Progress report
Immunoglobulins and the gut

Immunoglobulins are glycoproteins which are synthesized by plasma cells. There are five known classes in man. IgG, IgM, and IgA mediate humoral immunity. IgE constitutes the reaginic antibodies which are of importance in the pathogenesis of allergic diseases. A specific function for the fifth class, IgD, is unknown.

In addition to the carbohydrate moiety, an immunoglobulin molecule is composed of four polypeptide chains, a pair of one of the two antigenically distinct types of light chains (κ or λ; MW about 22,000) and a pair of heavy chains (MW 55,000-75,000). κ and λ light chains are common to all immunoglobulin classes, but heavy chains are specific to a particular class (eg, γ chain to IgG, μ chain to IgM, and α chain to IgA). An IgM molecule (MW about 950,000; 19S) is a polymer of five of the basic immunoglobulin units linked by sulphydryl bonds between heavy chains. The IgA which is found in serum (MW 160,000; 7S) differs from the secretory IgA found in secretions bathing mucosal surfaces; the latter (MW 380,000; 11S) is a dimer of the basic IgA unit combined with another protein—the 'secretory' or 'transport piece' (MW 60,000). 'Secretory piece', which is a glycoprotein with a high content of glycine characteristic of other mucins, probably stabilizes the secretory IgA molecule and renders it more resistant to proteolysis.

Papain cleavage of an immunoglobulin yields three fragments, two consisting of a light chain and a part of a heavy chain (Fab piece) and the third the remaining parts of both heavy chains (Fc piece). Antigen-combining functions of the immunoglobulin molecule are mediated by the Fab region, whereas non-antigen-combining functions, such as complement fixation (by IgG and IgM), passive cutaneous sensitization, and binding to monocytes, are mediated by the Fc region.

The Gut as a Central Lymphoid Organ

In birds there is a lymphoepithelial structure situated dorsal to the cloaca, known as the bursa of Fabricius, which is responsible for the efferent limb of humoral (B cell dependent) immunity. Neonatal abolition of the bursa in birds is followed by subnormal development of germinal centres and plasma cells, impaired production of immunoglobulins, and deficient antibody responses. It has been suggested that plasma cells are dependent on the integrity of this organ, primitive stem cells having to sojourn in the bursa in order to undergo further differentiation.

The mammalian equivalent of the bursa of Fabricius is not known with certainty, but may well be lymphoid tissue associated with the gastrointestinal tract. There is one human disease in which the defect in the immune system is analogous to that found in the neonatally bursectomized bird, that is, the Bruton type of hypogammaglobulinaemia. In this disease, which is characterized fundamentally by a defect in the efferent limb of humoral (B cell-dependent) but not cellular (T cell-dependent) immunity, there is a lack of lymphoid tissue in the tonsils, adenoids, and appendix.

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The Gastrointestinal Secretory Immune System

In man immunoglobulins of different classes have been demonstrated in gastrointestinal secretions\(^5,6\) and, using immunofluorescent staining techniques, plasma cells containing each of the five classes of immunoglobulins have been demonstrated in the lamina propria of the gastrointestinal tract.\(^{22-29}\) IgA is the predominant immunoglobulin in these secretions\(^5,6\), and plasma cells containing IgA predominate in the lamina propria.\(^{23-25,27,28}\) In contrast the content of IgD and IgE in gastrointestinal secretions is very small and IgD- and IgE-containing cells in the lamina propria are very sparse,\(^{25,27-29}\) even though the gut is one of the important sites of IgE-containing cells.\(^{29}\) In general the relative concentrations of the different immunoglobulin classes in gastrointestinal secretions correlates with the distribution of different immunoglobulin-containing plasma cells in the corresponding area of mucosa, and does not correlate with the concentrations of immunoglobulins in serum.\(^5,6,30\)

