Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Secretory IgA (S-IgA) binds commensal flora and other intestinal antigens and is considered an important part of the T-cell-independent mucosal immune system. This unique antibody is produced in great abundance and has a complex synthetic and secretory pathway. The biologic activities of S-IgA as a mucosal barrier have been established for more than 3 decades, and yet the lack of this antibody is one of the most common of the primary immune defects. This chapter outlines what is currently known about the gastrointestinal conditions and diseases that occur in three of the primary immune diseases in which S-IgA is absent.

SELECTIVE IgA DEFICIENCY

Incidence and genetics
IgA deficiency is the most common primary immune deficiency disease of humans, affecting as many as 1:400 individuals (Hanson, 1983; Hammarstrom et al., 2000). Although most IgA-deficient individuals are healthy, the absence of IgA is associated with the development of certain diseases, including allergy, recurrent infections, and autoimmune disease (Schaffer et al., 1991; Cunningham-Rundles, 2003; Hammarstrom et al., 2000). The genetic elements controlling IgA secretion have not been identified. In most cases the inheritance appears to be sporadic, but IgA deficiency may be inherited in an autosomal dominant or recessive fashion. Immunoglobulin abnormalities can be found in other family members, the most common defect being common variable immunodeficiency. Several studies have noted a higher frequency of mother-to-child inheritance of IgA deficiency than of father-to-child inheritance (Koistinen, 1976; Oen et al., 1982; Vorechovsky et al., 2000). One explanation is the potential transplacental passage of anti-IgA antibodies, which could result in IgA deficiency in the infant. The offspring of 27 IgA-deficient mothers have been examined; 12 had IgA levels more than 1 standard deviation (SD) below normal, and 7 had levels more than 2 SDs below normal. Of the seven with the lowest IgA levels, five had mothers who had anti-IgA antibodies during gestation (Petty et al., 1985).

Certain major histocompatibility haplotypes, HLA-A1, -B8, and -DW3, are particularly common in IgA deficiency, and linkage to specific genetic locus (i) is a subject of ongoing investigation. Haplotype analysis, linkage disequilibrium, and homozygosity mapping has indicated that HLA-DQ/DR is a major IgA deficiency gene locus (Kralovicova et al., 2003). However, this situation is complex since different histocompatibility genes appear to be linked to the immune defect in different pedigrees (De la Concha, 2002). Whatever genetic abnormality may underlie IgA deficiency, it is not always a stable defect, since IgA deficiency can disappear spontaneously, can be induced by viral infections, and can be caused by a number of disparate drugs such as phenytoin, penicillamine, captopril, and Tegretol. IgA deficiency has also been transferred or corrected by bone marrow transplantation (Schaffer et al., 1991).

Immunologic abnormalities
Humoral defects
Although S-IgA is known to be important in mucosal immunity, most people who are IgA-deficient are healthy. In fact, the earliest report described IgA deficiency in two healthy young physicians (Rockey et al., 1964). The usual explanation is that the healthy IgA-deficient individuals have increased levels of secretory IgM in mucosal secretions that compensate for S-IgA (Brandtzæg et al., 1987) or that IgA-deficient subjects who have the most illnesses may also be deficient in IgG2, a defect linked to the inheritance of Gm allotypes (Oxelius et al., 1995). Additional immunologic deficits have been identified in IgA deficiency that could increase susceptibility to infection; these include a relatively poor response to carbohydrate antigens, even if IgG2 subclass levels are normal (Hammarstrom et al., 1985), and a deficiency of IgG4 without IgG2 deficiency (French et al., 1995). Although all of these explanations have merit, the presence or level of IgM in secretions is not well correlated with health in IgA deficiency,
and IgG subclass and antibody deficits are not usually found in those who have more illnesses.

In vitro studies
The essential characteristics of IgA deficiency include a greatly reduced number of IgA-bearing B cells and a generalized failure of maturation of IgM-bearing lymphocytes into IgA-secreting plasma cells. IgA-deficient subjects have low but detectable numbers of circulating IgA B cells, but these may have a relatively immature phenotype, bearing both IgA and IgM isotypes (Conley and Cooper, 1981). Another consistent feature is a general paucity of IgA-bearing plasma cells in the intestinal tract (Crabbé and Heremans, 1967). In a number of early studies, B cells from IgA-deficient subjects were cultured with mitogens to determine their ability to secrete IgA; in most cases, little if any IgA was produced (Luzi et al., 1986). Islam et al. (1994), showed that pokeweed mitogen-stimulated peripheral blood lymphocytes of IgA-deficient subjects have a significant decrease in switch μ- to switch α-junctions and a profound decrease in Cα membrane mRNA expression, suggesting a generalized failure of switching to IgA production. Two types of defects, low expression of both secreted and membrane forms of productive C α mRNA in IgA-switched B cells and impaired IgA switching, were characterized in IgA-deficient subjects homozygous for the common major histocompatibility complex (MHC) haplotype (HLA-B8, SC01, DR3). This could reflect a blockade in post-IgA switch differentiation of B cells (Wang et al., 1999).

In the past 25 years, a number of potential reasons for failure of terminal differentiation of B cells to IgA secretion in IgA deficiency have been described, including inadequate or defective T helper cells, IgA-specific T cell suppressor cells, intrinsic B-cell defects, and in some cases the transplacental passage of maternal anti-IgA antibodies, which might suppress fetal IgA development. T-cell immunity has been emphasized because it has been tempting to suggest that a T-cell regulatory abnormality could underlie the lack of terminal B-cell differentiation. T cells of most IgA-deficient subjects do appear capable of supporting IgA production by normal B cells, suggesting that these T cells can provide the necessary cellular factors for IgA differentiation; however, more subtle T-cell defects have not been excluded (Hanson, 1983; Shaffer et al., 1991; Cunningham-Rundles, 2003).

Cytokines and IgA production
Antigen-stimulated B cells undergo isotype switch and terminal differentiation into IgA-secreting plasma cells under the influence of a number of cytokines. CD4+ T cells, in particular, regulate IgA production in the mouse and perhaps in humans, involving secretion of interleukin-2 (IL-2), IL-5, IL-6, and IL-10. A number of studies point to transforming growth factor (TGF)-β as a key cytokine in this process, prompting isotype switch and committing antigen-primed B cells to secrete IgA. With this in mind, investigators have tested B cells of IgA-deficient subjects under a number of conditions to assess the role of cytokines in IgA deficiency.

In one study, B cells of IgA-deficient subjects were found capable of secreting IgA when stimulated by a combination of anti-CD40 antibody, Staphylococcus aureus, and IL-10; while IL-10 was not absolutely required for IgA secretion for B cells of normal donors, for IgA-deficient subjects it appeared necessary for IgA secretion (Briere et al., 1994). TGF-β has also been investigated; serum levels of TGF-β in IgA-deficient sera were less than in the serum of normal donors, but the biologic meaning of this is unclear (Muller et al., 1995). Islam et al. (1994) found no difference in TGF-β mRNA in IgA-deficient individuals compared with controls. In another study, mitogen-stimulated mononuclear cells of IgA-deficient patients with the common MHC haplotype HLA-B8, -DR3 had significantly reduced IL-5 production (Lio et al., 1995).

Animal models of IgA deficiency
In addition to the nude mouse, which is IgA-deficient, there are a few other animal models of IgA deficiency. First, transgenic IgA−/− knockout mice have been generated by targeting the entire IgA switch region and the 5′ half of the constant region (Harriman et al., 1999; Mbawuike et al., 1999). A second, more indirect model emphasizes the role of TGF-β1 in isotype switch and secretion of IgA; TGF-β1 knockout has partial IgA deficiency (van Glinkel et al., 1999), and the TGF-β1R knockout has impaired mucosal IgA responses (Cazac and Roes, 2000). Similarly, mice with a deletion of IL-5R α-chain (IL-5R α−/−) have lower levels of IgA in mucosal secretions than do wild-type mice, but the levels of IgA in serum are not reduced (Hiroi et al., 1999). IL-5 is important for the development of IgA B cells in the intestine (and perhaps elsewhere), and disruption of the IL-5 receptor reduces mucosal antibody responses. In a different model, the tumor necrosis factor and lymphotixin α (a double knockout, TNF/LT-α−/−) mouse has only low numbers of total IgA-producing cells, no Peyer’s patches, and no mucosal IgA. Mice lacking exon 2 of the polymeric Ig receptor (pIgR) have very reduced S-IgA, but here, serum IgA levels are markedly increased (Shimada et al., 1999).

