

THE JOURNAL OF
ALLERGY
AND
CLINICAL IMMUNOLOGY

VOLUME 87

NUMBER 1, PART 1

Continuing Medical Education

This continuing medical education self-assessment program is sponsored by The American Academy of Allergy and Immunology and provided through an educational grant from Fisons Corporation.

Immunoglobulin deficiency syndromes and therapy

David P. Huston, MD, Arthur F. Kavanaugh, MD, Patricia W. Rohane, MD, and Marilyn M. Huston, PhD *Houston, Texas*

Immunoglobulin-deficiency syndromes are a heterogeneous group of disorders clinically defined by increased frequency of, and susceptibility to, infections. Many of these syndromes are being classified into discrete pathogenic entities, although they may have similar clinical presentations. In some cases, the critical defect is inherited. In other cases, the critical defect is acquired but may require a genetic predisposition. The association of multiple immune defects with some of the immunoglobulin-deficiency syndromes is consistent with both the complexity of cellular interactions within the immune system and the sensitivity of the integrity of the immune system to a variety of developmental signals. Our current understanding of the cellular and molecular basis for immunoglobulin deficiencies, the clinical features that

Abbreviations used

V:	Variable
D:	Diversity
J:	Joining
C:	Constant
IL:	Interleukin
MHC:	Major histocompatibility complex
XLA:	X-linked agammaglobulinemia
CVID:	Common variable immunodeficiency
sIgA:	Secretory IgA
IM:	Intramuscular
IV:	Intravenous
TdT:	Terminal deoxynucleotidyl transferase
EBV:	Epstein-Barr virus
GI:	Gastrointestinal

From the Immunology Sections, Departments of Medicine and of Microbiology and Immunology, Baylor College of Medicine, and The Methodist Hospital, Houston, Texas.

Supported in part by National Institutes of Health Grants A124664 and A121289.

Reprint requests: David Huston, MD, The Methodist Hospital, 6565 Fannin, MS F-501, Houston, TX 77030.

12/20073

characterize immunoglobulin-deficiency syndromes, and the therapy of immunoglobulin deficiencies will be emphasized in this article.

B CELL ONTOGENY

Bone marrow (or fetal liver) lymphoid stem cells, within the appropriate microenvironment, give rise to either T cell or B cell progenitors. These lymphoid

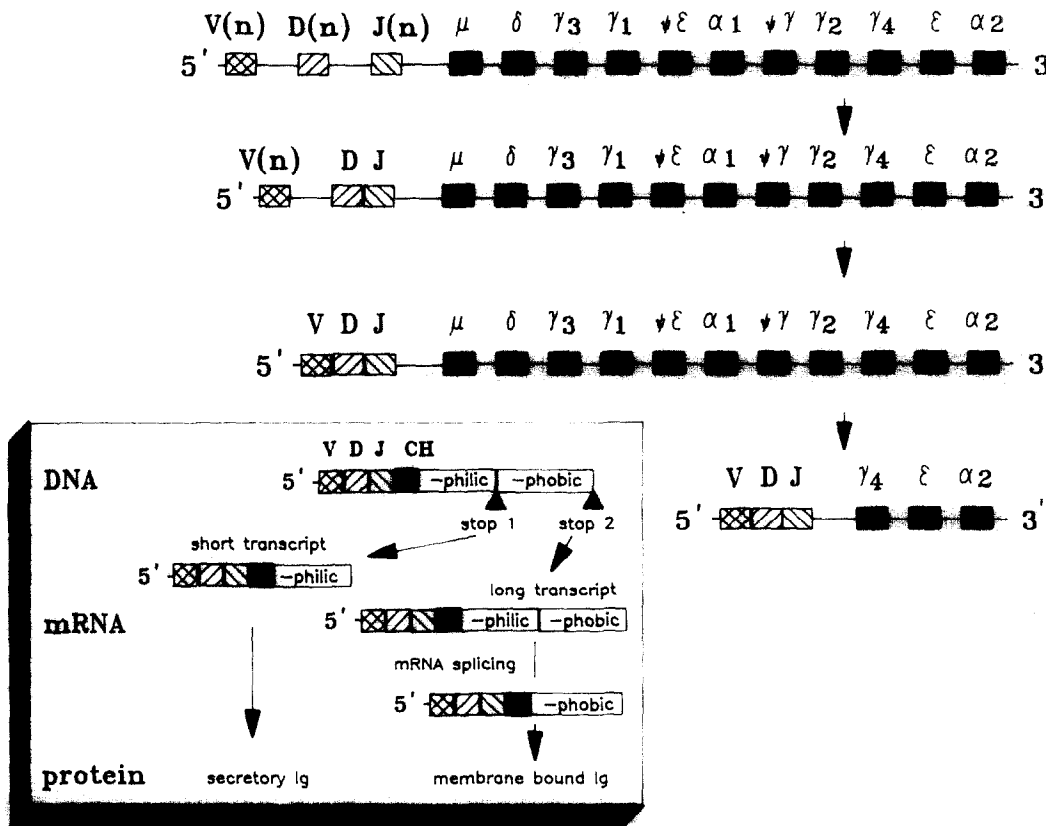


FIG. 1. Sequential rearrangement of the heavy chain gene exons. The orderly rearrangement of selected exons encoding V, D, and J regions allows the transcription of mRNA complementary to a specific VDJ segment along with the mu C region exons. Isotype switching requires further rearrangement to juxtapose the same VDJ segment with a more 3' C region gene, as is demonstrated for switching from mu to gamma 4. *Inset* illustrates that membrane-bound or secretory immunoglobulin can be produced from the same genes by use of different stop codons at the 3' end. If the first stop codon is used, a short transcript is obtained that is translated into a secretory protein containing a hydrophilic carboxy terminus. Read through of the first stop codon results in a long transcript in which the hydrophilic coding region is removed by splicing. The ultimate protein product is anchored to the cell membrane via a hydrophobic carboxy terminus.

stem cells, as well as all other nucleated cells of non-B cell lineage, contain the germline DNA configuration of immunoglobulin genes. Heavy chains are encoded by genes on the long arm of chromosome 14 at band q32.¹ Kappa chains are encoded by genes on chromosome 2 at band p11, and lambda chains are encoded by genes on chromosome 22 at band q11.² The overall organization of the immunoglobulin genes on each chromosome is similar, with the 5' end containing the structural genes for the variable domains of the heavy and light chains and the 3' end containing the structural genes for the constant domains. Commitment of a lymphoid progenitor cell to the B cell lineage is initiated by rearrangement of the heavy chain genes. A schematic model of the human immunoglobulin heavy chain gene is illustrated in Fig. 1.

There are up to 300 variable regions (V_H), 20 diversity regions (D_H), and six joining regions (J_H), followed by a single constant region (C_H) gene for each heavy chain isotype.³ Antibody diversity ensues from coupling the heavy chain VDJ recombinational possibilities with those of the light chain gene repertoire, allowing for $>10^6$ possible different antigen binding-site configurations. This recombinational potential may well be augmented by somatic mutation, accounting for the remarkable plasticity of the immune system. (T cell receptors are generated by a similar combination of V, D, J, and C region domains.)