Most of the IgA present in gastrointestinal secretions is in the secretory (11S) form.\(^5,6\) Secretory IgA is not synthesized as an entity at a single site of synthesis. The 7S IgA immunoglobulin units are probably synthesized by the local IgA-containing plasma cells which are in the lamina propria in close relationship to the enterocytes.\(^31\) In contrast ‘secretory piece’ is probably synthesized in enterocytes, since these cells alone, together with the corresponding intercellular spaces and the surface mucous layer, stain immunofluorescently with antisecretory piece antibody.\(^5,31\) The combination of ‘secretory piece’ with monomeric or dimeric\(^{32}\) IgA is thought to take place in close relationship to the enterocytes.\(^31,33\) The different sites of synthesis of the IgA units and ‘secretory piece’ are emphasized by other experimental data. Free ‘secretory piece’ has been found in amniotic fluid and urine from premature infants, while the foetal and neonatal gastrointestinal tract contains no demonstrable IgA-containing cells.\(^{34,35}\) In addition free ‘secretory piece’ has been found in selective IgA deficiency.\(^4\) At least some of the relatively small amount of 7S IgA which appears in gastrointestinal secretions is probably derived directly from serum 7S IgA, and this is not utilized to any appreciable extent in the synthesis of secretory IgA.\(^{36,37}\) Only a small proportion of 7S IgA synthesized in the wall of the intestine in man is normally delivered to serum.\(^38\)

The plasma cells in the mucosa of the gastrointestinal tract and the secretion of immunoglobulins, in particular secretory IgA, constitute parts of a local mucosal immune defence system.\(^6\) Secretory IgA in gastrointestinal secretions contains antibodies, for instance isohaemagglutinins and viral and bacterial antibodies.\(^5\) Active immunization with orally administered antigens, such as poliomyelitis vaccine, results in local gastrointestinal production of antibodies which appear in gastrointestinal secretions and are predominantly of secretory IgA type.\(^5,6,39,40\) The secretory immune response tends to be limited to the area of mucosa exposed to antigen and this localized immune response has memory.\(^6\) After parenteral passive immunization antibodies sometimes appear in gastrointestinal secretions.\(^5\)

The gastrointestinal secretory immune system is distinct, developing and functioning to a large extent independently of that responsible for the formation of serum antibodies.\(^5\) Reduced numbers of IgA-containing plasma cells have been found in the intestine of germ-free adult animals,\(^41\) an obser-
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viation which lends support to the view that the development of the pre-
dominantly IgA-containing plasma cell system in the mucosa of the gastro-
intestinal tract depends largely on local antigenic stimulation. Clearly defined
differences exist in the antibody response to antigenic stimulation found in
secretions of the gastrointestinal tract and serum. For instance, gastrointesti-
ally administered antigens (local antigenic stimulation) can in certain
instances induce an antibody response in gastrointestinal secretions in the
absence of the inducement of appropriate serum antibodies and conversely
parenterally administered antigens can induce antibody responses in serum in
the absence of antibody responses in gastrointestinal secretions. In other
instances either gastrointestinally or parenterally administered antigens
induce both serum antibodies and gastrointestinal secretory antibodies, antigen presumably reaching antibody-synthesizing sites distant from the site
of antigen administration. Furthermore after antigenic stimulation the titres
of antibodies in gastrointestinal secretions and serum may vary independently.
Gastrointestinal secretory antibody titres often correlate better with resistance
to and recovery from certain infections than corresponding serum titres.

The mechanism of the antiviral and antibacterial action of secretory IgA
is not known with certainty. Although IgA, in contrast to IgM and certain
subclasses of IgG, does not usually fix complement, one group of investigators
have found that secretory IgA did fix complement in the presence of lysozyme
(which is synthesized by enterocytes) with resultant lysis of Escherichia coli.
This work has not been corroborated. The current view is that while IgA
does not appear to fix complement by the conventional pathway it can fix com-
plement by the alternate pathway that does not involve C1, C2, and C4, but
does consume the later components.

In addition to antiviral and antibacterial antibodies a number of auto-
antibodies have been detected in intestinal secretions in several diseases of
the gastrointestinal tract. However, an important role for such antibodies
in the pathogenesis of disease has not been established.

Immunoglobulin-losing Gastroenteropathies

Whether loss of immunoglobulins from the plasma into the gastrointestinal
tract is an important process in the catabolism of these proteins in normal
subjects is controversial, because none of the techniques available for
quantitating gastrointestinal protein loss is wholly satisfactory. However,
available data suggest that such protein loss is probably only of minor
importance in the normal metabolism of immunoglobulins. It has been
shown, however, that more than 70 diseases affecting the gastrointestinal
tract are associated with increased gastrointestinal loss of plasma proteins,
which almost certainly include the immunoglobulins. Such loss of plasma
proteins, at least in some diseases, is believed to be non-selective. Consequently the serum concentrations of the two proteins with the slowest
fractional turnover rate, albumin and IgG, tend to be reduced to a relatively
greater extent than the serum concentrations of other proteins, whose intra-
vascular pools tend to be replenished more quickly.