The role of external antigens in the development of secretory immunity has also been examined in mouse systems. Mice fed a balanced diet composed of amino acids have poorly developed gut-associated lymphoid tissue (GALT) and low levels of S-IgA, indicating that food proteins themselves may play a role in the maturation of the gut-associated lymphoid system (Da Silva Menezes et al., 2003).

IgA deficiency and the gastrointestinal tract
Role of S-IgA
S-IgA is a polypeptide complex consisting of a secretory component (SC) covalently attached to dimeric IgA and contains one joining (J) chain. S-IgA is generally directed to bacteria, viruses, and proteins normally restricted to the intestinal tract (Table 64.1). It also prevents attachment and agglutinate antigens to reduce absorption of these substances from mucosal surfaces by direct antibody-mediated exclusion. The general inability of IgA to fix complement suggests
that S-IgA serves to clear antigens while provoking little in
the way of inflammation. The S-IgA molecular complex con-
tains large amounts of attached carbohydrates that can bind
to pathogens (Schroten et al. 1998). For example, fucose,
linked α1-2 to galactose on the SC N-glycans, competes
with Helicobacter pylori for binding to gastric receptors (Falk,
et al., 1993; Boren et al., 1993). Free SC binds to
Escherichia coli (Wold, et al., 1990; de Oliveira, et al., 2001),
toxin A from Clostridium difficile (Dallas and Rolfe 1998), and both free
and S-IgA-bound SC interacts specifically with a surface
protein of Streptococcus pneumoniae (Hammerschmidt et al.
1997; Zhang et al., 2000). These lectin capacities constitute
an important mechanism by which pathogens can be pre-
vented from adherence to epithelium. S-IgA also bind to
type 1–fimbriated E. coli, which expresses a mannose-specific
lectin (Wold et al., 1990). These bacterial binding sites on S-
IgA allow IgA to participate in both innate and adaptive
immunity (Royle et al., 2003).

Other roles for IgA in mucosal immunity have been iden-
tified. Dimeric IgA secreted by plasma cells is selectively
transferred through epithelial cells via the polymeric
immunoglobulin receptor by transcytosis. After cleavage of
this receptor to release the SC, S-IgA is discharged into the
mucosal lumen. IgA can also complex other antigens that
have escaped into the mucosal lamina propria and transport
them across epithelial cells to facilitate antigen removal
(Kaetzel et al., 1991). Dimeric IgA transiting through cells in
this way can also impede the replication of intracellular
antiviral viruses and thus may play an intracellular antiviral
role (Mazanec et al., 1992).

**Table 64.1. Specific Secretory IgA Antibodies**

| Bacterium                | Virus         | Fungus        | Protozoan | Other          |
|--------------------------|---------------|---------------|-----------|----------------|
| Escherichia coli         | Rotavirus     | Candida albicans |         |                |
| Salmonella               | Poliovirus    | Giardia       |          |                |
| Shigella                 | Echovirus     |               |          |                |
| Vibrio cholerae          | Coxsackievirus|               |          |                |
| Bordetella pertussis     | Respiratory syncytial virus |          |          |                |
| Streptococcus mutans     | Influenza     |               |          |                |
| Streptococcus mitis      | Arbovirus     |               |          |                |
| Streptococcus salivarius | Semliki       |               |          |                |
| Clostridium difficile    | Rose River    |               |          |                |
| Clostridium tetani       | Japanese B    |               |          |                |
| Lipoteichoic acid        | Dengue        |               |          |                |
| Streptococcus pneumoniae | Mumps         |               |          |                |
| Tetanus toxoid           | Human immunodeficiency |         |          |                |
| Endotoxin                |               | Herpes simplex |          |                |
| Neisseria meningitidis   | Herpes zoster |               |          |                |
| Haemophilus influenzae b | Coronavirus   |               |          |                |
|                          | Rubella       |               |          |                |
|                          | Cytomegalovirus|              |          |                |

**Substitution of IgM or IgG isotypes for IgA**

With regard to the biologic actions of S-IgA, a number of
studies have been done in the last few decades to determine
what effect the lack of this immunoglobulin has on people
who are IgA-deficient. In IgA deficiency there is a paucity
of IgA-secreting plasma cells in the submucosa of all secretory
tissues, little or no S-IgA in mucosal fluids, and the substitu-
tion of IgM-secreting plasma cells for IgA-secreting cells in
the intestinal tract (Brandtzaeg et al., 1987). The substitution
of IgM for the IgA isotype may have a biologic role, although
the data for this hypothesis are relatively meager. The
colostrum of IgA-deficient subjects contains abundant
amounts of IgM (Barros et al., 1985), and the saliva of IgA-
deficient individuals does contain biologically active IgM
antibody, such as secretory IgM to Streptococcus mutans
(Arnold et al., 1977). On the other hand, secretory IgM may
not confer mucosal protection equivalent to that of S-IgA.
IgA-deficient blood donors harbor poliovirus longer after
oral vaccination than normal subjects do (Savilahti et al.,
1988). Additionally, secretory IgM is subject to rapid degra-
dation in the intestinal lumen (Richman and Brown, 1977).
Whether IgM serves the same role as IgA is also challenged
by another study; Mellander et al. (1986) attempted to relate
the number of respiratory tract infections in IgA-deficient
subjects to the level of IgM in saliva, hypothesizing that an
inverse relationship was likely to be present. These studies
showed that there was no such relationship. Norhagen and
associates (1989) have also questioned the view that IgM can
compensate for IgA deficiency, since they could not relate
salivary IgM levels to health or frequency of illness in 63
IgA-deficient subjects. However, Fernandes et al. (1995) found that IgA-deficient children with increased levels of salivary anti-Streptococcus mutans of the IgM isotype had fewer dental caries, suggesting a protective role for this antibody. In addition, S-IgM antibodies may be intrinsically less biologically efficient, resulting, for example, in more prolonged excretion of vaccine viruses than seen in normal subjects (Savilahli et al., 1986).

Other studies point to a mucosal substitution of IgG, as well as IgM, in IgA deficiency. Oral vaccination of IgA-deficient subjects with cholera vaccine results in increased IgG and IgM antibody responses, as judged by immunoglobulin-secreting cells retrieved from the intestine and peripheral blood; in normal subjects, an IgA response to this vaccine is predominant (Friman et al., 1994). Nilssen et al. (1993a) analyzed IgA-deficient subjects with and without IgG2 deficiency to determine the isotype of this response; after oral cholera vaccination, these individuals had an increased number of IgG-Producing intestinal B cells. Even though IgG-secreting mucosal cells might be important in local immunity in IgA deficiency, complement activation by immune complex-associated IgG could lead to unregulated mucosal inflammation.

One would assume that the compensatory mechanisms of the intestinal tract in IgA deficiency would be similar in the respiratory tract, but this seems not to be the case; in the upper airway at least, IgA-deficient subjects may have a large number of IgD-producing cells (Brandtzæg et al., 1995). Since IgD cannot act as a secretory antibody (not being able to bind the polymeric immunoglobulin receptor), it presumably could not serve as a substitute for the lacking IgA.

Other immunologic alterations

In addition to the secretory antibodies present in the gastrointestinal tract, the lamina propria of the normal intestinal mucosa contains numerous T lymphocytes, some of which enter the surface epithelium. Most of these intraepithelial lymphocytes (IELs) in the small bowel express CD8, while CD4+ IELs coexist in the colon. Although IgA-deficient individuals seem to have an increased number of IELs, most of these lymphocytes also express CD8. Compared with those in normal subjects, an increased proportion of these T cells appears activated, bearing the IL-2 receptor (CD25). Klemola et al. (1995) found that IgA-deficient and control subjects had the same number of γδ T cells, whereas Nilssen et al. (1993b) found that healthy IgA-deficient subjects appeared to have an increased number of γδ T cells. Increased numbers of activated IELs in IgA deficiency might serve as a useful check on lymphocyte proliferation and/or the amount of local antibody produced. IgA-deficient patients with celiac disease given gluten have a further increase in the number of CD8+ T cells in the epithelial compartment (Klemola et al., 1995), suggesting that these cells may be responding to luminal antigens.

Jejunal and crypt epithelial expression of the class II MHC antigen DR is similar in IgA-deficient patients to that in normal controls (Klemola et al., 1995). For IgA-deficient patients with celiac disease, DR expression is normal while they are on a gluten-free diet but enhanced after gluten challenge. The biologic meaning of this is not certain; since the density of the DR antigen on antigen-presenting cells may dictate the magnitude of the immune response, enhanced DR expression might augment the hypersensitivity to food and/or microbial antigens.

