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Foreword

While there is no doubt that clinical medicine and research go hand in hand, it does have considerable merit to reflect periodically on the progress in research. This allows one to gain or regain one's perspective and, on occasion, may channel the reader's thinking and future efforts along new and brighter paths.

Frontiers of Gastrointestinal Research will serve as a means of communicating current thoughts and trends in research and gastroenterology. Each volume will contain a number of original contributions pertinent to a particular aspect of the main topic to which the volume is devoted. It is in this fashion that 'Frontiers' will complement the existing publications in gastroenterology.

LEO VAN DER REIS
Editor in Chief

Contents

The Immunological Basis of Coeliac Disease

ADRIAN P. DOUGLAS

The Immunopathology of Intestinal Granulomatous Disease

WALTER R. THAYER, jr.

Ulcerative Colitis

D. P. JEWELL

Chronic Active Hepatitides

IAN R. MACKAY

Front. gastrointest. Res., vol. 1, pp. 1–11 (Karger, Basel 1975)

Alimentary and Gastrointestinal Allergy[1]

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Contents

I. Introduction

The term allergy is much misused; but it can be defined, and there is no better substitute. Immunologists use the term to describe an altered reactivity to an antigenic substance, as first suggested by VON PIRQUET. The clinician should properly only use the term when the pathophysiological changes he observes can be ascribed to a well-defined process in which allergic reactivity is the underlying mechanism.

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II. Types of Allergic Reactions

On the basis of current knowledge of immune reactions, a classification into four basic types has been widely accepted. Type I or anaphylactic allergy describes the reaction between a substance possessing antigenic determinants, the allergen, and immunoglobulins of IgE class (or IgND) called reagins: since the reaginic antibody is markedly cytophilic, the reaction involves cell membranes. Those cells, which contain powerful pharmacologically active amines such as ubiquitous mast cells, release their contents as a consequence of the reaction on their surfaces. These are not complement-dependent reactions. However, a histamine-releasing substance, anaphylatoxin, may be formed *in vivo* in the serum as a consequence of allergen-reagin complexing and triggering complement interactions. The histamine so released may play a role in producing symptoms.

In type II reactions circulating antibodies of a class capable of activating complement (IgG and especially IgM) react with antigens of the cell surface or antigens or haptens attached to the cell surface. The activation of complement is a major factor in causing damage to the target cell.

Type III reactions are those in which soluble complexes of antigen and antibody, formed in the presence of antigen excess, activate complement and exert a toxic effect on cells of tissues primarily or secondarily as a consequence of inducing damage to the cells of blood vessels. Immune complexes possess a number of properties, including that of underlying anaphylatoxin production (already referred to), which may play an undefined role in pathogenesis.

Delayed or type-IV reactions involve interaction of allergen and 'allergized' cells of the mononuclear type. The result is a subacute or chronic inflammatory response involving cell damage or destruction. The mechanism is quite unclear, and the extent to which various factors – such as complement activation – may contribute to the picture of chronic inflammatory response is uncertain. The best example of this type is the tuberculin reaction.

III. Allergic Reactions in the Gastrointestinal Tract

The human gastrointestinal tract comprises a number of more or less differentiated structures in which conditions would allow any of the above types of allergic reactions to occur. Since its function is as a receptor and processor of food, it is regularly exposed to exogenous allergens (both proteins and haptens), and to enzymatic breakdown products of proteins which may

themselves be allergenic [29]. In addition, the tract – particularly its lower part – is a reservoir for microorganisms, some of the products of which are allergenic. It may also be infested with parasites such as pathogenic protozoa, nematodes, and the like. Finally, components of its own structures may themselves serve as allergens, as a consequence of alterations of tolerance or antigenic configuration. These have not been implicated in acute type-I reactions, but they may be involved in type-III or immune-complex reactions and in cell-mediated chronic inflammatory type-IV reactions.

It may be argued that a working understanding by the practising gastroenterologist of these phenomena is important for a number of reasons. Intolerance of specific foods often presents as an intractable clinical problem. The causes are poorly defined. Individual food prejudices may be cultural or – in an indeterminate number of instances – expressions of underlying organic causes. Of these, deficiency of specific digestive or other enzymes and allergy are probably most common. Most often the patient's problems remain unresolved. A second reason is that chronic or relapsing inflammatory diseases of unknown etiology, involving the stomach and small and large bowel, are prevalent and constitute a large part of gastrointestinal practice. The clinician is now armed with a number of drugs and uses them to treat these conditions, but their effectiveness is mostly poorly evaluated and the side effects are not inconsiderable. Further, for many reputable clinicians, the term allergy seems to connote an ill-defined and not quite reputable area of medicine, in which there is a lack of correlation of skin-testing, desensitization, allergenic exclusion, and therapeutic success. Yet the means to investigate whether allergy underlies some cases of gastrointestinal disease are now becoming available.