The mechanisms of increased gastrointestinal loss of immunoglobulins
include bulk loss of lymph fluid in intestinal lymphangiectasia, Whipple’s
disease, lymph fistulae and right ventricular failure, and exudation in
inflammatory and ulcerative lesions such as ulcerative colitis, regional
enteritis, and tumours. In many diseases such as adult coeliac disease, hypogammaglobulinaemia, hypertrophy of the gastric mucosa, amyloid infiltration of the intestine, and allergic gastroenteropathy, the mechanism of the increased enteric loss of plasma proteins is obscure.

When due to increased gastrointestinal loss low serum concentrations of immunoglobulins are associated with shortened survival half lives of these proteins in serum, but humoral immune responses are little impaired and the frequency of infections is not appreciably increased. However, patients with disorders of the gastrointestinal lymphatics in addition to having low serum concentrations of immunoglobulins, also have marked lymphocytopenia due to loss of lymphocytes from the circulation into the gastrointestinal tract. Such lymphocyte depletion is associated with impaired cellular (T cell-dependent) immune responses, in particular profound skin anergy and impaired homograft rejection.

**Intestinal Absorption of Immunoglobulins**

At least some protein molecules can cross the intestinal mucosa into the circulation without being degraded. However, little is known about the mechanisms involved with the notable exception of the immunoglobulins. In the neonatal rat transference of passive immunity from mother to young involves the transport of antibody molecules in colostrum or milk in an immunologically competent form across the small intestinal mucosa into intestinal lymphatics. It has been demonstrated that this process is selective, shows species specificity, can be competitively inhibited, and is associated with protein catabolism. Based on these experimental findings an hypothesis for the mechanism of intestinal protein transport in the neonatal rat has been put forward by Brambell. It was proposed that there is initial non-specific uptake of protein molecules into pinocytotic vacuoles in the enterocyte. It was also assumed that the proportion of the protein molecules taken up that are selectively transported would become bound to specific receptors, adapted for homologous protein, on the walls of these vacuoles and that such binding would protect molecules from catabolism.

Recently experimental data have been obtained in the neonatal rat which in large measure lend support to and extend Brambell’s hypothesis. It was shown that of the five classes of immunoglobulins only IgG is transported across the intestinal mucosa to any appreciable extent. Further, although there was some non-selective uptake of several different proteins in the intestinal wall, the uptake of IgG involved an additional specific process, a finding contrary to one of the assumptions inherent in Brambell’s hypothesis. It was shown that a major process involved in the selective uptake and transport of IgG is saturable, ie, there is a maximum absolute amount of IgG which can be taken up and transported per unit time. In addition the part of the structure of the IgG molecule which mediates these processes is the Fc and not the Fab region. This selective intestinal transport of IgG was shown to be associated with the formation of high molecular weight complexes, containing IgG, in the intestinal wall. Appreciable transport of IgG took place only across the upper one third of the small intestine and this was the only part of the gut in which complexing could be demonstrated. No complexing was apparent in the small intestine of animals greater than 21 days of age, that is,
after the termination of the selective transport process. Cortisone acetate (given on days 11-13) inhibited both the selective transport and complexing of IgG. Thus selective transport of IgG and complexing of IgG appear to be closely related phenomena. The IgG complexes did not represent IgG trapped in lysosomal vesicles, but IgG bound to cell membranes, in particular to the enterocyte microvillous membrane. This binding of IgG was critically dependent on the pH of the surrounding medium. There was considerable binding at pH 6.4 but none at pH 8.0. These data are consistent with a modification of Brambell’s hypothesis. It is suggested that there are specific receptors for the Fc region of the IgG molecule on the enterocyte microvillous membrane of the neonatal rat to which IgG molecules become attached before the formation of pinocytotic vacuoles. The presence of such receptors on the cell surface would explain the specificity of the uptake as well as the transport processes. The saturability of the uptake and transport of IgG would reflect competition for a limited number of cell surface receptors. The attachment of IgG molecules to the cell receptors could prevent the degradation of IgG molecules by the contents of both the intestine and pinocytotic vacuoles. After transcellular movement pinocytotic vacuoles probably release the IgG molecules into the villous lacteal or via the Golgi apparatus into the intercellular spaces. The major effects of minor changes in pH on the binding of IgG to membranes may be of physiological importance in the transport process. Binding of IgG to enterocyte microvillous membranes would be facilitates by the slightly acid medium of the lumen of the small intestine of the neonatal rat and the release of IgG from receptors would be facilitated by the slightly alkaline extracellular fluids.