Intestinal infections

Gastrointestinal infections clearly occur with increased frequency in IgA deficiency (Table 64.1). The best-known infecting organism is Giardia lamblia; presumably the lack of S-IgA permits the attachment and proliferation of this protozoan on the intestinal epithelium. Other infections such as with Campylobacter occur with increased frequency in the absence of IgA. Although the role of S-IgA in resistance to Helicobacter pylori in normal subjects is not proved, the fact that IgA-deficient subjects of a wide age range have no higher than expected incidence of H. pylori infections and the same levels of serum titers to H. pylori suggests that S-IgA plays a relatively minor role in mucosal protection against this microbe (Bogstedt et al., 1996).

Other gastrointestinal diseases

Aside from infections, a number of other gastrointestinal diseases occur in IgA-deficient subjects, including the inflammatory, autoimmune, and neoplastic conditions outlined in Table 64.2.

Nodular lymphoid hyperplasia

Probably the most common intestinal abnormality in IgA deficiency is nodular lymphoid hyperplasia. These lymphoid nodules may be focal but are usually multiple in antibody deficiency syndromes, are most commonly 5 mm or so in size, and are found predominantly in the lamina propria and submucosa of the small intestine but occasionally in the large intestine, rectum, or stomach. These nodules can be associated with mucosal flattening and if large enough can cause obstruction or be on the leading edge of intussusception. The lesions may be so multiple and produce so much villous flattening that malabsorption develops. Immunofluorescence studies usually demonstrate a proliferation of IgM plasma cells. This is in contrast to the lymphoid nodules in the gastrointestinal tract in hypogammaglobulinemic patients; in the latter, plasma cells are often greatly reduced in number and tend to contain an expanded population of B lymphocytes.

Nodular lymphoid hyperplasia is not considered a precursor of intestinal lymphoma, but in a few cases, lymphoma has developed in this setting. Nodular lymphoid hyperplasia and malabsorption may occur in IgA deficiency in the absence of giardiasis, and malabsorption may occur without nodular lymphoid hyperplasia. In one report, an unusual syndrome of malabsorption, IgA deficiency, diabetes mellitus, and a common HLA haplotype (HLA-B8 and -DRW3) was reported for three persons in a kindred of 43 individuals (van
Thiel et al., 1977). Severe diarrhea in association with lymphoid hyperplasia and/or malabsorption may be difficult to treat.

Celiac disease
Approximately 1:200 individuals with celiac disease is IgA-deficient (Crabbé and Heremans, 1967). S-IgA can bind wheat gluten and gliadin; thus, there could be abnormal handling of wheat antigens in its absence. Intestinal biopsy specimens from patients with selective IgA deficiency and celiac disease are similar to those from nonimmunodeficient patients with celiac disease (with the exceptions noted below), and the response to a gluten-free diet in IgA-deficient celiac patients is similar to that of non-IgA-deficient subjects. However, serologic detection and monitoring of therapy are more difficult in subjects with IgA deficiency, as they will not have the hallmark antibodies, serum IgA against endomysium or reticulin, or tissue transglutaminase. Serum IgG tissue transglutaminase levels, however, are elevated in IgA-deficient patients with celiac disease and can be used as a disease marker (Korponay-Szabo et al., 2003). Whereas non-IgA-deficient celiac subjects may have increased mucosal synthesis of IgA and IgM rheumatoid factors, IgA-deficient subjects with celiac disease may produce only IgM rheumatoid factors, illustrating again the tendency for substitution of IgM for IgA in the IgA-deficient intestinal tract (Hallgren et al., 1996).

Autoimmunity
In autoimmune gastrointestinal diseases, autoantibodies to the relevant target tissues may be documented; it is less clear whether anti-basement membrane antibodies, which are found in the sera of some IgA-deficient individuals, play a role in tissue damage. These are generally rare in IgA-deficient patients. In one case, a serum antibody to epithelial cells was found in association with total villous atrophy and malabsorption (McCarthy et al., 1978). Pernicious anemia has been described in IgA deficiency but appears to be less common than in common variable immune deficiency (Quigley et al., 1986).

Neoplasia
The development of cancers, particularly adenocarcinoma of the stomach (Fig. 64.1), or lymphomas, which are usually of B-cell origin, has been suggested as being associated with IgA deficiency (Schaffer et al., 1991), but this may be coincidental because of the relative frequency of IgA deficiency in the general population.

Gastrointestinal bacteria
S-IgA has antibody specificity for fimbriated E. coli and can agglutinate these bacteria, preventing gastrointestinal epithelial attachment. Because of this antibody adhesion, most of the E. coli isolated from the intestine of a normal subject are coated with IgA. IgA-deficient subjects carry fewer type 1 fimbriated bacteria than do normal subjects, suggesting that

Table 64.2. Gastrointestinal Diseases in Selective IgA Deficiency

| Type of Disease | Examples |
|----------------|----------|
| Infectious     | Giardia, Campylobacter, Clostridium, Salmonella, rotavirus, bacterial overgrowth |
| Inflammatory   | Nodular lymphoid hyperplasia, Crohn’s disease, celiac disease, ulcerative colitis, pancreatic insufficiency, cholelithiasis, villous atrophy, food allergy, lactose intolerance |
| Autoimmune     | Pernicious anemia, aphthous stomatitis, autoimmune hepatitis, primary biliary cirrhosis, achlorhydria, Henoch-Schönlein syndrome, antiepithelial antibody leading to villous atrophy |
| Neoplastic     | Lymphoma, adenocarcinoma of the stomach |

Fig. 64.1. Adenocarcinoma of the stomach in a 29-year-old IgA-deficient woman. Her brother, who was also IgA-deficient, had the same cancer.
the absence of S-IgA affects the type of bacterial colonization in the colon. In the absence of S-IgA, fimbriated E. coli isolates also appear to have decreased adherence to colonic epithelial cells, suggesting that IgA influences the level of fimbrial expression of intestinal bacteria. IgA-deficient subjects are also more likely to harbor E. coli with potentially inflammatory properties (Friman et al., 1996, 2002). IgA-deficient subjects are also subject to bacterial overgrowth in the jejunum (Pignata et al., 1990). Since IgA-deficient subjects have intestinal immunity and perhaps altered bacterial intestinal flora, serum titers of antibody to intestinal bacteria have been analyzed. Cardinale et al. (1995) found increased IgM levels of antibody to E. coli in the serum of IgA-deficient subjects.

**Absorption of dietary antigens**

Although most intestinal antigens are prevented from entering the systemic circulation, serum antibodies to dietary antigens are found in the sera of all immunocompetent humans, demonstrating that these substances are absorbed in sufficient quantities to immunize. Antibodies to cow’s milk proteins are present in 98% of infants between the ages of 7 and 27 weeks of age, with the highest titers at ages 3 to 6 months. Antibodies of the IgG isotype predominate in serum of normal subjects, although Mestecky et al. (1987) detected IgA antibodies to a number of dietary antigens in these sera. IgG1, IgG2, and IgG4 antibodies were the predominant IgG isotypes; for IgA, antibodies of the IgA1 isotype predominated in both serum and secretions.

That sera of IgA-deficient patients are much more likely to contain precipitating antibodies to cow’s milk than that of normal subjects was one of the first demonstrations that S-IgA constitutes an important barrier to the absorption of dietary proteins (Buckley and Dees, 1969). We and others have shown that serum of IgA-deficient subjects contains increased amounts of antibody to a wide variety of food antigens such as casein, bovine immunoglobulin, bovine albumin, α-lactalbumin, chicken ovalbumin, and gliadin (Buckley and Dees, 1969; Cunningham-Rundles et al., 1979; Cardinale et al., 1995), suggesting globally increased antigen absorption. For obscure reasons, IgA-deficient sera often have more antibody to bovine γ-globulin than other milk proteins, which is strange considering that this protein is only a very minor constituent in comparison with the other proteins in milk.