The first step in immunoglobulin assembly involves the association of a D_H with a J_H region, followed by juxtapositioning of this DJ with a V_H . Association of the V_H and DJ region promotes the transcription of mRNA complementary to the rearranged VDJ seg-

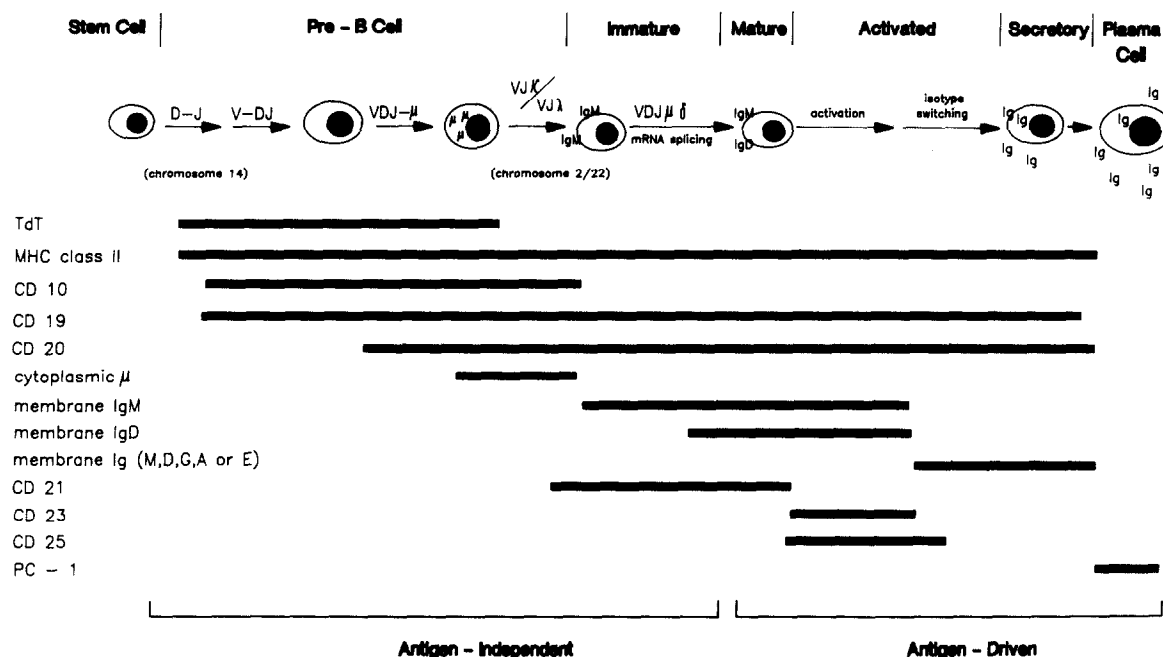


FIG. 2. B cell differentiation.

ment and the adjacent mu C region gene for production of the cytoplasmic mu chain.⁴ Successful rearrangement of the heavy chain gene on one of the fourteenth chromosomes is associated with inactivation of the heavy chain gene on the complementary chromosome 14 (allelic exclusion). Rearrangement of the light chain genes is staggered behind that of the heavy chain. The kappa and lambda genes differ from the heavy chain genes in that they lack D regions, their V_L and J_L regions are organized differently, and they contain only one C region. Kappa light chain rearrangement is attempted first. If this is unsuccessful, lambda chain rearrangement proceeds, although exceptions to this order have been reported. It is probable that association of a light chain with the complete mu gene product shuts off recombinase activity, and thus further rearrangement.⁵ Assembly of the intact antibody takes place in the Golgi apparatus. Production of the cell-surface immunoglobulin occurs by removal of a 3' hydrophilic coding region by splicing of the mRNA, resulting in a protein with a hydrophobic tail (Fig. 1, *inset*). After activation, the mRNA is terminated at the first polyadenylation site, resulting in a hydrophilic terminus for secreted immunoglobulin. The B cell can also use alternate splice sites to produce simultaneously both IgM and IgD. Successful immunoglobulin assembly and expression is concomitant with exodus of the B cell from the bone marrow.

To switch heavy chain isotype, additional DNA rearrangements must occur whereby the VDJ segment

is juxtaposed with a more 3' constant region by looping out intervening DNA and splicing of the switch region 5' to mu with the switch region preceding the C region gene to be transcribed (Fig. 1). Isotype switching is thus considered to proceed only in the 3' direction.

Both immunoglobulin and T cell-receptor recombination are robust processes mediated in part by consensus (highly conserved) recombination sequences. Similar sequences can also be found on other chromosomes. Errant interchromosomal, rather than normal intrachromosomal, recombination can result in lymphoid malignancy. With Burkitt's lymphoma, sporadic cases are due to mistakes in isotype switching, whereas endemic forms are due to aberrant VDJ recombination, resulting in both cases in chromosomal translocation.⁶ Consensus recombination sequences are often found near these sites of chromosomal translocation.⁷ Chromosomal translocations involving IgH and T cell-receptor genes characterize B and T cell neoplasia, respectively.⁸ Chromosomal translocations occurring at the pre-B cell level become apparent as clinical neoplasms after activation.⁷ Additional accrual of successive gene deletions and translocations with time may be associated with progression to a more malignant phenotype.⁹ Thus, events at several stages of lymphoid cell maturation can result in neoplasia.

B cell ontogeny can be broadly divided into antigen-independent and antigen-driven segments. Flow cytometry and monoclonal antibodies have enabled fur-

ther phenotypic distinction of successive stages of B cell growth and differentiation.^{10, 11} The correlation of B cell phenotype and immunoglobulin gene rearrangements is illustrated in Fig. 2. TdT, an enzyme that randomly inserts bases into a DNA sequence, is found in lymphoid stem cells as well as T and B cell precursors, and can be detected by cytochemical staining. Dual staining for TdT and for CD10, the common acute lymphoblastic leukemia antigen (CALLA), identifies early B cells. In addition, the B cell-restricted molecules CD19 and CD20 are expressed on early B cells and persist until activated B cells mature into plasma cells that express the PC-1 antigen. Mature resting B cells, capable of antigen-driven differentiation, are distinguished by their coexpression of membrane IgM and IgD, as well as the increased expression of CD21 (CR1, the receptor for the C3d cleavage product of the third component of complement and also an attachment molecule for EBV). On activation in the presence of the cytokine IL-4, CD23 (Fc ϵ R₂, the low affinity Fc receptor for IgE) is expressed; with isotype switching, CD23 is lost.¹² Activation also decreases CD21 expression, whereas CD25 (the IL-2 receptor) expression increases.¹² Thus, B cells can be phenotypically distinguished at numerous stages of their growth and differentiation.

The antigen-driven activation of mature, resting B cells can occur via T cell-independent or T cell-dependent mechanisms. T cell-independent activation can occur with selected polysaccharide antigens, resulting in an IgM response. However, most antigen-driven B cell responses are T cell-dependent. Likewise, amplification of antibody production and isotype switching are under T cell regulation. After antigen cross-linking of membrane immunoglobulin, T cell-dependent B cell proliferation and differentiation to plasma cells require the appropriate sequential involvement with cytokines. The list of such cytokines is rapidly expanding, as is the pharmacopoeia of recombinant molecules from cloned cytokine genes. Of particular interest has been the differential effects of some cytokines on isotype production.