The historical example of DICKE's observations on the beneficial effects of gluten exclusion in celiac disease is unlikely to be repeated very often, but well-conducted trials of dietary exclusion and rational use of such drugs as antihistamines and antiinflammatory agents in conditions where there is a possibility of allergic involvement may lead to therapeutic advances and even changes in understanding of the fundamental causes of some gastrointestinal diseases. It is even possible that gastrointestinal disturbances dismissed as 'functional' or as irritable bowel disease may in some instances prove to have an allergic basis.

Other contributions to this volume deal with possible involvement of cell-mediated type-IV allergic reactions – particularly involving autoallergens in chronic gastritis, regional enteritis, and nonspecific ulcerative colitis. The pathogenic significance of immune complexes involving type-III reactions is discussed by JEWELL in relation to nonspecific ulcerative colitis. The various

ways in which wheat gluten or the products of its partial proteolysis may be involved in causing and perpetuating small intestinal lesions in celiac disease are treated fully by DOUGLAS.

Therefore, the remainder of this chapter will be directed mainly to presentation of evidence for acute or type-I allergic responses and their investigation and management; it will also include consideration of such poorly understood phenomena as allergic and esinophilic gastroenteritis and some of the recent evidence suggesting that chronic mucosal damage may result from allergic reactions to dietary proteins other than wheat gluten, such as those of milk and soya bean.

IV. Acute Gastrointestinal and Alimentary Allergy

The occurrence of acute allergic reactions as a consequence of ingesting specific proteins by sensitive individuals is well documented. Reactions may be chiefly in the gastrointestinal tract (gastrointestinal allergy) or occur elsewhere in the body (alimentary allergy). An important historical example was that of KÜSTNER who reacted with urticaria, conjunctival oedema, bronchial congestion, and vomiting to ingestion of cooked fish – even in trace amounts and without his knowledge [24]. With PRAUSNITZ, he devised the test named after them, which first provided good evidence that specific antibodies were involved in acute food allergy. ISHIZAKA and ISHIZAKA [17] have published data which suggest that these antibodies, the so-called reagins, are of the IgE class of immunoglobulins. These investigators have shown [30] that there are IgE-containing plasma cells in the mucosa of the small intestine which could be responsible for producing specific IgE antibody as a consequence of stimulation by allergens in the alimentary tract.

The Prausnitz-Küstner (PK) test is of great value for detecting specific reagins, but the risks of transmitting viral hepatitis have resulted in its rarely being used recently in man. It cannot be elicited in lower mammals, but it can be in other primates; these may provide a useful tool, as may the recently described use of human skin *in vitro* [12]. However, the sera of only about two thirds of subjects with a clear-cut clinical history of severe, acute-type gastrointestinal and alimentary allergy will give positive PK tests. A radioallergosorbent technique has been devised and may prove to be a highly sensitive means of detecting specific reagins [34]. The results show a very high concordance with provocation tests. Generally, skin testing has provided poor correlation and has tended to fall into disrepute [27].

V. Significance of Circulating Antibodies

Detection of IgG and IgM serum antibodies to various dietary proteins by standard techniques such as gel diffusion and passive hemagglutination has revealed only that both sensitive and apparently nonsensitive and healthy individuals may have demonstrable antibodies to milk and other proteins in their sera. Such antibodies may occur more frequently, and their mean titer may be higher in subjects with chronic inflammatory bowel diseases such as celiac disease; but these findings could be a consequence of increased immunological activity in the inflamed intestinal mucosa. The alternative explanation of increased absorption of macromolecules such as dietary proteins by damaged intestinal epithelium seems less likely. There is a suggestion in the work of SAPERSTEIN *et al.* [26] that the presence of heat-stable serum antibodies to milk proteins, demonstrable by passive cutaneous anaphylaxis (PCA) in the guinea pig, correlates with allergy to cow's milk in children. There was a poor correlation with reactions to oral challenge with the same protein [11], and in a study by COLLINS-WILLIAMS and SALAMA [6] positive PCA reactions to milk protein were obtained only with the sera of subjects allergic to milk proteins when they were ingesting milk. JEWELL and TRUELOVE [19] found a higher incidence of atopy – manifest as asthma, hay fever, and eczema – in subjects with ulcerative colitis and Crohn's disease than in healthy people but they found no evidence of specific reagins to milk proteins in these diseases, using a red cell-linked antigen-immunoglobulin technique. Such studies should probably be expanded to examine a broader spectrum of potential allergens. Demonstrations in intestinal secretions of specific antibodies to dietary proteins have not been of diagnostic value so far.