In man the transference of passive immunity from mother to young takes place across placental entodermal epithelial cells, cells which, like the enterocyte, contain pinocytotic vacuoles and have microvilli on their free surface.

**Alpha Chain Disease**

In one of the diseases in which there is a proliferation of abnormal plasma cells (lymphoma) associated with the production of appreciable quantities of a particular immunoglobulin and/or immunoglobulin fragment, the abnormal plasma cells are localized, at least initially, to the wall of the small intestine and the immunoglobulin fragment produced in excess is a part of the heavy chain of IgA (α chain). This disease has been designated alpha chain disease. The disorder has been diagnosed in subjects from diverse geographical and ethnic origins, usually in the second to fourth decades. It is associated with finger clubbing and evidence of intestinal malabsorption, such as impaired absorption of fat, d-xylose, and vitamin B₁₂. The wall of the small intestine is thickened and the lamina propria contains an abundance of plasma cells, which often appear to be immature. Immunofluorescent staining of these abnormal cells has revealed poor fluorescence with anti-IgA conjugates, compared with that given by intestinal plasma cells in normal subjects, and no fluorescence at all with anti-κ and λ light chain conjugates. These findings suggest that the export protein synthesized by these abnormal cells is alpha chain. Furthermore synthesis of alpha chain by a jejunal mucosal biopsy from one of these patients has been demonstrated in tissue culture.
Appreciable amounts of free alpha chain have been found in serum and also in some cases in jejunal fluid, urine, and saliva. The alpha chain exists in serum devoid of light chains in a highly polymerized form and migrates on electrophoresis between the alpha 2 and beta globulins.\textsuperscript{82,85} The alpha chains belong to a single subclass of IgA (alpha 1). Serum concentrations of albumin, IgG, and IgM are reduced. One patient with alpha chain disease in whom there was apparently involvement of the respiratory tract has been described.\textsuperscript{87}

Treatment of the condition has usually been along similar lines to those advocated for other proliferative disorders of plasma cells, for instance with intermittent prednisone and melphalan or cyclophosphamide therapy. Such treatment has been associated with clinical improvement, a decrease in faecal fat excretion, and increases in the serum concentrations of albumin, IgG, and IgM.

**Immunoglobulins, Coeliac Disease, and Malabsorption**

In spite of much careful research into the aetiology of coeliac disease, the mechanism by which damage to the intestinal mucosa is induced in this disease has not been established, but the possibility that it arises primarily as a consequence of an immunological event cannot be excluded.\textsuperscript{88}

The serum concentration of IgA tends to be increased in patients with untreated coeliac disease, in common with a number of inflammatory lesions of the gastrointestinal tract such as regional enteritis and ulcerative colitis.\textsuperscript{89--93} The increased serum content of IgA is presumably to a large extent the result of an increased contribution of 7S IgA from the lamina propria of the intestine,\textsuperscript{94} even though the number of intestinal IgA-containing plasma cells may not be increased.\textsuperscript{95} In addition secretory 11S IgA can be detected in the serum of a much higher proportion of patients with coeliac disease and also regional enteritis and ulcerative colitis than normal subjects.\textsuperscript{96} In contrast to IgA the serum concentration of IgM tends to be low in coeliac disease.\textsuperscript{90,92,93,97} Although low serum concentrations of IgM in this disease can be due to increased enteric loss, the usual cause appears to be a decreased synthetic rate,\textsuperscript{98} there being reduced numbers of IgM-containing plasma cells in the bone marrow.\textsuperscript{95} However, in the jejunal mucosa, but not the rectal mucosa, the number of IgM-containing plasma cells is increased even when the serum IgM concentration is low and the patient is on a strict gluten-free diet, while the number of IgA-containing plasma cells is relatively decreased.\textsuperscript{95,97,99} Furthermore the concentration of IgM is increased and that of IgA relatively decreased in jejunal secretions.\textsuperscript{95} An increased number of IgM-containing plasma cells in the jejunal mucosa is not specific for coeliac disease, since a similar observation has been made in ulcerative colitis.\textsuperscript{100} Studies of the concentrations of IgG, IgD, and IgE in serum and jejunal secretions and the numbers of IgG-, IgD-, and IgE-containing plasma cells in the jejunal mucosa of patients with coeliac disease have failed to provide any evidence which might implicate any of these immunoglobulin classes in the pathogenesis of the disease.\textsuperscript{90,92,93,98,101,102}