Murine studies have shown IL-4 enhances IgG1 and IgE production, whereas it down regulates the production of other isotypes.¹³ Conversely, interferon- γ has been demonstrated to selectively increase IgG2a synthesis and depress synthesis of the other isotypes. These initial findings with murine B cells have established a foundation on which definitive studies on human B cell isotype regulation have begun. Although parallels with murine studies have not always been found for human B cell maturation, several cytokines have been demonstrated to affect human B cell activation, proliferation, and differentiation in a specific manner (Table I). IL-1 effects initial B cell activation

by inducing B cell-surface receptors for the succession of stimulatory cytokines that follow.¹⁴ IL-2 promotes the growth and differentiation of activated B cells.^{15, 16} The importance of IL-2 for B cell maturation is implied by the presence of high affinity IL-2 receptors on activated B cells. IL-4 increases B cell class II MHC molecule (DR, DP, and DQ) expression and synergizes with other ILs to enhance the early proliferative response of activated B cells.¹⁶ Recently, IL-4 was demonstrated to specifically enhance IgE production.¹⁷ IL-4-enhanced IgE production is dependent on T cell-B cell interaction via T cell receptors and MHC class II molecules.¹⁸ IL-4 also induces B cell expression of CD23, for which the exact physiologic role remains to be elucidated.¹² IL-5 enhances the growth and differentiation of activated B cells and can increase IgA synthesis three- to fourfold.¹⁹ Because of this differential effect on isotype production, IL-5 is proposed as a major regulatory molecule for mucosa-associated lymphoid cells. IL-5 also augments IL-4-induced IgE production when a suboptimal IL-4 concentration is used. By contrast, greater quantities of IL-4 completely negate the IL-5-mediated IgA potentiating effect. IL-6 stimulates an increased rate of immunoglobulin secretion in terminally differentiated B cells.²⁰ Interferon- γ enhances the effect of IL-2 and antagonizes the effect of IL-4 on B cell maturation but, by itself, is not considered to deliver a complete growth and differentiation signal.¹⁶ Recently, IL-7 has been identified and demonstrated to promote proliferation but not differentiation of pre-B cells.^{21, 22} Further classification of cytokine networks may provide a blueprint for a better understanding of pathogenic defects responsible for immunoglobulin dysregulation.

IMMUNOGLOBULIN DEFICIENCY SYNDROMES

The attempt of the World Health Organization to classify primary immune deficiencies resulted in 27 designated syndromes.²³ Each of these syndromes may include a defect in immunoglobulin production. Not included among these syndromes are secondary immune deficiencies resulting from hypercatabolism, increased losses, or iatrogenic immunosuppression. This article will focus on selected primary immune deficiency syndromes in which defective immunoglobulin production is the predominant feature.

X-linked (Bruton's) agammaglobulinemia

XLA is clinically characterized by the onset of severe, recurrent bacterial infections after 6 months of age because of the gradual decline in placentally transferred maternal IgG and the infant's inability to effectively produce all immunoglobulin isotypes.^{24, 25}

Although diagnosis of XLA in young male subjects is secured where pedigree analysis reveals early infectious deaths in the maternal male lineage, a positive family history is lacking for 45% to 50% of all cases, suggesting that spontaneous mutation can be a pathogenic mechanism.²⁶

In XLA, T cell-mediated immunity is intact as evidenced by positive delayed hypersensitivity skin tests, normal in vitro proliferative responses by peripheral blood mononuclear cells to T cell mitogens, antigens, and allogenic cells, and normal numbers of T cells and T cell subsets.²⁷ Morphology of the thymus and the thymic-dependent areas of the peripheral lymphoid organs is normal. By contrast, plasma cells and mature, surface immunoglobulin-positive B cells are virtually absent from the blood and peripheral lymphoid tissues, resulting in the absence of germinal centers.²⁷ Rarely, pre-B cells or immature B cells can be identified in the peripheral blood.²⁸ B cell precursors are found in normal numbers in the bone marrow of patients with XLA. Serum IgG concentration is <200 mg/dl with IgA and IgM markedly reduced for age. Usually, immunoglobulins are undetectable by conventional nephelometry or radial immunodiffusion assays but may be detectable by the more sensitive RIA or ELISA.

The concise definition of XLA as a disease characterized by an absence of B cells in the peripheral circulation without metabolic abnormalities or evidence of other immunodeficiency in the pedigree belies the heterogeneity of this disease. In addition to familial versus nonfamilial cases, some authors have described "major" and "minor" forms, whereas other authors include "typical" and "atypical" cases of XLA. Atypical cases include girls with classic XLA pathology and pedigrees featuring affected male members lacking even pre-B cells. In addition, immunoglobulin deficiency is not absolute; in the patient population, there is a range of B cell numbers and immunoglobulin levels in the peripheral blood.²⁹

Bacterial infections are the major complication of XLA.^{24, 25, 30} These infections typically involve the upper and lower respiratory tract and may rapidly progress to sepsis with disseminated infection. Bronchiectasis with respiratory failure is a major cause of morbidity and mortality in patients surviving to middle age. XLA may also be complicated by viral infections. Chronic disseminated echovirus infection is of special concern because it can cause a fatal meningoencephalitis. Increased susceptibility to enterovirus infection also predisposes to postvaccine poliomyelitis.³¹ Therefore, live vaccines are contraindicated for patients with XLA, as well as for patients with other severe forms of agammaglobulinemia. GI complications include malabsorption and infections

TABLE I. Effects of cytokines on human B cell proliferation and differentiation

Cytokine	Effects
IL-1	Promotes initial B cell activation
IL-2	Promotes growth and differentiation of activated B cells
IL-4	Enhances growth of activated B cells Increases B cell class II MHC expression Induces CD23 expression Enhances IgE production
IL-5	Enhances growth and differentiation of activated B cells, especially for IgA production Synergizes with IL-4 for optimal IgE production
IL-6	Increases rate of immunoglobulin secretion by terminally differentiated B cells Required for IL-4-induced IgE production
IL-7	Promotes proliferation but not differentiation of pre-B cells
Interferon- γ	Enhances IL-2 effects Antagonizes IL-4 effects

with *Giardia lamblia* and *Campylobacter jejuni*. Approximately one third of patients with XLA develop mono- or polyarticular arthritis with sterile effusions, and ultimately contracture deformities. Unfortunately, the incidence of lymphoreticular malignancy can be as high as 6%.³²

A consensus on the level of the B cell defect in XLA has not been reached. Schwaber and Chen³³ have characterized two forms of XLA that appear to result from defective rearrangement of immunoglobulin heavy chain genes at different stages of early B cell differentiation.³³ In the major form, pre-B cells from the bone marrow produce a truncated mu chain lacking VDJ-encoded antigens. This truncation results from transcription of the mu C region gene before DJ region rearrangement. Such B cells fail to migrate from the bone marrow. Although pre-B cells expressing only a truncated mu chain are readily detected in normal bone marrow, they can predominate in the bone marrow of patients with XLA. In the minor form, truncated mu and delta chains are produced from transcription of DJC (mu/delta) as DJ rearrangements occur, but transcription proceeds without V region rearrangement. Normal numbers of B cells bearing

cell surface mu and delta chains are found in the peripheral blood, but light chains are not detected.³⁴ Mu chains without associated light chains can be expressed on the cell surface when truncation excludes V regions that are required for binding of the glucose-regulated heavy chain binding protein that serves to retain immunoglobulin molecules within the endoplasmic reticulum until complete assembly.

Evidence that defective gene rearrangement may not be the only explanation for the pathophysiology of XLA comes from studies of the rare immunoglobulin-producing cells in patients with XLA. Immunoglobulin-secreting EBV-transformed cell lines can be obtained from these patients that have V_H rearrangement and are not of limited clonality. Moreover, peripheral B cells from patients with XLA have an immature cell-surface phenotype even after they have completed VDJ rearrangement.^{32, 35} Somatic fusion studies have demonstrated that the heavy-chain genes in patients with XLA are completely normal and that immunoglobulin synthesis can be rescued by fusion with mouse myeloma cells. Retention of the defective human X chromosome in these hybrids does not inhibit immunoglobulin synthesis.³⁶ Since gene rearrangements in B and T cell lineages are believed to use the same recombinase enzymes, and yet the T cell function in XLA is normal, some other factor encoded on the X chromosome is lacking in this disease. To date, the abnormal gene has been localized to the long arm of the X chromosome between Xq21.3 and Xq22.³⁷ Because the gene defect in XLA is limited to lymphoid cells that can be removed and restored to the patient without harm and because X chromosome abnormality does not confer a negative effect, this disease is an excellent candidate for gene replacement therapy.