VI. Alactasia and Food Intolerance

Earlier some subjects intolerant to cow's milk might have been regarded as allergic to one or more of its proteins. In recent years, though, the gastrointestinal disturbances following ingestion of cow's milk have been associated with a failure to handle its lactose content, the failure being due to deficiency of β-galactosidase in the jejunal brush border [8]. As a result the absorption of lactose is impaired, and the disaccharide accumulates in the lumen of the intestine where it is metabolized by bacteria. Just how it produces all the symptoms ascribed to it is unclear, although the diarrhea is probably due to the water-retaining effect of lactose and its subunits. The amounts of lactose

necessary to produce gastrointestinal disturbance appear from the studies of CADY *et al.* [5] to be so large as to cast doubt on whether alactasia is often the major cause for cow's milk intolerance. The studies of LIU *et al.* [22] suggest that a deficiency of intestinal lactase may occur secondarily as a consequence of mucosal damage caused by sensitivity to milk protein. This seems to be a possibility worth further investigation. A similar situation occurs in celiac disease associated with ingestion of wheat gluten, where lactase-deficiency certainly occurs – apparently as a consequence of damage to the jejunal mucosa. Although milk intolerance occurs in some untreated celiac subjects, it is not very common, and cow's milk is a most useful component of the diet in this disease.

VII. Criteria of Gastrointestinal Allergy

INGELFINGER *et al.* [16] critically reviewed the evidence for gastrointestinal allergy 25 years ago and put forward reasonable criteria which should be met in order to establish such a diagnosis. One of these criteria, namely disturbance consequent on introduction of the suspected allergen into the diet unknown to the subject under investigation, seems not to have been achieved in a systematic way in cases of immediate sensitivity, though it has been more successfully applied in celiac disease, in which the delayed type of response is held by many to be involved. Our own studies of immediate-response reactions, using so-called elemental diets, have been disappointing, because the diets have been poorly tolerated by otherwise healthy subjects. The other essential criterion – evidence that intolerance of a foodstuff is due to immunological reactions – is very hard to meet directly, both in the case of immediate and delayed-type reactions. An example of the latter is again celiac disease, where the controversy between proponents of the enzyme-deficiency theory and those of the immunological theory continues. In the case of immediate-type reactions, manifest anaphylaxis is acceptable evidence of immune response – especially if associated with a positive PK reaction; but less dramatic responses are still properly viewed with doubt, since their immune basis cannot be established with certainty.

The subject of so-called milk allergy in infants has been reviewed recently [13]. According to HEINER *et al.* [15], 0.3–0.7% of infants are sensitive to cow's milk, but most tend to become tolerant as they mature. The commonest symptom is diarrhea. WALDMANN *et al.* [33] have described a number of children with a severe type of food intolerance which they term allergic gastro-

enteropathy. The features are abdominal discomfort, nausea, vomiting, and diarrhea after ingestion of specific foods; there are frequently rashes and respiratory disturbances, and protein-losing enteropathy and gastrointestinal blood loss occur. In our present state of ignorance, it appears legitimate to regard these patients as belonging in the same spectrum as HEINER's infants, who failed to thrive and developed iron-deficiency anemia as a consequence of gastrointestinal bleeding while fed on cow's milk. Exclusion of cow's milk from the diet resulted in remissions in both groups of patients. One feature of WALDMANN'S patients was the circulating eosinophilia and eosinophilic infiltration of the intestinal lamina propria, and LEINBACH and RUBIN [21] have published small-bowel biopsies taken from such patients in which villous atrophy was very marked. It seems likely that those patients who have been somewhat arbitrarily classified as having eosinophilic gastroenteritis are likely to be manifesting what may well be a similar basic disturbance. Finally, GRYBOSKI [14] and SACCA [25] have described subjects in whom rectal mucosal lesions of a chronic inflammatory type, as seen in nonspecific ulcerative colitis, were perpetuated by ingestion of cow's milk and disappeared following its exclusion.

Consideration of the range of clinical and pathological features displayed by patients reported under the various labels mentioned above suggests that many of the basic types of allergic response may result from immune sensitization to dietary antigens. The determinants of the type of reaction which will predominate are clearly not established. Celiac patients who have been effectively brought into remission by gluten exclusion present a wide spectrum of responses to reintroduction of gluten. These range from a gradual deterioration of small-intestinal function associated with chronic mucosal inflammation and subtotal atrophy (possibly manifestations of type-III and -IV allergic reactions) to acute anaphylactoid reactions manifested by massive cramping, diarrhea, fever, and leucocytosis, which has been termed gliadin shock [20]. SHINER [28], using electronmicroscopy, has studied sections of small-intestinal mucosa taken from celiac children in remission who were challenged with gluten 2–98 h preceding biopsy. Significant changes were noted to occur in a time relationship compatible with a concept of antigen-antibody complex formation in connective tissue with resulting damage to vascular endothelial and epithelial basement membranous structures.