**Immune complexes and dietary antigens**

Another measure of antigen absorption is detection of circulating immune complexes after eating. Circulating immune complexes, containing bovine proteins, appear in the sera of IgA-deficient subjects as early as 15 to 30 minutes after milk ingestion and remain for at least 2 to 4 hours (Cunningham-Rundles et al., 1979; Cunningham-Rundles, 1986). Of 25 IgA-deficient patients, circulating immune complexes were found in the serum of 24 patients after milk ingestion over a period of 2 hours; 15 of these subjects had enough milk antigen in the serum to be detected by a method as insensitive as agar diffusion. There did not appear to be any predictable relationship between the amount of immune complex formed and the amount of serum or salivary IgA. Some IgA-deficient subjects with no serum or salivary IgA had no circulating immune complexes following milk ingestion, whereas other individuals with readily detectable serum and salivary IgA had large amounts of immune complexes after drinking milk. Some subjects who had only modest deficits of serum IgA (levels of 30 to 60 mg/dL) had large amounts of bovine antigens detectable in their sera after drinking milk. These data showed that even individuals with a relatively leaky intestinal tract can have serum IgA levels that are only modestly reduced; some of these individuals would not normally be classified as immune-deficient. On the other hand, the level of immune complex in the circulation after drinking milk was closely related to the level of serum antibody to bovine milk proteins (P < 0.01) (Cunningham-Rundles, 1986).

**Consequences of antigen absorption**

**Association with autoimmunity**

In IgA deficiency, circulating immune complexes in the serum are associated with an increased likelihood of autoimmune disease (Cunningham-Rundles et al., 1981). Although a reason for this association has not been defined, the presence and/or degree of the intestinal permeability defect could lead to the excessive absorption of numerous exogenous antigens to which a variety of antibodies could then be raised. Some of these exogenous antigens could share antigenic cross-reactivity with endogenous antigens and perhaps serve as a stimulus to autoimmune formation. In addition to the large amount of antibody to dietary proteins discussed earlier, IgA-deficient serum also contains antibodies to a bovine mucoprotein constituent of the fat globule membrane formed by the bovine mammary gland in the process of milk formation (Butler and Oskvig, 1974), showing that unexpected bovine epithelial antigens can stimulate antibody production. Other dietary constituents could present additional unusual antigenic components to which an IgA-deficient subject could become sensitized. It is also possible that tissue damage by immune complexes could secondarily stimulate autoantibody production and provoke autoimmune disease.

**Anti-idiotypic antibodies**

Another effect of the absorbed gastrointestinal antigens is the production of autologous anti-idiotypic antibodies, or antibodies directed to the variable regions of antibodies directed to the absorbed antigens. Antibodies to bovine casein have been detected in the sera of IgA-deficient donors with large amounts of anticasin antibodies (Cunningham-Rundles, 1982); they participate in immune complex formation, along with the inciting antigen and original antibody. Since at least some anti-idiotypic antibodies made by the IgA-deficient individual were found directed at the binding site of the primary antibody, it seems likely that casein antigen and the anti-idiotype could bind alternatively to the primary antibody, depending on the serum concentration of the antigen. After drinking milk, for example, a large amount of
casein might be present, which would tend to displace the anti-idiotype from the anticasein antibody. After a period of fasting, the amount of casein antigen in the blood might be lower, and the immune complex present would be more likely to contain idiotype and anti-idiotype.

The curious part of this phenomenon is the appearance of idiotype and anti-idiotype in the blood of IgA-deficient individuals at the same time (Cunningham-Rundles, 1982). One explanation could be that the continued absorption of dietary casein stimulates the production of anticasein antibody, despite such controls as the anti-idiotypic antibodies can supply. Another possibility is that the anti-idiotypes may serve to stimulate further anticasein antibody production. Although other anti-idiotypic antibodies (anti-anti-ovalbumin, for example) have not been sought, it seems probable that numerous additional anti-idiotypes related to gastrointestinal antigens are present in the sera of IgA-deficient patients.

**Nonimmunologic mucosal abnormalities**

Although the best-described differences between normal and IgA-deficient individuals are those of the immunologic system, nonimmunologic differences in mucosal architecture are also present. Goblet cells were found increased in the nasal mucosa in IgA deficiency (Karlson *et al.*, 1985), but this was not found by another investigator who studied the intestinal tract. In the same study, the median percentage of crypt cells in mitosis was higher in IgA deficiency than in controls, suggesting chronic antigen stimulation (Klemola *et al.*, 1995). Giorgi *et al.* (1986) found that the small intestinal mucosa of children with IgA deficiency displayed unusual pathologic changes, some of which were detectable at only the ultrastructural level. These lesions included extensive alterations of the surface epithelium, areas of missing glycocalyx, and enterocytes with “frayed” microvilli. Since these abnormalities were found in the absence of ongoing disease, the authors believed these changes to be characteristic of “normal” IgA-deficient individuals. Gut permeability to lactulose, L-rhamnose, is increased, as demonstrated by abnormally large urinary excretion of these compounds, which shows that IgA-deficient subjects have excessive gastrointestinal tract absorption of these larger-molecular-weight substances (Pignata *et al.*, 1990). Since these substances are immunologically inert, this tendency to confirm the notion that structural gastrointestinal lesion(s) may be present in addition to the lack of IgA. The lesions described could permit the absorption of antigens from the intestinal lumen, even in the presence of local compensations (such as increased IgM) for S-IgA.

**COMMON VARIABLE IMMUNODEFICIENCY**

**Incidence and genetics**

Common variable immunodeficiency disease (CVID) is a primary immunodeficiency disease with an estimated incidence of 1:30,000 to 1:60,000. Serum levels of IgG, IgA, and usually IgM are low, and there is little or no antibody production, which leads to recurrent infections, particularly of the sinopulmonary tracts (Cunningham-Rundles, 1999; Hermaszewski and Webster, 1993; Hammarstrom *et al.*, 2000). Although it is generally suspected that CVID is a genetic disease, the cause(s) are unknown and indeed may vary among different subjects. Patients with CVID are more likely than controls to have inherited the MHC antigens HLA-B8 and -DR3; the same antigens are found in increased prevalence in IgA deficiency. For this reason and the fact that some families may have some members with CVID and others with IgA deficiency, these two diseases are considered genetically related abnormalities (Schaffer *et al.*, 1989; Vorechovsky *et al.*, 1995; Kralovicova *et al.*, 2003).

**Immunologic defects**

CVID has the basic phenotype of a humoral immune defect, since serum immunoglobulin levels are low and antibody production is severely impaired. Although some patients have low numbers of B cells, more than half of all patients also have significant T-cell deficiencies, including poor proliferation to mitogens, lack of response to antigens, and subnormal production of IL-2, IL-4, IL-5, γ-interferon, and B-cell differentiation factor. As is found for IgA-deficient subjects, stimulating B cells of CVID subjects with anti-CD40 and IL-10 can elicit IgA production in some; the B cells of about half of these subjects can produce normal amounts of IgG and IgM (Nonoyama *et al.*, 1993), demonstrating that the B-cell defects in these subjects are not necessarily irreversible.

**Mucosal immunologic defects**

In IgA deficiency, there is a lack of maturation of IgA-producing B cells, but in CVID the differentiation of all B cells to plasma cells is impaired. Although there are considerable numbers of J-chain-synthesizing early B cells in the intestinal tract, there is a generalized paucity of all immunoglobulin staining cells and a severe depletion of plasma cells, IgA being the most affected isotype and IgM the least affected (Herbst *et al.*, 1994).

Although plasma cells are scarce, for CVID patients with chronic or intermittent diarrhea, mucosal biopsy samples are likely to show a mononuclear cell infiltrate, in some cases severe enough to resemble graft-versus-host disease. Granulomatous lesions are not uncommon, as has been found for CVID subjects in general (Cunningham-Rundles, 1989). Although the number of IELs in IgA-deficient subjects is normal or somewhat increased, for patients with CVID, IELs are significantly increased, especially for patients with villous atrophy. There was no relationship between IEL and peripheral blood CD4:CD8 ratios (Nilsson *et al.*, 1993b).

**Gastrointestinal diseases**

**Incidence**

Gastrointestinal symptoms and diseases are one of the commonest and (perhaps after respiratory tract infections) most
Infectious and inflammatory disease
Infections and diseases of the gastrointestinal tract are common in CVID (Table 64.4); the main organisms are outlined in Table 64.3. Patients with CVID exhibit a number of pathologic gastrointestinal changes, including patterns superficially resembling graft-versus-host disease, inflammatory bowel disease, villous atrophy associated with mucosal inflammation, or even Whipple’s disease; however, the diagnostic features of these diseases are lacking. In some patients the inflammatory process may well have an autoimmune component.

Investigating CVID subjects with symptoms of gastritis, Zullo et al. (2001) detected H. pylori infection in 14 (41%) of 34 patients and observed chronic active gastritis involving both antrum and body more frequently in H. pylori–positive patients (79%) than H. pylori–negative patients (20%). Multifocal atrophic gastritis was also found more frequently in infected patients (50%) than uninfected patients (10%). Overexpression of p53 was found in six patients (18%), including one with normal gastric mucosa (Zullo et al., 2001).