In normal female subjects, X chromosome inactivation is random in all tissues resulting in mosaicism of allelic expression. This is also true for female carriers of XLA in T cells and granulocytes, but not in B cells. Only B cells expressing the normal allele mature and are found in the peripheral blood. Since peripheral B cells from normal individuals are allelic mosaics, the allelic homozygosity of peripheral B cells from XLA carriers forms the basis for a test to identify XLA carriers long before the gene is identified.^{38, 39}

Currently, the primary treatment for XLA is gammaglobulin replacement. Such replacement is effective in reducing the frequency and severity of virtually all the complications of XLA. Even partial restoration of serum IgG levels is associated with clinical improvement. Long-term or intermittent antibiotic prophylaxis has also been effective in further reducing

the frequency and severity of infections. However, morbidity from sinopulmonary disease may not be completely prevented because of the failure of immunoglobulin replacement therapy to restore antibodies at mucosal surfaces.³²

Common variable immunodeficiency

CVID is a heterogeneous group of immunologic disorders characterized by panhypogammaglobulinemia and recurrent infections.^{23, 25} Typically, total immunoglobulin levels are <350 mg/dl, and total IgG levels are <250 mg/dl. Most patients with CVID present clinically after the age of 10 years, although congenital forms do occur. Although both CVID and XLA are characterized by panhypogammaglobulinemia and recurrent infections, there are major differences between these two disorders. Distinction can be most difficult if CVID is initially observed during infancy. However, with CVID, there are usually normal numbers of surface immunoglobulin-bearing B cells in the peripheral blood.²⁷ In addition, with CVID, there is an increased propensity to develop generalized lymphadenopathy, hepatosplenomegaly, noncaseating granulomata of the lung, liver, and spleen, and amyloidosis, all of which are manifestations of chronic inflammation. A variety of autoimmune disorders also occur with CVID, in spite of impaired antibody production.²⁵ Five percent of patients with CVID develop pernicious anemia (gastritis, achlorhydria, and absent intrinsic factor), which carries an increased risk for adenocarcinoma of the stomach. Hematologic disorders are common (50% of all patients with CVID) and are frequently caused by autoantibodies. Coombs' positive hemolytic anemia, immune thrombocytopenic purpura, or antibody-mediated leukopenia can occur. Rheumatoid arthritis-like polyarthropathy, thyroiditis, and polymyositis are additional autoimmune phenomena associated with CVID. Furthermore, patients with CVID are at increased risk for pseudolymphoma and lymphoreticular malignancies, primarily of B cell lineage. Although CVID is considered to be an acquired disorder, there are few documentations of true acquisition. Congenital rubella infection, EBV infection, and certain medications (e.g., phenytoin) have been causally linked to CVID. Some patients have been observed to progress from selective isotype deficiencies to CVID.

Recurrent bacterial infection of the sinopulmonary tract is the most common clinical manifestation of CVID, the severity of which varies remarkably between individuals.³⁰ Pneumonia is the most prevalent infectious complication (82%), followed by sinusitis (60%). *Haemophilus influenzae*, *Pneumococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus*

aureus are the most frequent infecting organisms. More than 50% of untreated patients develop bronchiectasis. Respiratory failure, the final complication of bronchiectasis, is the most common cause of death. The GI tract is also a common site for infection.⁴⁰ Recurrent *Giardia*, *Salmonella*, rotavirus, and *Campylobacter* infections may result in chronic diarrhea. Although overwhelming viral infections are uncommon in patients with CVID, devastating chronic echovirus meningoencephalitis and paralytic disease caused by poliovirus have occurred. Patients with CVID may also develop aggressive forms of hepatitis B and hepatitis C. As with XLA, vaccination with attenuated live virus is not recommended for patients with CVID. Fungal, mycobacterial, and protozoal infections (*pneumocystis carinii*) occur in CVID at a higher than expected frequency, as can a particularly severe form of mycoplasma arthritis.³⁰

Another major complication of CVID is a sprue-like syndrome characterized by noninfectious chronic diarrhea, malabsorption, lactose intolerance, and weight loss.⁴⁰ Approximately two thirds of patients with this syndrome will have nodular lymphoid hyperplasia of the small intestine. The remaining one third will have lymphocytic infiltrates of the lamina propria and blunting of the intestinal villi. Almost one third of the patients afflicted with chronic diarrhea will develop adenocarcinoma or lymphoma of the bowel.

The immunologic dysregulation implicated in the pathogenesis of CVID is pleomorphic.^{25, 32, 41} Approximately 80% of patients have an intrinsic B cell-maturation defect. The remaining 20% have a T cell defect characterized by either deficient helper T cell activity or excessive suppressor T cell activity. Rarely, monocytes, natural killer cells, or autoantibodies to B or T cells have also been implicated as the basis for CVID. Peripheral blood T cells are phenotypically and numerically normal, and the peripheral lymphoid organs and the thymus are morphologically normal. T cell-proliferative responses to T cell mitogens range from moderately depressed to normal. Antigen-specific antibody responses are reduced or undetectable, presumably reflecting the decreased antibody synthesis rather than defective antigen processing or defective antigen-specific responses. B cell-proliferative responses to B cell mitogens range from completely absent to normal. B cells from most patients with CVID fail to produce immunoglobulin when their lymphocytes are stimulated in vitro with the T cell-dependent mitogen, pokeweed. On occasion, the block in immunoglobulin secretion can be overcome by the combination of both the B cell mitogen, *Staphylococcus aureus* Cowen's strain I and

pokeweed. EBV, a T cell-independent polyclonal B cell activator, can sometimes stimulate otherwise unresponsive B cells to produce immunoglobulin. B cells from a few patients synthesize, but do not secrete, immunoglobulin when cells are stimulated with mitogen, presumably because of an immunoglobulin glycosylation defect. Last, an occasional patient's B cells produce normal amounts of immunoglobulin when cells are stimulated in vitro with mitogen. The B cells in this final group are believed to fail in vivo because of a circulating inhibitory factor. Pathogenic mechanisms for drug-induced hypogammaglobulinemia may involve induction of suppressor T cells, as has been reported with phenytoin.⁴²

Cytokine defects have been documented and implicated in the pathogenesis of a few cases of CVID. Defective IL-2 production by T cells, suboptimal B cell response to IL-4 coincident with defective T cell IL-4 secretion, and defective T cell IL-6 production (but normal IL-2 and IL-4 production) have each been singly described in patients with CVID.^{43, 44} Recently six of 11 patients with CVID were found to have IL-6 serum levels three to 16 times higher than normal levels.⁴⁵ B cell IL-6 "resistance" might be a contributing pathogenic factor in these cases. At the present time, the involvement of cytokine disorders in CVID is speculative.

