) The classification of allergic reactions underlying disease. In *Clinical Aspects of Immunology* (Coombs, R.R.A. and Gell, P.G.H., eds) Blackwell Science
- 3 Haynes, B.F. and Fauci, A.S. (2001) Disorders of the immune system. In *Principles of Internal Medicine* (Braunwald, E. et al., eds), pp. 1805–1913, McGraw-Hill
- 4 Descotes, J. and Choquet-Kastylevsky, G. (2001) Gell and Coombs's classification: is it still valid? *Toxicology* 158, 43–49
- 5 Carlisle, M.S. et al. (1991) Intestinal mucus entrapment of *Trichinella spiralis* larvae induced by specific antibodies. *Immunology* 74, 546–551
- 6 Finkelman, F.D. et al. (1997) Cytokine regulation of host defense against parasitic gastrointestinal nematodes: lessons from studies with rodent models. *Annu. Rev. Immunol.* 15, 505–533
- 7 Heidelberger, M. (1941) Quantitative chemical studies on complement or alexin I. *Method. J. Exp. Med.* 73, 681–694
- 8 Miller, G.W. and Nussenzweig, V. (1975) A new complement function: solubilization of antigen-antibody aggregates. *Proc. Natl. Acad. Sci. U. S. A.* 72, 418–422
- 9 Takahashi, M. et al. (1976) Mechanism of solubilization of immune aggregates by complement. Implications for immunopathology. *Transplant. Rev.* 32, 121–139
- 10 Fohlman, J. and Friman, G. (1993) Is juvenile diabetes a viral disease? *Ann. Med.* 25, 569–574
- 11 Strand, M.R. and Pech, L.L. (1995) Immunological basis for compatibility in parasitoid–host relationships. *Annu. Rev. Entomol.* 40, 31–56
- 12 Christensen, B.M. and Forton, K.F. (1986) Hemocyte-mediated melanization of microfilariae in *Aedes aegypti*. *J. Parasitol.* 72, 220–225

News & Features on BioMedNet

Start your day with *BioMedNet's* own daily science news, features, Research Update articles and special reports. Every two weeks, enjoy *BioMedNet Magazine*, which contains free articles from *Trends*, *Current Opinion*, *Cell* and *Current Biology*. Plus, subscribe to Conference Reporter to get daily reports direct from major life science meetings.

<http://news.bmn.com>

Here is what you will find in News & Features:

Today's News

Daily news and features for life scientists.

Sign up to receive weekly email alerts at <http://news.bmn.com/alerts>

Special Report

Special in-depth report on events of current importance in the world of the life sciences.

Research Update

Brief commentary on the latest hot papers from across the life sciences, written by laboratory researchers chosen by the editors of the *Trends* and *Current Opinions* journals, and a panel of key experts in their fields.

Sign up to receive Research Update email alerts on your chosen subject at <http://update.bmn.com/alerts>

BioMedNet Magazine

BioMedNet Magazine offers free articles from *Trends*, *Current Opinion*, *Cell* and *BioMedNet News*, with a focus on issues of general scientific interest. From the latest book reviews to the most current Special Report, *BioMedNet Magazine* features Opinions, Forum pieces, Conference Reporter, Historical Perspectives, Science and Society pieces and much more in an easily accessible format. It also provides exciting reviews, news and features, and primary research. *BioMedNet Magazine* is published every 2 weeks.

Sign up to receive weekly email alerts at <http://news.bmn.com/alerts>

Conference Reporter

BioMedNet's expert science journalists cover dozens of sessions at major conferences, providing a quick but comprehensive report of what you might have missed. Far more informative than an ordinary conference overview, Conference Reporter's easy-to-read summaries are updated daily throughout the meeting.

Sign up to receive email alerts at <http://news.bmn.com/alerts>