Subjects with immune deficiency who are infected with hepatitis viruses (B and C) are at risk for more severe disease than subjects with normal immunity; the outcome of exposure to contaminated intravenous immune globulin solutions has been reported (Razvi et al., 2001).

Nodular lymphoid hyperplasia
Perhaps the commonest gastrointestinal abnormality in CVID is nodular lymphoid hyperplasia, characterized by multiple discrete nodules of lymphoid tissue, located diffusely throughout the intestinal tract but particularly in the small intestine (Fig. 64.2). Originally giardiasis infections were believed to be the most likely cause of these lymphoid nodules, but this is rarely the case. In most situations no treatment is required, but nodular hyperplasia can be associated with malabsorption, diarrhea, and weight loss. The most satisfactory treatment drugs include metronidazole or atabrine (especially if Giardia is found) or broad-spectrum antibiotics to reduce bacterial overgrowth. Other treatments include exclusion of lactose and, if necessary, low doses of corticosteroids for short periods. Nodular lymphoid hyperplasia may precede the development of intestinal lymphoma in CVID (Castellano et al., 1992).

Malabsorption
Occasionally severe diarrhea and malabsorption occurs in CVID without nodular lymphoid hyperplasia or other explanation, even after a thorough gastrointestinal evaluation. Bacterial overgrowth can occur in the setting of antibody deficiency and may result in nutrient deficiency due to com-

Table 64.4. Gastrointestinal Diseases and Number of Occurrences in 248 Subjects with Common Variable Immunodeficiency (CVID)∗

| Diagnosis                                         | Female | Male |
|---------------------------------------------------|--------|------|
| Nodular lymphoid hyperplasia                       | 9      | 1    |
| Ulcerative colitis                                 | 2      | 2    |
| Ulcerative proctitis                               | 2      | 1    |
| Crohn's disease                                    | 1      | 8    |
| Malabsorption, no other diagnosis                  | 7      | 3    |
| Giardiasis                                         | 4      | 4    |
| Protein-losing enteropathy                         | 2      | 1    |
| Sprue-like disease                                 | 3      | 3    |
| Malnutrition necessitating total parenteral nutrition | 2   | 3    |
| Cyto megalovirus enteritis                         | 1      | 0    |
| Intestinal lymphangiectasia                        | 1      | 0    |
| Intestinal granulomatous disease                   | 1      | 0    |
| Campylobacter disease                              | 3      | 2    |
| Salmonella disease                                 | 2      | 1    |

∗ Moriuchi et al., 1990.
* Most likely underestimated.

Table 64.3. Gastrointestinal Diseases in Common Variable Immunodeficiency

| Type of Disease | Examples                                                                 |
|-----------------|--------------------------------------------------------------------------|
| Infectious      | Giardia, Campylobacter, Clostridium, rotavirus, Cryptosporidium, cytomegalovirus, Helicobacter pylori, Coccidioides, bacterial overgrowth |
| Inflammatory    | Nodular lymphoid hyperplasia, aphthous stomatitis, Crohn's disease, celiac disease, ulcerative colitis, cholelithiasis |
| Autoimmune      | Pernicious anemia, autoimmune hepatitis                                  |
| Neoplastic      | Lymphoma, adenocarcinoma of the stomach                                   |
petition by the bacteria. A trial of broad-spectrum antibiotics can be useful in determining whether bacterial overgrowth is the cause of the malabsorption. This may include impaired absorption of fat, d-xylose, minerals, fat-soluble vitamins (such as vitamin A, D, and E), zinc, and vitamin B₁₂. Zinc deficiency, which worsens T cell dysfunction, can itself be associated with diarrhea, which can further complicate the immunologic picture (Dardenne, 2002.) Intestinal biopsies may reveal changes similar to those seen in celiac sprue, but a more striking mononuclear infiltrate may develop, giving a nodular appearance to the mucosa. In these cases, edematous loops of small bowel may be found on computed tomography (Fig. 64.3). Use of an elemental diet or total parenteral nutrition is sometimes required (Teahon et al., 1994). Corticosteroids may reduce the diarrheal fluid loss and can result in dramatic improvement (Ruan et al., 1996), but long-term use can lead to a highly significant risk of opportunistic infections. In a rare case, cholestyramine has been found of value (Sperber and Mayer, 1988).

**Inflammatory bowel diseases**

Inflammatory bowel disease also occurs in CVID; in a panel of 187 patients, 16 had Crohn’s disease and 4 had ulcerative colitis. The medical management is the same as for nonimmunodeficient patients, including 5-aminosalicylate compounds, antibiotics such as metronidazole or ciprofloxacin, steroids or budesonide, or other immune modulators such as 6-mercaptopurine or azathioprine. Inflammatory bowel disease in CVID subjects seems to be more difficult to control than in nonimmunodeficient subjects, but fistulae and large areas of scarring are less commonly found. Infliximab may be useful in managing such cases. Celiac disease has also been reported in CVID; rigorous wheat elimination would be required to reverse the chronic diarrhea, but this diet should be used only if clear pathologic changes are demonstrated (Figs. 64.4 and 64.5).

**Neoplastic disease**

There is an increased incidence of gastrointestinal malignancy in CVID, specifically stomach cancer and B-cell lymphomas. Four patients in an early report of 50 subjects developed carcinoma of the stomach (Hermans et al., 1976). In a study in Great Britain, 7 CVID patients in a group of 220 had gastric cancer (Kinlin, 1985). In the United States, gastric cancer was found in one person in a group of 98 CVID patients, although lymphoma was found in 11. Of these, one patient had an intestinal (jejunal) lymphoma (Cunningham-Rundles, 1999). Subjects with CVID may also be particularly susceptible to the development of mucosa-associated lymphoid tissue (MALT)-type lymphomas (Cunningham-Rundles et al., 2002.) Recent work to estimate the incidence of cancer in Denmark and Sweden has been reported (Mellemkjaer et al., 2002).

**Pernicious anemia**

Pernicious anemia is a well known but relatively rare complication of CVID that occurs usually in the absence of autoantibodies to intrinsic factor and parietal cells. Cellular autoimmunity has been demonstrated in some cases (James et al., 1974.) The relationship between this, atrophic gastritis, achlorhydria, and stomach cancer has not been proven in CVID but may exist, as for other patients with this complex.

**Antigen absorption**

Since patients with hypogammaglobulinemia also lack S-IgA, one might expect that patients with this defect could have an
equally excessive gastrointestinal permeability compared with IgA-deficient patients. In the analysis of a series of such patients, large amounts of bovine casein and bovine \( \gamma \)-globulin were found in the serum (Cunningham-Rundles et al., 1984). The amount of foreign protein in these sera could not be correlated with gastrointestinal disease nor to any specific immunologic parameter; however, for still unknown reasons, higher levels of these antigens in the blood were related to splenomegaly. Unlike IgA-deficient patients, hypogammaglobulinemic patients produce antibodies poorly or not at all, and the ingested dietary proteins do not elicit antibody production. Thus, dietary antigens do not engage in immune complex formation with endogenous immunoglobulin, although after infusions of intravenous immunoglobulin, immune complexes containing dietary antigens can be detected.

X-LINKED AGAMMAGLOBULINEMIA

Inheritance and immunologic defects
X-linked agammaglobulinemia (XLA), a more uncommon humoral immune defect than CVID, is due to an abnormality of an X chromosome–encoded B-cell cytoplasmic tyrosine kinase necessary for B-cell maturation (Conley et al., 1994). The hallmark of the illness is very low to absent serum immunoglobulins and absent or nearly absent circulating B cells. Males with XLA usually become ill in the first year of life, commonly experiencing respiratory or gastrointestinal tract infections (Lederman and Winklestein, 1985).

Mucosal immunologic defects
In classic cases of XLA, there are no lymphoid germinal centers, and nodular lymphoid hyperplasia does not develop. Plasma cells are lacking and there is no immunoglobulin secretion in mucosal fluids.

Gastrointestinal disease

**Infectious and inflammatory disease**
Although male infants may first present with gastrointestinal disease, chronic gastrointestinal disease appears less commonly in XLA than in CVID. On clinical presentation, 31 of 98 patients in the largest reported series of XLA patients had acute gastrointestinal infections and 3 had perirectal abscesses, but chronic gastrointestinal tract infections were found in only 10 of the 98 patients (10.2% for XLA, as opposed to 32% to 80% in CVID). Nine patients of the group were found to have infections with *Giardia lamblia*; there was one case each of salmonella infection and

---

**Fig. 64.4.** A small-bowel series was performed for a 76-year-old male with common variable immunodeficiency (CVID) and very poor T-cell function who had intermittent diarrhea, bloating, weight loss, and abdominal pain for 5 years; a large loop of inflamed small bowel can be noted in the right lower quadrant, consistent with Crohn’s disease.