Acquired panhypogammaglobulinemia and thymoma are two clinical disorders that are well documented to occur concurrently.⁴⁶ Approximately 6% of patients with thymoma are either panhypogammaglobulinemic at the time of initial diagnosis or become so at a later point. These patients develop pure red cell aplasia eight times more often than patients with thymoma alone. These patients also have a greatly diminished bone marrow pre-B cell and peripheral B cell population associated with an expanded suppressor T cell population, suggesting that immunologic dysregulation may contribute to the hypogammaglobulinemia. Rapid reversal of pure red cell aplasia may occur postthymectomy, but hypogammaglobulinemia usually remains.⁴⁷

The principal treatment of CVID is gammaglobulin replacement, as well as assiduous use of antibiotics for active infection.³² Pyogenic complications are greatly attenuated, and concomitant with gammaglobulin replacement, the incidence of bronchiectasis has declined. Often, the arthropathy, and sometimes the chronic diarrhea, responds to gammaglobulin replacement. Metronidazole is recommended for treatment of all patients with proven giardiasis and for empiric use after a search for the etiology of diarrhea has proved unsuccessful. Oral tetracycline may be helpful if bacterial overgrowth syndrome is suspected.

TABLE II. Characteristics of IgG subclasses

	IgG1	IgG2	IgG3	IgG4
% Normal serum IgG	60-70	20-30	5-8	1-3
MW (kd)	146	146	170	146
MW heavy chain (kd)	52	52	60	52
Hinge region amino acids	15	12	62	12
Interchain disulfide bonds	2	4	12	2
T _{1/2} (days)	21	21	7	21
Allotypic markers	4-10	1	14	0
Complement fixation	++	+	+++	---
Fc receptor binding	+++	±	+++	+
Cryoglobulin formation	++	+	+++	+
<i>Staphylococcus</i> protein A binding	+	+	---	+
Transport across placenta	++	+	++	++
Antipolysaccharide antibodies	+	+++	---	++
Antiprotein antibodies	+++	+	++	+

MW, Molecular weight.

In some patients, diarrhea may respond to cholestyramine, and an occasional remission is observed in particularly recalcitrant diarrheal cases with oral prednisone.

IgG subclass and antigen-specific immunoglobulin deficiency

Soon after discovery of IgG subclasses, the association between their deficiency and recurrent pyogenic infections was noted.⁴⁸ Paradoxically, there are perfectly healthy individuals who lack each of the IgG subclasses to varying degrees. Very rarely, subclass deficiencies result from gene deletions.⁴⁹ Pedigree analysis on these patients revealed major gene deletions in other family members with and without clinical manifestations. Therefore, the clinical relevance of an IgG-subclass deficiency is predicated on the affected patient's ability to respond to antigenic challenge.

IgG1, IgG2, IgG3, and IgG4, named in order of their frequency of occurrence as myeloma proteins and their serum concentrations, are structurally similar, possessing approximately 95% homology in the primary amino acid sequence of their heavy chain C domains.⁵⁰ The greatest divergence occurs in the hinge region, with IgG3 having a modified and then quadrupled repeat of the 12 to 15 amino acid hinge region found in the other IgG subclasses. There is sufficient structural heterogeneity such that the four subclasses manifest distinct physiochemical characteristics and biologic effector functions (Table II). Part of this diversity is a relative restriction in the antigen specificity within the subclasses.⁵¹ Protein antigens are bound more frequently by IgG1 and IgG3, whereas carbohydrate antigens are preferentially bound by IgG2 and

IgG4.

Implicit in the assignment of significance to deficiencies of the IgG subclasses is the acceptance of what constitutes a deficiency. If concentration is used and normal is taken as the mean $\pm$ 2 SD, then, by definition, 2.5% of the population is deficient in each subclass. However, this type of analysis may not be appropriate because the frequency distribution of IgG2, IgG3, and IgG4 is skewed rather than gaussian.⁵² In addition, physiologic variation may influence subclass concentration. Although advanced age is not reliably associated with alterations in subclasses, there is significant variation during infancy and childhood. Serum IgG levels reach their nadir at 3 to 6 months of age as maternally derived immunoglobulin wanes. Thereafter, the IgG subclasses reach maximum levels at different times; that is, adult levels of IgG1 are achieved at 5 to 7 years of age, IgG3 at 7 to 9 years, IgG4 at 9 to 11 years, and IgG2 at about 10 years.⁵³ Interestingly, some bone marrow-transplant recipients have a similar delay of IgG2 and IgG4 production, fail to respond to polysaccharide antigens, and are prone to bacterial infections. Although this delay is reminiscent of childhood B cell development, helper T cell deficiency may contribute to this phenomena. Genetic factors also influence "normal" subclass levels. The best delineated of these factors is allotypes that exist for all the subclasses except IgG4. There is a correlation between mean concentration of IgG2 and IgG3 and their respective Gm allotypes. The most important confounding factor in the definition of IgG subclass deficiency is the imperfect correlation between clinical symptoms and any given concentration of the subclasses. For the present time then, levels of IgG subclasses below the reported

lower limit of normal should be interpreted as consistent with, but not diagnostic of, an underlying defect in humoral immunity.

The association between recurrent sinopulmonary infections and low serum levels of IgG subclasses has long been established.⁴⁸ Since it is impossible to assign significance to deficiencies of the subclasses based solely on statistical ranges, prevalence data for clinically important subclass deficiencies are presently unavailable. However, there are data on such deficiencies in populations selected for an apparent increased susceptibility to infections. Dependent on the population surveyed, as many as 25% of referred patients have been found to be deficient in one subclass. In adults, IgG3 deficiency is the most common, and female patients outnumber male patients. In children younger than 16 years, IgG2 is most commonly deficient, and male children predominate.⁵⁴ Deficiencies of a single isotype are more common than combinations. When the latter occurs, their frequency is as might be expected from their heavy chain gene position proximity (e.g., IgG2 to IgG4). There is also an association between selective IgG subclass deficiencies and other primary immunodeficiency disorders, including ataxia-telangiectasia, complement protein deficiencies, and, perhaps most importantly, IgA deficiency. Of symptomatic patients with IgA deficiency, up to 15% may have concurrent IgG subclass deficiency.⁵⁵

The most prominent sequela of IgG-subclass deficiency is recurrent infection of the upper and lower respiratory tract. The spectrum of infectious organisms is usually limited to normal pathogens, in contrast to the opportunistic organisms encountered in various other immunodeficiencies. Affected patients may respond well to appropriate and aggressive antibiotic therapy. Left unchecked, however, their infections may easily become pernicious. Potential tissue injury, especially in the lungs, provides the impetus for identification and assiduous treatment of these patients.

Symptomatic selective subclass deficiencies are typically associated with slightly different clinical presentations. Isolated IgG1 deficiency is rare.⁵⁴ Since IgG1 compromises the majority of total serum IgG, affected patients are not dissimilar to patients with panhypogammaglobulinemia. As such, they may be asymptomatic or suffer a spectrum of infectious complications ranging from mild upper respiratory tract infections to sepsis. In addition, features commonly associated with panhypogammaglobulinemia, such as lymphoid hyperplasia, sprue-like GI symptoms, and autoimmune phenomena, may be observed.