Circulating antibodies to gluten or gluten extracts have been found in patients with coeliac disease, but the titres do not correlate closely with the activity of the disease. Circulating antibodies to other food proteins have also been found in patients with this disease and circulating antibodies to gluten and other dietary proteins have also been found in patients with diseases
of the gastrointestinal tract other than coeliac disease.\textsuperscript{108–108} Similarly antibodies to gluten or gluten extracts and other food proteins have been detected in jejunal secretions in patients with coeliac disease and patients with other intestinal diseases.\textsuperscript{108,109} Even so the incidence of antibodies to gluten in jejunal secretions is appreciably higher in coeliacs than in non-coeliacs.\textsuperscript{108,109} However, antibodies to food proteins found in jejunal secretions are not necessarily synthesized locally by the jejunal mucosa. They may be derived from the circulation. Indeed the antibodies to food proteins found in both serum and jejunal secretions in patients with coeliac disease could merely reflect an increased permeability of the intestinal mucosa to food proteins. These problems of interpretation have been circumvented by recent studies of the synthesis of immunoglobulins and antibodies by jejunal biopsies. It has been shown that the intestinal mucosa of patients with coeliac disease, but not those with other gastrointestinal diseases, responds to gluten challenge \textit{in vivo} with a striking increase in the synthesis of IgA and IgM.\textsuperscript{110} In addition, regardless of whether antibody to gluten is present or absent in serum or secretions, jejunal biopsies of patients with coeliac disease in remission do not produce antibodies to gluten, whereas jejunal biopsies from the same patients, but not from normal control subjects, can and do produce antibodies to gluten in response to the administration of gluten \textit{in vivo}.\textsuperscript{111} The increased synthesis of immunoglobulins by jejunal biopsies after gluten challenge could be largely accounted for by the synthesis of antibodies to gluten. This response occurs within the intestinal mucosa where the pathological process is taking place and it occurs early during the gluten challenge. The role of locally produced antibodies to gluten in the pathogenesis of coeliac disease has yet to be determined. The synthesis of these antibodies may be the primary pathological event or it may be a secondary phenomenon which may or may not mediate tissue injury. The predisposition to respond to gluten with a local intestinal antibody response may be related to the possession of a certain histocompatibility antigen, eg, HL-A\textsuperscript{8}.\textsuperscript{112} A particular histocompatibility gene may be related to a particular immune response gene. Alternatively a particular histocompatibility gene may represent proteins on the surfaces of cells which may serve as binding sites (receptors) for materials of pathological significance. In this context it is of interest that gluten binds to surfaces of enterocytes of patients with coeliac disease but not to those of normal individuals.\textsuperscript{23} Such binding may lead to direct tissue injury or it may facilitate the local antigluten-antibody response which then results in tissue injury. It has recently been suggested that the intestinal lesion in this disease may be induced by a local Arthus type of reaction initiated by a local excess of IgM-precipitating and complement-fxing antibodies to gluten.\textsuperscript{113,114}

As in coeliac disease, the small intestinal mucosa of patients with selective IgA deficiency (type IV dysgammaglobulinaemia) also contains an infiltrate of predominantly IgM-containing plasma cells.\textsuperscript{115,116} In this context it is of interest that there may be a higher incidence of selective IgA deficiency in patients with coeliac disease than in the general population.\textsuperscript{95,117–119}

There are a number of diseases other than coeliac disease in which abnormal concentrations of immunoglobulins in serum and gastrointestinal secretions may be associated with intestinal malabsorption.\textsuperscript{94} This applies in particular to a proportion of patients with primary acquired hypogammaglobulinaemia and certain types of dysgammaglobulinaemia, eg, types I and IV. The evidence of malabsorption includes impaired absorption of fat, d-xylose, and vitamin
B12. In some there is increased bacterial overgrowth in the small intestine, in some there is intestinal infestation with *Giardia lamblia*, and in some the histology of the jejunal mucosa shows partial or subtotal villous atrophy or nodular lymphoid hyperplasia.\textsuperscript{116,120–125} At the present time the relationship between these various abnormalities and reduced concentrations of immunoglobulins has not been clearly defined.

E. A. JONES

Department of Medicine, Royal Free Hospital, London

References


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E A Jones

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