**Fig. 64.5.** An indium-labeled leukocyte scan for a 42-year-old woman with common variable immunodeficiency (CVID) and very poor T-cell function, who had severe diarrhea and weight loss, showed massive uptake of labeled cells in the cecum, terminal ileum, descending colon, and rectum. Evolving right-lower-lobe pneumonia also was detected. The diagnosis was Crohn’s disease.
enteropathogenic *E. coli* infection (Lederman and Winkelstein, 1985). Systemic enterocytopathic human orphan virus (ECHO), coxsackievirus, and vaccine-related polio infections, harbored in the intestinal tract, have caused severe morbidity and high mortality rates among XLA patients (R.E. McKinney *et al.*, 1977.) Campylobacter infections also occur in XLA. For unclear reasons, typical inflammatory bowel disease, malabsorption, and celiac disease are quite uncommon in XLA. With the lack of antibody production, autoantibody-based gastrointestinal diseases are not found.

**Neoplasia**

The incidence of lymphoma in XLA does not appear to be increased as it is for patients with CVID, but in a group of 98 patients, 2 had lymphoma: 1 had lymphoma of the terminal ileum and the other had a reticulum cell sarcoma of the bowel (Lederman and Winkelstein, 1985). Perhaps more important in XLA is an apparent increase in rapidly progressive colon cancer (van der Meer *et al.*, 1993).

**Antigen absorption**

The subject has not been studied in as much detail as in patients with selective IgA deficiency or CVID, but males with XLA also appear to have less gastrointestinal tract permeability to dietary antigens. Three subjects with XLA, for example, had very little detectable dietary protein antigen in their sera, in comparison with a group of subjects with CVID (Cunningham-Rundles *et al.*, 1984).

**CONCLUSIONS**

The three congenital immunodeficiency diseases discussed previously present a range of naturally occurring immunologic abnormalities; the unifying theme, lack of S-IgA, is common to all. This defect leads to a variety of infections and inflammatory conditions, but for each deficiency disease the manifestations vary. The role of IgA in intestinal immunity has been clarified by a number of studies, but what compensations are brought to bear when IgA is lacking is a mystery. Perhaps additional immune defects, yet to be discovered, exist in the IgA-deficient subjects who become ill. Another mystery is the relative lack of gastrointestinal disease in males with XLA, who have no B-cell immunity, compared with patients with CVID, who usually make some amount of functioning antibody. Perhaps here the most plausible explanation is that males with XLA have excellent T-cell immunity, whereas subjects with CVID usually have T-cell defects. Recent studies in knockout mice have indicated an essential role for T cells and cytokine regulation in intestinal mucosal integrity; perhaps it is the lack of these regulatory factors that predisposes patients with CVID to inflammatory mucosal diseases. Continued study of the congenital immune deficiency diseases will permit further analysis of normal gastrointestinal immunity.

**REFERENCES**

Arnold, R. R., Cole, M. F., Prince, S., McGhee, J. (1977). Secretory IgM antibodies to *Streptococcus mutans* in subjects with selective IgA deficiency. *Clin. Immunol. Immunopathol.* 8, 475–486.

Barros, M. D., Porto, M. H. O., Leser, P. G., Greemach, A. S., Carrierno-Sampaio, M.M.S. (1985). Study of colostrum of a patient with selective IgA deficiency. *Allergol. Immunopathol. (Madrid)* 13, 331–334.

Bodstedt, A. K., Nava, S., Wadsstrom, T., and Hammarstrom, L. (1996). *Helicobacter* infections in IgA deficiency: lack of role for the secretory immune system. *Clin. Exp. Immunol.* 105, 202–204.

Boren, T., Falk, P., Roth, K. A., Larson, G., and Normark, S. (1993). Attachment of *Helicobacter pylori* to human gastric epithelium mediated by blood group antigens. *Science* 262, 1892–1895.

Brandzaeg, P. (1995). The role of humoral mucosal immunity in the induction and maintenance of chronic airway infections. *Ann. J. Respir. Crit. Care Med.* 151, 2081–2086.

Brandzaeg, P., Karlsson, G., Hansson, G., Petrusson, B., Bjorkander, J., and Hanson, L. A. (1987). The clinical condition of IgA deficient patients is related to the proportion of IgD and IgM producing cells in the nasal mucosa. *Clin. Exp. Immunol.* 67, 626–636.

Brandzaeg, P., Nilsson D. E., Rognum, T. O. O., and Thran, P. S. (1991). Ontogeny of the mucosal immune system and IgA deficiency. *Gastroenterol. Clin. North Am.* 20, 397–439.

Briere, F., Bridon, J. M., Chevet, D., Souillet, G., Bienvenu, F., Guret, C., Martinez-Valdez, H. and Bangereau, J. (1994). Interleukin 10 induces B lymphocytes from IgA deficient patients to secrete IgA. *J. Clin. Invest.* 94, 97–104.

Buckley, R. H., and Dees, S. C. (1969). The correlation of milk precipitins with IgA deficiency. *N. Engl. J. Med.* 231, 465.

Butler, J.E., and Oskvig, R. (1974). Cancer, autoimmunity and IgA deficiency, related by a common antigen-antibody system. *Nature* 249, 30.

Caldile, F., Friman, V., Carlsson, B., Bjorkander, J., Armenio, L., and Hanson, L. A. (1995). Aberrations in titer and avidity of serum IgM and IgG antibodies to microbial and food antigens in IgA deficiency. *Adv. Exp. Med. Biol.* 371, 713–716.

Castellano, G., Moreno, D., Galvao, O., Balestín, C., Colina, F., Mollejo, M., Morillas, J. D., and Solis-Herruzo, J. A. (1992). Malignant lymphoma of jejunum with common variable hypogammaglobulinemia and diffuse nodular hyperplasia of the small intestine. A case study and literature review. *J. Clin. Gastroenterol.* 15, 128–135.

Cazac, B. B., Roes, J. (2000). TGF-beta receptor controls B cell responsiveness and induction of IgA in vivo. *Immunity* 13, 443–451.

Conley, M. E., and Cooper, M. D. (1981). Immature IgA B cells in IgA deficient patients. *N. Engl. J. Med.* 305, 495.

Conley, M. E., Parolini, O., Rohrer, J., and Campana, D. (1994). X-linked agammaglobulinemia: new approaches to old questions based on the identification of the defective gene. *Immunol. Rev.* 138, 5–21.

Crabbé, P. A. and Heremans, J. F. (1967). Selective IgA deficiency with steatorrhea. A new syndrome. *Am. J. Med.* 42, 319–326.

Cunningham-Rundles, C. (1982). Naturally occurring autologous anti-idiotypic antibodies: participation in immune complex formation in selective IgA deficiency. *J. Exp. Med.* 155, 711–719.

Cunningham-Rundles, C. (1986). Analysis of the secretory immune barrier in IgA deficiency. *Ann. Allergy* 57, 31–35.

Cunningham-Rundles C. (2001). Physiology of IgA and IgA deficiency [review]. *J. Clin. Immunol.* 21(5), 303–309.

Cunningham-Rundles, C. (2003). Selective IgA deficiency. In *Immunologic Disorders of Infants and Children* (ed. E. Stiehm). New York: Academic Press, in press.

Cunningham-Rundles, C., Brandeis, W. E., Good, R. A., and Day, N. K. (1979). Bovine antigens and the formation of circulating immune complexes in selective IgA deficiency. *J. Clin. Invest.* 64, 270–272.

Cunningham-Rundles, C., Brandeis, W. F., Pudifin, D. J., Day, N. K., and Good, R. A. (1981). Autoimmunity in selective IgA deficiency: relationship to anti-bovine protein antibodies, circulating immune complexes and clinical disease. *Clin. Exp. Immunol.* 45, 299–304.
Cunningham-Rundles, C., Carr, R. I., and Good, R. A. (1984). Dietary protein antigenemia in humoral immunodeficiency disease: correlation with splenomegaly. Am. J. Med. 76, 181–185.

Cunningham-Rundles, C., Bodian, C. (1999). Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin. Immunol. 92, 34–48.