Another piece of evidence for great variation in responsiveness is that some subjects with celiac disease exhibit sensitivity to minute amounts of ingested gluten, whereas others can tolerate quite appreciable amounts. This is clearly a very complex matter, involving the state of the allergen (for instance,

whether it is cooked or uncooked), the mode of its presentation, the types of antibody and allergised cells involved, and the reactive sites. Allergens other than gluten may be involved. Thus AMENT and RUBIN [1] have documented a similar small-intestinal sensitivity to soy protein, the mucosal changes being apparently identical with those occurring in gluten-induced enteropathy. Soy protein has frequently been implicated as an allergen, sometimes being associated with anaphylactic reactions [10].

Further studies of gastrointestinal allergies to other foodstuffs, using intestinal biopsy as a probe, should establish whether inflammatory infiltration and villous atrophy of the lamina propria of the jejunum are common to all these maladies or not.

Recently FREIER and BERGER [9] have reported four infants, intolerant to cow's milk protein, whose sera gave positive PK reactions with β-lactoglobulin. When treated by mouth with disodium cromoglycate, which inhibits type-I reactions, the infants ceased to react to milk. This interesting study may provide a model for well-designed therapeutic trials in the future.

VIII. Immune Deficiency

A subject to which increasing attention is now being directed is that of immune deficiency and gastrointestinal disease. There is a recent claim that a temporary IgA deficiency at 3 months of age may result in subsequent development of type-I or atopic reactions to dietary proteins as a consequence of overstimulation of a normally responsive IgE system during the IgA deficient period [31]. Whether IgA deficiency is the decisive factor in this situation is still obscure, since its functions in the gastrointestinal tract are not fully understood. Further more, its absence, which occurs in 1 out of 700 healthy persons [3], is by no means always associated with any other abnormalities of structure or function. Secretory IgA antibodies may serve to inhibit the passage of antigens across the epithelial barrier and thus prevent development of other antibodies, such as reagins, capable of producing tissue damage. BUCKLEY and DEES [4] have reported an abnormal incidence of serum precipitin antibodies to cow's milk protein in IgA-deficient subjects, which would support this concept. AUGUSTIN [2], however, has adduced evidence against such a protective role of IgA and believes that allergic disease occurs as a consequence of early contact with allergens and a genetically favored IgE pathway of antibody formation.

One chronic disease of the gastrointestinal tract which may have an

immunological basis, celiac disease, shows a greater than chance association with selective IgA deficiency [7]. In a second disease, chronic gastritis of pernicious anemia, good evidence exists for a similar association with a more widespread deficiency of IgG, M, and A [32]. It is possible that IgA may form nonpathogenic complexes with tissue antigens formed by cellular breakdown and thus protect against development of pathogenic autoallergic reactions. Such a possibility is highly speculative.

IX. Allergic Response to Intestinal Parasites

There is experimental evidence that expulsion of nematodes from the gastrointestinal tract is a consequence of immediate-type hypersensitivity or intestinal anaphylaxis [18]. MURRAY [23] has postulated that in rats antigenic stimuli by *Nippostrongylus brasiliensis* may induce synchronous development of new populations of mast cells and of plasma cells producing IgE, A, and G. IgE (reagin) reactions with *N. brasiliensis* antigen at the mucosal surface result in an acute or explosive reaction which releases pharmacological mediators which cause IgA and IgG plasma cells to release their antibodies in turn and to facilitate passage of these antibodies intercellularly to the intestinal lumen, where they immobilize the parasite. There is no published evidence for such a chain of events in intestinal infestation in man, but the concept is an attractive one and may provide a stimulus for future studies.

X. Conclusion

To conclude, it seems proven beyond reasonable doubt that some acute reactions in man are a consequence of gastrointestinal allergy. However, there is a large amount of indecisive evidence which suggests that such reactions may be much more common than has yet been proved. Conversely, many acute or subacute gastrointestinal disturbances are rather glibly termed allergic without adequate proof. In the case of chronic relapsing inflammatory disease of the gastrointestinal tract, there is no convincing evidence that immune processes are causative. In celiac disease there is some persuasive evidence that wheat gluten may exercise its undoubted toxic effects through some immune mechanism. In atrophic gastritis of pernicious anemia, autoallergic phenomena are detectable in all but a small percentage of subjects, but there are still links missing in the pathogenic chain.