Since most carbohydrate antigens preferentially induce an IgG2 response, it is not surprising that defi-

ciency of this subclass may be associated with recurrent infection by polysaccharide encapsulated bacteria. IgG2-deficient children generate significantly less specific antibody in response to immunization with the capsular polysaccharide of *H. influenzae* when they are compared to control subjects.⁵⁶ Patients lacking the G2m(n) allotypic marker have a similar deficiency. By contrast, IgG2-deficient patients respond normally to protein-antigen vaccination. Differentiating asymptomatic from symptomatic IgG2-deficient patients may be the ability to generate effective antibodies against specific microbial pathogens. Healthy subclass-deficient individuals may shift a specific response from the deficient isotype to another type as a compensatory mechanism. Indeed, marked variation in the ability of subclass-deficient patients to accomplish this shift has been reported.⁵⁷ Therapeutic modulation of the dominant isotype produced can be accomplished by immunization with conjugates of protein and polysaccharide antigens, such as the recently introduced diphtheria toxoid/*H. influenzae* type b vaccine.⁵⁸ This has been useful in producing IgG1 anticarbohydrate antibodies in young or IgG2-deficient children who are frequently unresponsive to polysaccharide vaccines. However, since IgG2-deficient individuals may suffer recurrent infections with nonencapsulated organisms, the lack of anticarbohydrate antibodies may not be sufficient to explain the humoral immunodeficiency in affected patients. It has been noted that patients with a combined IgG2-IgG4 or IgG2-IgA deficiency may be more severely compromised than patients with selective IgG2 deficiency. Finally, associations have been noted between IgG2 deficiency and ataxia-telangiectasia, in which there is a proclivity to recurrent upper respiratory tract infections. In contrast, the IgG2 deficiencies reported with intractable childhood epilepsy and idiopathic thrombocytopenia purpura do not predispose to recurrent infections, and the pathophysiologic basis underlying the association is uncertain.

Symptomatic IgG3 deficiency is most typically manifest as recurrent upper and lower respiratory tract infection.⁵⁹ Pulmonary involvement, which may be complicated by bronchiectasis and obstructive airway disease, may be observed with greater frequency in a combined IgG1-IgG3 deficiency. Given that IgG3 is the predominant subclass in the primary response to various viral protein antigens and since appropriate cultures of symptomatic IgG3-deficient patients often fail to identify bacterial pathogens, it has been postulated that IgG3 deficiency predisposes patients to recurrent viral upper respiratory tract infections. Perhaps also of note is that most of the IgG response against *Moraxella (Branhamella) catarrhalis* as well as to the M component of *Streptococcus pyogenes*

resides within the IgG3 subclass. These two organisms may be difficult to identify as pathogens, given their relatively low numbers in documented infections as well as their occasional presence in asymptomatic individuals. With vaccination, IgG3-deficient patients tend to have normal responses to both protein antigens (e.g., diphtheria toxoid and tetanus toxoid) that elicit a large IgG1 response, as well as to carbohydrate antigens (e.g., pneumococcal vaccine and *H. influenzae* type b vaccine) that elicit predominantly an IgG2 response.

The issue of IgG4 deficiency is more controversial. Some authors have reported cases of severe life-threatening infections in which low IgG4 was the only immunologic abnormality noted, and there was a beneficial effect of replacement therapy. However, approximately 15% of the population have insufficient IgG4 to be detected by radial immunodiffusion assay, and thus, the significance of "deficiency" is uncertain.⁶⁰ Until the more widespread application of tests with sufficient sensitivity to enable accurate establishment of normal values, IgG4 deficiency should be considered mostly in the context of concurrent IgG2 or IgA deficiency.

The relevance of IgG subclass deficiencies is that they may serve as markers of an underlying defect in humoral immunity in symptomatic patients. Whether caused by restricted V region gene usage or other mechanisms, subclass deficiencies are germane only to the extent they reflect a subnormal ability to produce specific antibodies. That antigen specific antibodies are the sine qua non of competent humoral immunity has been underscored recently by studies documenting normal quantitative levels of all immunoglobulin isotypes but subnormal responses to immunization with specific antigens.⁶¹ Since these occurred in the context of an increased frequency of infections, they were significant. In most such cases, the deficiency has been demonstrated to all polysaccharides tested, but for some patients, the defect was restricted to certain polysaccharide antigens, suggesting a more specific deficiency. Normal quantitative isotype concentrations, but impaired antibody response to polysaccharide antigens, has previously been noted in the Wiskott-Aldrich syndrome. In the hyper-IgE syndrome, impaired responses to both polysaccharide and protein antigens have been noted. Although some affected patients had low IgG2 levels, this finding provides insufficient explanation for the breadth of their humoral immune deficiency. In summary, determination of antigen-specific antibody responses allows the assignment of significance to subnormal serum concentrations of immunoglobulins and, independent of these levels, defines a focal humoral immunodeficiency.

Indications for replacement therapy with immunoglobulin for IgG subclass deficiencies are not as clear-cut as they are for agammaglobulinemia.⁶² Conservative treatment reserves such therapy for patients with culture-documented recurrent bacterial infections, suboptimal clinical responses to antibiotics, and impaired antigen-specific IgG responses. However, reports of clinical benefit in some patients with quantitatively low levels of selected IgG subclasses, irrespective of impaired IgG responses to specific protein or polysaccharide antigens, have led to an ongoing, randomized, controlled study evaluating the efficacy of immunoglobulin replacement in such patients.

IgA deficiency

Selective IgA deficiency is defined by a serum IgA level <5 mg/dl with normal serum IgM and IgG levels.⁶³ The reported incidence ranges from one in 300 to one in 3040 healthy blood donors, many of whom are asymptomatic. IgA is the major immunoglobulin expressed in body secretions and hence is located on all mucousal surfaces where it synergizes with other host-defense mechanisms to neutralize pathogenic toxins, invasive bacteria, and cytotoxic viruses. There are two structurally and serologically distinct IgA subclasses, each encoded by a specific heavy chain C region. Both subclasses are usually markedly reduced or absent in selective IgA deficiency, although isolated deficiencies of each have been described. IgA1 represents 65% to 95% of monomeric circulating IgA, whereas IgA2 represents approximately 50% of the secreted polymeric form. Construction of sIgA begins when two IgA molecules are bound together with the J chain in the mucosa-associated plasma cell.⁶⁴ Dimeric IgA is then released into the interstitial milieu in which it binds in a ligand-receptor interaction to the secretory component anchored in the basal aspect of the glandular epithelial cell membrane. It is subsequently transported through the epithelial cell in an endocytotic vacuole, and the entire complex (IgA dimer, J chain, and secretory component) is released onto the mucosal surface after enzymatic cleavage occurs in the proximal portion of the secretory component; sIgA, in teleologic terms, is well suited for the mucosal membrane microenvironment. The secretory component apparently imparts proteolytic resistance on sIgA, although some common bacterial pathogens have countered this molecular defense mechanism by elaboration of specific human IgA proteases.

Some authors report that most patients with selective IgA deficiency are completely asymptomatic, whereas other authors suggest that many patients are prone to frequent infections that vary in intensity

from mild to severe.⁶⁵ The remarkably variable clinical presentation of IgA deficiency may partially be explained by two observations. First, asymptomatic IgA-deficient individuals have been demonstrated to produce IgM along the upper respiratory tract mucosa and have IgM in salivary secretions.⁶⁶ This phenomenon was not observed in symptomatic patients. The corollary found in a number of symptomatic IgA-deficient patients is an associated IgG2/IgG4 or IgG3 subclass deficiency,⁶⁷ which may predispose to recurrent sinopulmonary tract infections with an increased risk for development of impaired lung function.⁶⁸

Chronic GI tract infections are not a common feature of IgA deficiency, although giardiasis has been reported in some patients. Nodular lymphoid hyperplasia of the small intestine, ulcerative colitis, Crohn's disease, and a sprue-like diarrheal illness occur with increased frequency. IgA deficiency also has been associated with an increased frequency of a variety of autoimmune disorders,⁶⁹ including rheumatoid arthritis (1.6%), juvenile rheumatoid arthritis (2%), and systemic lupus erythematosus (2.6%). Other autoimmune disorders reported in conjunction with cases of IgA deficiency are thyroiditis, pernicious anemia, chronic active hepatitis, dermatomyositis, Sjögren's syndrome, autoimmune adrenal insufficiency, and immune thrombocytopenic purpura. Patients may have a slightly increased risk for lymphoreticular malignancies. Selective IgA deficiency has also been associated with atopic disease.^{63, 70} The incidence varies between one in 22.5 to one in 200 preselected individuals with asthma, atopic dermatitis, allergic rhinitis, or urticaria. IgA is believed to contribute toward the prevention of food-protein antigenemia, and in its absence, the GI mucosa may become permeable to many ingested proteins. Seventy-five percent of the IgA-deficient population have high-titer IgG anti-cow's milk protein antibodies that frequently form circulating immune complexes with cow's milk protein, although most of these patients are asymptomatic.