Cunningham-Rundles, C., Cooper, D. L., Duffy, T. P., Strauchen, J. (2002). Lymphomas of mucosal-associated lymphoid tissue in common variable immunodeficiency. Am. J. Hematol. 69, 171–8.

Dallas, S. D., and Rolfe, R. D. (1998). Binding of Clostridium difficile toxin A to human milk secretory component. J. Med. Microbiol. 47, 879–888.

Da Menezes, S. J., Mucida, de S D., Cara, D. C., Alvarez-Leite, J. I., Russo, M., Vaz, N. M. and Caetano, de Faria A. M. (2003) Stimulation by food proteins plays a critical role in the maturation of the immune system. Int. Immunol. 15, 447–455.

Dardenne M. (2002). Zinc and immune function. Eur. J. Clin. Nutr.

Friman, V., Nowrouzian, F., Adlerberth, I., Wold, A. E. (2002). Ultra-structural findings in the jejunal mucosa of children with common variable immunodeficiency. Clin. Exp. Immunol. 95, 215–221.

Friman, V., Quiding, M., Czerkinsky, C., Nordstrom, I., Larsson, L., de Oliveira, I. R., de Araujo, A. N., Bao, S. N., and Giugliano, L. G. (2001). Binding of lactoferrin and free secretory component to enterotoxigenic Escherichia coli. FEMS Microbiol. Lett. 203, 29–33.

Falk, P., Roth, K. A., Boren, T., Westblom, T. U., Gordon, J. I., and Normark, S. (1993). An in vitro adherence assay reveals that Helicobacter pylori exhibits cell lineage–specific tropism in the human gastric epithelium. Proc. Natl. Acad. Sci. USA 90, 2035–2059.

Fernandes, F. R., Nagao, A. T., Mayer, M. P., Zelante, F., and Carneiro-Sampato, M. M. (1995). Compensatory levels of salivary IgM anti-Streptococcus mutans IgA-deficient patients. J. Invest. Allergol. Clin. Immunol. 5, 1515.

French, M. A., Denis, K. A., Dawkins, R., and Peter, J. B. (1995). Severity of infections in IgA deficiency: correlation with decreased serum antibodies to pneumococcal polysaccharides and decreased serum IgG2 and/or IgG4. Clin. Exp. Immunol. 100, 47–53.

Friman, V., Quiding, M., Czerkinsky, C., Nordstrom, I., Larsson, L., Ericson, D., Bjorkander, J., Theman, K., Kilander, A., Homgren, J., et al. (1994). Intestinal and circulating antibody-forming cells in IgA-deficient individuals after oral cholera vaccination. Clin. Exp. Immunol. 95, 226.

Friman, V., Adlerberth, I., Connel, H., Svanborg, C., Hansson, L. A., and Wold, A. E. (1996). Decreased expression of mannose-specific toxin A to human gastric epithelium. Proc. Natl. Acad. Sci. USA 93, 1442–1452.

Friman, V., Nowrouzian, F., Adlerberth, I., Wold, A. E. (2002). Clinical observations in 50 patients with selective IgA deficiency: correlation with decreased serum antibodies to pneumococcal polysaccharides and decreased serum IgG2 and/or IgG4. Clin. Exp. Immunol. 100, 47–53.

Hansson, L. A. (1983). Selective IgA deficiency. In Primary and Secretory Immunodeficiency Disorders (ed. R. K. Chandra). Edinburgh: Churchill Livingstone, 62–84.

Harriman, G. R., Bougue, M., Fong, P., Finegold, M., Pacheco, S., Bradley, A., Zhang, Y., Mbawulue, I. N. (1999). Targeted deletion of the IgA constant region in mice leads to IgA deficiency with alterations in expression of other Ig isotypes. J. Immunol. 162, 2521–2529.

Herbst, E. W., Armbruster, M., Rump, J. A., Buscher, H. P., and Peter, H. H. (1994). Intestinal B cell defects in common variable immunodeficiency. Clin. Exp. Immunol. 95, 215–221.

Hermans, P., et al. (1976). Idiopathic late onset immunoglobulin defi-
ciency: clinical observations in 50 patients. Am. J. Med. 61, 221–237.

Hermanszewske, R. A. and Webster, A. D. B. (1993). Primary hypogammaglobulinemia: a survey of clinical manifestations and complica-
tions. Q. J. Med. 86, 31–42.

Hiroi, T., Yanagita, M., Iijima, H., Iwataki, K., Yoshida, T., Takatsu, K., Kyono, H. (1999). Deficiency of IL-5 receptor alpha-chain selectively influences the development of the common mucosal immune system independent IgA-producing B-1 cell in mucosa-associated tissues. J. Immunol. 155, 821–828.

Islam, K. B., Baskin, B., Nilsson, L., Hammarstrom, L., Sideras, P., and Smith, C. I. (1994). Molecular analysis of IgA deficiency. Evidence of impaired switching to IgA. J. Immunol. 1, 1442–1452.

James, D., Asherson, G., Chanarin, I., Coghill, N., Hamilton, S., Himsworth, R. L., Webster, D. (1974). Cell-mediated immunity to intrinsic factor in autoimmune disorders. Br. Med. J. 4, 494–496.

Kaeltsch, C. S., Robinson, J. K., Chintalacharuvu, K. R., Van, J. P., and Lamm, M. E. (1991). The polymeric immunoglobulin receptor (secretory component) mediates transport of immune com-
plexes across epithelial cells: a local defense function for IgA. Proc. Natl. Acad. Sci. USA 88, 8796–8800.

Karlson, G., Hanson, L. A., Petrusson, B., et al. (1985). Goblet cell number in the nasal mucosa relates to cell-mediated immunity in patients with selective antibody deficiency syndromes. Int. Arch. Allergy Appl Immunol. 78, 86–91.

Kralovicova, J., Hammarstrom, L., Plebani, A., Webster, A. D., Vorechovsky, L. (2003). Fine-scale mapping at IGAD1 and genome-wide genetic linkage analysis implicate HLA-DQ/DR as a major suscept-
ibility locus in selective IgA deficiency and common variable immunodeficiency. J. Immunol. 170, 2765–2775.

Klinin, L. J. (1985). Prospective study of cancer with hypogammaglobulinemia. Lancet 1, 263–265.

Klemola, T., Savilahti, A., Arato, A., Ormala, T., Partanen, J., Eland, C., and Koskimies, S. (1995). Immunohistochemical findings in jejunal specimens from patients with IgA deficiency. Gut 37, 519–523.

Korponay-Szabo, I. R., Dahlbom, I., Larsson, C., and Koskimies, S. (1995). Immunohistochemical findings in jejunal specimens from patients with IgA deficiency. Gut 37, 519–523.

Lederman, H. M. and Winkelstein, J. (1985). X-linked agammaglobul-
linemia: an analysis of 96 patients. Medicine 64, 145–156.

Lio, D., D’Anna, C., Gervasi, F., Cigna, D., Modica, M. A., Candore, G., and Caruso, C. (1995). In vitro impairment of interleukin 5 production in HLA-B8, DR3-positive individuals: implications for immunoglobulin A synthesis dysfunction. Hum. Immunol. 44, 170–174.

Luzi, G., Kabagawa, H., Crain, M. J., and Cooper, M. D. (1986). Intracellular neutralization of virus by immunoglobulin A antibodies: aberrant pattern in IgA deficient donors. Mol. Microbiol. 32, 35–42.

Giorgi, P. L., Catassi, C., Shabanti, A., Bearzi, I., and Cinti, S. (1993). Ultra-structural findings in the jejunal mucosa of children with IgA deficiency. 3. Pediatr. Gastroenterol. Nutr. 5, 092–390.

Hallgren, J., Knuston, F., Lavo, B., and Hallgren, R. (1996). Increased mucosal synthesis of rheumatoid factor (RF) in coeliac disease. Clin. Exp. Immunol. 103, 94–98.

Hammerschmidt, S., Talay, S. R., Brandtzaeg, P., and Chhatwal, G. S. (1997) SpsA, a novel pneumococcal surface protein with specific binding to secretory immunoglobulin A and secretory compo-
ent. Mol. Microbiol. 25, 1113–1124.

Hammarstrom, L., Persson, M. A. A., and Smith, C. I. E. (1985). Immunoglobulin subclass distribution of human anti-carbohy-
drate antibodies: aberrant pattern in IgA deficient donors. Immunology 54, 021–026.

Hammarstrom, L., Vorechovsky, I., Webster, D. (2000). Selective IgA deficiency (SGaAD) and common variable immunodeficiency (CVID). Clin. Exp. Immunol. 120, 225–31.

Hansson, L. A. (1983). Selective IgA deficiency. In Primary and Secretory Immunodeficiency Disorders (ed. R. K. Chandra). Edinburgh: Churchill Livingstone, 62–84.
McKinney, R. E. Jr., S. L. Katz, and C. M. Wilfert. (1987). Chronic enteroviral meningoencephalitis in agammaglobulinemic patients. Rev. Infect. Dis. 9:334–356.

Mbawuike, I. N., Pasero, S., Acuna, C. L., Switzer, K. C., Zhang, Y., Harriman, G. R. (1999). Mucosal immunity to influenza without IgA: an IgA knockout mouse model. J. Immunol. 162, 2530–2537.

Mellander, L., Bjorkander, J., Carlson, B., and Hanson, L. A. (1986). Secretory antibodies in IgA deficient and immunosuppressed individuals. J. Clin. Immunol. 6, 284–291.

Mestecky, J., Czerwinski, C., Russell, M. W., Brown, T. A., Prince, S. J., Moldoveanu, Z., Jackson, S., Michale, S. M. and McGhee, J. R. (1987). Induction and molecular properties of secretory and serum IgA antibodies for environmental antigens. Ann. Allergy 59, 54–59.

Moriuchi, H., Takayanagi, T., Yamasaki, S., Yasui, M., Morii, K., Yanai, M., Yanagi, T., Tsuji, Y. (1990). Pernicious anemia in a patient with hypogammaglobulinemia. Acta Paediatr. Jpn. 32, 311–314.

Muller, F., Aukrust, P., Nilssen, D. E., and Froland, S. S. (1995). Reduced serum level of transforming growth factor–beta in patients with IgA deficiency. Clin. Immunol. Immunopathol. 76, 203–208.

Nilssen, D. E., Friman, V., Theman, K., Bjorkander, J., Kilateder, A., Holmgren, J., Hanson, L. A., and Brandtzaeg, P. (1993a). B cell activation in duodenal mucosa after oral cholera vaccination in IgA deficient subjects with or without IgG subclass deficiency. Scand. J. Immunol. 38, 201–208.

Nilssen, D. E., Aukrust, P., Florland, S. S., Muller, F., Froland, S. S., Aukrust, P., Florland, S. S., Muller, F., Nilssen, D. E., Friman, V., Theman, K., Björkander, J., Kilander, A., and Nilssen, D. E., Friman, V., Theman, K., Björkander, J., Kilander, A., and Froland, S. S. (1995). Inadequacy of mucosal IgM antibodies in selected variable immunodeficiency patients. J. Clin. Immunol. 15, 5367–5373.

Schaffer, F. M., Palermos, J., Zhu, Z. B., Barger, B. O., Cooper, M. D., and Volanakis, J. E. (1989). Individuals with IgA deficiency and common variable immunodeficiency share polymorphisms of major histocompatibility complex class III genes. Proc. Natl. Acad. Sci. USA 86, 8015–8019.

Scher, E. H., Mondal, A., and Schaffer, F. M. (1990). Intestinal permeability in children with immunodeficiency syndromes. N. Engl. J. Med. 313, 1620–1625.

Pignata, C., Budillon, G., Monaco, G., Nani, E., Cuomo, R., Parrilli, G., and Spadari, S. (2002). Reduced serum level of transforming growth factor–beta in IgA deficient subjects with or without IgG subclass deficiency. Scand. J. Immunol. 65, 205–212.

Ruan, E. A., Komorowski, R. A., Hogan, W. J., and Soergel, K. H. (1996). Nongranulomatous chronic idiopathic enterocolitis: clinicopathologic profile and response to corticosteroids. Gastroenterology 111, 629–637.

Royle, L., Roos, A., Harvey, D. J., Wormald, M. R., Van Gijswijk-Janssen, D. J., Redwan, E. R., Wilson, I. A., Daha, M. R., Dwek, R. A., Rudd, P. M. (2003). Secretory IgA and O-glycans provide a link between innate and adaptive immune systems. J. Biol. Chem. 278, 20140–20153.

Raychoudhury, S., Klemola, T., Carlson, B., Mellander, L., Stenvik, M., and Hovi, T. (1988). Inadequacy of mucosal IgM antibodies in selective IgA deficiency: excretion of attenuated polio viruses is prolonged. J. Clin. Immunol. 8, 89–94.

Schaffer, F. M., Palermos, J., Zhu, Z. B., Barger, B. O., Cooper, M. D., and Volanakis, J. E. (1989). Individuals with IgA deficiency and common variable immunodeficiency share polymorphisms of major histocompatibility complex class III genes. Proc. Natl. Acad. Sci. USA 86, 8015–8019.

Schaffer, F. M., Mondelo, R. C., Volanakis, J. E., and Cooper, M. D. (1991). IgA deficiency: Immunodef. Rev. 3, 15–40.

Shimada, S., Kawaguchi-Miyashita, M., Kushiho, A., Satoko, T., Nanno, M., Sako, T., Matsuoka, Y., Sudo, K., Tagawa, Y., Iwakura, Y., Ohwaki, M. (1999). Generation of polymeric receptor–deficient mouse with marked reduction of secretory IgA. J. Immunol. 15, 5367–5373.

Sperber, K. E. and Mayer, L. (1988). Gastrointestinal manifestations of common variable immunodeficiency. In Gut and Intestinal Immunity (ed. Ragnoff, M. F.). New York: WB Saunders.

Sarker, J., Tame, M. H., Price, A. B., Weston, J., and Bjarnason, I. (1994). Studies on the enteropathy associated with primary hypogammaglobulinemia. Gut 35, 1244–1249.

Takahashi, K., Webster, A. D., Price, A. B., Weston, J., and Bjarnason, I. (1994). Enteropathy associated with primary hypogammaglobulinemia. Gut 35, 1244–1249.

Uren, T. K., Johansen, F. E., Wijburg, O. L., Koentgen, F., Brandtzaeg, P., Strugnell, R. A. (2003). Role of the polymeric Ig receptor in mucosal IgA cell homeostasis. J. Clin. Immunol. 170, 2531–2539.

van der Meer, J. W., Weening, R. S., Schellekens, P. T., van-Munster, I. P., and Nagengast, F. M. (1993). Colorectal cancer in patients with X-linked agammaglobulinemia. Lancet 341, 1439–1440.

van Ginkel, F. W., Wahl, S. M., Kearnney, J. F., Kweon, M. N., Fujihashi, K., Burrows, P. D., Kyono, H., McGhee, J. R. (1999). Partial IgA deficiency with increased Th2-type cytokines in TGF-beta 1 knockout mice. J. Immunol. 163, 1951–1957.

van der Meer, J. W., Weening, R. S., van-Munster, I. P., and Nagengast, F. M. (1993). Colorectal cancer in patients with X-linked agammaglobulinemia. Lancet 341, 1439–1440.

Vorechovsky, I., Cullen, M., Carrington, M., Hammarstrom, L., Weinger, A. D. (2008). Common variable immunodeficiency (CVID): a reappraisal of IgA1D in IgA deficiency and common variable immunodeficiency: identification and characterization of haplotypes shared by affected members of 101 multiple-case families. J. Immunol. 164, 4408–4416.

Washington, K., Stenzel, T. T., Buckley, R. H., Gottfried, M. R. (1996). Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. Am. J. Surg. Pathol. 20, 1240–1252.

Wang, Z., Yunis, D., Iriyoguen, M., Kitchens, B., Bottaro, A., Alt, F. W., Alper, C. A. (1999). Discordance between IgA switching at the DNA level and IgA expression at the mRNA level in IgA1 deficient patients. Clin. Immunol. 91, 263–270.

Wold, A. E., Mestecky, J., Tomana, M., Kobata, A., Ohbayashi, H., Endo, T., and Eden, C. S. (1990). Secretory immunoglobulin A carries oligosaccharide receptors for Escherichia coli type 1 fimbrial lectin. Infect. Immun. 58, 3073–3077.

Zhang, J. R., Mostov, K. E., Lamm, M. E., Nanno, M., Shimida, S., Ohwaki, M., and Tuomanen, E. (2000). The polymeric immunoglobulin receptor translocates pneumococci across human nasopharyngeal epithelial cells. Cell 102, 827–837.

Zullo, A., Romiti, A., Rinaldi, V., Vecchione, A., Tomao, S., Aiuti, F., Frati, L., Luzi, G. (1999). Gastric pathology in patients with common variable immunodeficiency. Gut 45, 77–81.