The occurrence of selective IgA deficiency is usually sporadic, although familial patterns of inheritance have been characterized.⁶³ Epidemiologic studies have suggested an association between IgA deficiency and several MHC supratypes possessing defects at the C4 or 21-hydroxylase gene loci.⁷¹ Selective IgA deficiency can be precisely defined at the molecular level for only a small group of families known to lack the IgA1 heavy chain C region gene. Most individuals with selective IgA deficiency have a grossly intact alpha heavy chain gene region. An IgA regulatory defect at the mRNA level has been described for some

cases.⁷² However, phenotypic studies have generally documented normal numbers of surface IgA-bearing B cells suggesting a block in terminal IgA-secreting B cell differentiation.⁷³ Some selective IgA deficiencies can be explained on the basis of circulating IgA-specific suppressor T cells.⁷⁴ Rarely a defect in the secretory piece results in a lack of sIgA with a normal serum IgA.⁷⁵ Recently, a T cell-derived IgA binding factor has been demonstrated to suppress selectively IgA production in vitro, suggesting yet another potential mechanism for selective isotype deficiencies.⁷⁶

IgA deficiency can result from exposure to a number of pharmacologic agents.⁶³ Phenytoin is most notable, although D-penicillamine, hydroxychloroquine, sulfasalazine, and sodium aurothiomalate have also been implicated with acquisition of selective IgA deficiency. Most cases of drug-induced IgA deficiency resolve when the causative agent is withdrawn. Transient selective IgA deficiency is especially common in children but usually reverts to normal before the age of 14 years and may simply be a manifestation of maturational delay in IgA humoral immunity.

IgA deficiency is also a feature of ataxia telangiectasia, a complex autosomal recessively inherited syndrome characterized by early development of lymphoproliferative malignancies, cerebellar ataxia, and prominent cutaneous telangiectases.⁷⁷ Serum IgA is either absent (50% of cases) or very low (30% of cases). Low serum IgG levels are also frequent (50% of cases) and usually caused by IgG2 deficiency. Most of these patients are plagued with repeated sinopulmonary infections and develop progressive bronchiectasis.

Therapy for IgA deficiency depends entirely on the clinical presentation. Bacterial infections should be promptly treated with antibiotics and, if this is necessary, with a prophylactic antibiotic regimen. Isolated IgA deficiency should not be treated with immunoglobulin replacement. Since all immunoglobulin preparations contain small amounts of IgA, replacement therapy in an IgA-deficient individual carries a significant risk for the induction of anti-IgA antibodies that are causally implicated in anaphylaxis on reexposure to IgA.⁷⁸ Symptomatic IgA-deficient patients with IgG-subclass deficiency and the inability to mount a specific IgG antibody response on antigenic challenge may benefit from immunoglobulin replacement therapy. However, a preparation manufactured to contain very low quantities of IgA should be used in an effort to minimize the risk for anaphylaxis. If transfusion of whole blood or plasma is medically indicated for an IgA-deficient individual, the risk of anaphylaxis can be decreased by selecting the blood

products from an IgA-deficient donor; cellular blood components from any ABO compatible donor may be used if they have been washed multiple times.

Hyper-IgM immune deficiency

The hyper-IgM syndrome is characterized by an elevated or normal serum IgM associated with very low serum IgG and IgA levels, and the syndrome is complicated by pyogenic infections. Often, a male familial predisposition, suggesting an X-linked pattern, has been observed, and occasionally, patients progress to panhypogammaglobulinemia.⁷⁹ Distinction from CVID is apparent from the serum IgM level. During infancy, distinction from XLA is apparent by the presence of surface IgM-positive B cells in the peripheral blood and lymphoid hyperplasia. However, surface-membrane IgG or IgA is low or absent. Clinically, patients with hyper-IgM syndrome also have lymphadenopathy, hepatosplenomegaly, GI disorders, and autoimmune conditions, especially hematologic.

Mitogen stimulation of lymphocytes from these patients results in IgM but not IgG or IgA production.⁸⁰ However, mitogen stimulation of patients' irradiated T cells cultured with control individuals' B cells have demonstrated normal helper T cell function for terminal differentiation for IgM, IgG, and IgA production. Conversely, the inability of control T cells to induce patient B cells to produce IgG and IgA suggests an intrinsic B cell defect, although Southern analyses have not revealed immunoglobulin heavy chain gene deletions. The capacity for a T cell line, derived from a patient with Sézary syndrome to induce IgG and IgA production by B cells from several patients with hyper-IgM syndrome, suggests a lack of T cells capable of switching B cell isotype production.⁸¹ The inability of control peripheral blood T cells to induce isotype switching by patient's B cells suggests that such a "switch" T cell might not normally be present in peripheral blood.

Despite the presence of normal or elevated levels of IgM and the capacity to produce IgM with antigenic specificity, these patients experience the same infection risks and complications as patients with CVID. Since these patients are severely deficient for IgG, they are candidates for gammaglobulin replacement therapy.

Selective IgM deficiency

This rare disorder is characterized by serum-IgM levels <10% of normal but normal serum levels of other isotypes.^{25, 32} The limited studies of some patients have reported defective helper T cells or excessive suppressor T cells as the cause for selective IgM deficiency.⁸² Most patients experience recurrent

sinopulmonary infections with encapsulated organisms and an increased incidence of gram-negative septicemia. Since serum IgG levels are normal, treatment has historically been limited to antibiotic treatment. However, defective antigen-specific IgG responses have been demonstrated, and for such patients, gammaglobulin is a therapeutic consideration.

DIAGNOSTIC EVALUATION

Foremost in identifying patients with immunoglobulin deficiencies is inclusion of immunoglobulin deficiency syndromes in the differential diagnosis. Since the diagnostic considerations for pediatric patients and adults include overlapping differentials, the workup will vary depending on the patients' age and the medical history of the patients and their families.²³ A common feature of all patients with clinically relevant immunoglobulin deficiency is infections. However, some of the inherited immunoglobulin deficiencies may be diagnosed at birth by analysis of blood from the umbilical cord.

Currently, initial assessment of patients suspected of an immunoglobulin deficiency includes quantitation of serum immunoglobulins. Electrophoresis is not satisfactory for such quantitation. IgG and IgG subclasses, IgM, IgA, and IgE should be measured by immunodiffusion, nephelometry, RIA, or ELISA. Age-related normal ranges must be used. Determination of IgD levels are possible but not clinically relevant. Measurement of serum albumin is useful when hypogammaglobulinemia secondary to a protein-losing syndrome is being considered. When XLA is being considered, peripheral blood mononuclear cells should be phenotyped for surface immunoglobulin (heavy and light chains) and CD19 or CD20. The possibility of a combined T cell- and B cell-inherited disorder should be assessed further by T cell phenotyping and in vitro T cell-proliferative responses. In adolescents or adults, acquired impairment of T cell responses can be determined by delayed hypersensitivity skin testing, in vitro T cell-proliferative responses, and T cell phenotyping.

Specific antibody responses can be measured against both protein and carbohydrate antigens. Isohemagglutinins are predominantly IgM antibodies against red blood cell carbohydrate antigens. Undetectable isohemagglutinins may reflect impaired IgM and usually also impaired IgG anticarbohydrate responses. IgG as well as IgM anticarbohydrate antibodies can be measured in serum before and 2 weeks after immunization with pneumococcal polysaccharide vaccine or unconjugated *H. influenzae* vaccine. The predominant subclass responses to these antigens is IgG2. However, routine use of the diphtheria toxin/*H. influenzae* type b conjugate vaccine that results

in an IgG1 response is obscuring the usefulness of measuring total levels of IgG anti-*H. influenzae* serum titers as a reflection of the integrity of IgG2 anticarbohydrate responses. Caution must also be exercised in interpreting anticarbohydrate antibody responses because the population older than 50 years has a reduced prevalence of such responses, and children mount weak anticarbohydrate responses before 2 years of age. Antiprotein responses are readily assessed by measuring antibodies to tetanus toxoid or diphtheria toxoid. The use of a standardized protein neoantigen, such as bacteriophage $\phi \times 174$, allows the evaluation of both primary and secondary responses.

THERAPY

The major goal of therapy for immunoglobulin-deficiency syndromes is to minimize the frequency and severity of bacterial infections. Antibiotics should be used promptly to treat acute infections, and long-term antibiotic prophylaxis should be considered for some patients. Experience has also clearly demonstrated that in cases of XLA, CVID, and hyper-IgM immunodeficiency, parenteral immunoglobulin therapy may prevent or retard the otherwise inexorable progression of tissue injury and end organ dysfunction. Replacement therapy with immunoglobulin should therefore be considered a primary therapeutic modality in these conditions. For patients with more selective immunoglobulin deficiencies, such as IgG subclass deficiencies and antigen-specific antibody deficiencies, immunoglobulin replacement therapy is more controversial. A conservative approach with such patients is to reserve immunoglobulin therapy for patients with culture-documented recurrent bacterial infections, suboptimal clinical responses to antibiotics, and impaired antigen-specific IgG responses.

Replacement therapy for the immunoglobulin-deficiency syndromes began auspiciously in 1952 when Bruton⁸³ successfully reduced the frequency and severity of infections in a boy with agammaglobulinemia using immune serum globulin. This preparation, obtained from pooled alcohol-fractionated serum, was administered IM. Although it is effective, several characteristics of the preparation make it less than an ideal form of immunoglobulin replacement therapy. Since it is administered IM, the amount that can be administered varies directly with muscle mass and is therefore limited for practical purposes to 100 mg/kg. Its absorption is slow and variable, with maximum serum levels achieved in 2 days to 2 weeks, thereby lessening its use in treating acute infections. In addition, there are several problems related to the injections themselves, including moderate local pain, sterile abscess formation, bleeding in patients with

hemostatic dysfunction, and the potential loss of injected immunoglobulin because of local proteolytic degradation. These factors provided the impetus for the development of IV immunoglobulin preparations.⁸⁴

Initial attempts at IV administration of immune serum globulin were often catastrophic. Activation of the complement cascade by aggregated IgG resulted in hemodynamic compromise. During the years, progressive refinement has resulted in IV immunoglobulin preparations consisting predominantly of monomeric IgG that retains effector function. Pooled human donor sera normally contain a broad spectrum of antibodies to ubiquitous organisms. Their preparation effectively partitions or inactivates all known transmissible agents tested to date, including human immunodeficiency virus. Currently, five licensed preparations are commercially available in the United States (Table III). They are therapeutically equivalent with regard to the spectrum of antibodies they possess. Preparations that contain the least IgA should be used when patients are treated with a combined IgG-IgA deficiency. When IM immunoglobulin is administered in equivalent amounts, it has been demonstrated to be as efficacious as IV administration.⁸⁵ The major difference is the amount of immunoglobulin that can be reliably delivered, and hence the serum level achieved. Therefore, in addition to the reasons noted above, IV immunoglobulin administration has largely supplanted IM immunoglobulin administration as the standard form of replacement therapy in immunoglobulin deficiencies.

The specifics of immunoglobulin replacement are somewhat controversial. It is clear that the serum level achieved varies directly with the amount administered. It has also been demonstrated in several studies that larger doses have provided greater protection against infection when larger doses are compared with lower doses (150 mg/kg IV versus 100 mg/kg IM,⁸⁶ 300 mg/kg IV versus 150 mg/kg IM,⁸⁷ and 600 mg/kg IV versus 200 mg/kg IV.⁸⁸ The optimum application of these observations depends, however, on several caveats. For example, it was observed in one study⁸⁹ that, whereas monthly high-dose (400 mg/kg IV) therapy reliably resulted in significantly increased serum IgG levels than did a lower dose (100 mg/kg IV), there was no dose-dependent difference in infections, illustrating the inexact correlation between serum concentration and clinical efficacy. Serum levels, in turn, depend on several variables. The disappearance of infused immunoglobulin is bimodal. There is an initial rapid decrease that results in 50% to 60% lower levels during the first 3 to 4 days after infusion that is believed to reflect, in large part, redistribution of the IgG to the extravascular compartment. Subsequently,

TABLE III. IV gammaglobulin preparations

Product	Manufacturer	Isolation	Product form	Comments
Gamimmune N	Cutter Biologicals, Berkeley, Calif., Division of Miles Laboratories	Cold ethanol fractionation; pH 4.0 treatment	5% in maltose; 10, 50, or 100 ml	Delivery pH 4.25, low IgG4
Gammagard	Baxter Healthcare Corp., Hyland Division, Glendale, Calif.	Cold ethanol fractionation; DEAE anion exchange chromatography	5% in glucose, glycine, and PEG; 0.5, 2.5, 5, or 10 gm lyophilized powder	Delivery pH 6.8, low-est IgA, low IgG4
IVEEGAM	Immuno-U.S. Inc., Rochester, Minn. (distributor; manufactured by Österreichisches Institut für Haemoderivate, Ges. M.B.H.)	Cold ethanol fractionation immobilized trypsin treatment; PEG fractionation	5% in glucose, lyophilized 0.5, 1, 2.5, or 5 gm powder	
Sandoglobulin	Sandoz Pharmaceuticals, East Rutherford, N.J. (distributor; manufactured by Swiss Red Cross)	Cold ethanol fractionation; pH 4.0 treatment in presence of pepsin	3% or 6% in sucrose; 1, 3, or 6 gm lyophilized powder	Delivery pH 6.6; can be reconstituted in 0.9% NaCl, H ₂ O,* D5W*
Venoglobulin-I	Alpha Therapeutics, Los Angeles, Calif. (fractionation DEAE anion exchange chromatography)	Cold ethanol fractionation; PEG	5% in mannitol; 2.5 or 5 gm lyophilized powder	Delivery pH 6.8

DEAE, Diethylaminoethyl; PEG, polyethylene glycol.

*Submitted for approval to Food and Drug Administration.

levels fall exponentially with a half-life approximating that of native immunoglobulin. Within this consistent pattern, there is some individual variability.⁹⁰ Also, the fractional catabolic rate varies in direct proportion to the serum IgG concentration. With greater amounts infused, there is greater loss, and a point of diminishing returns is reached. Therefore, replacement therapy must be individualized. Manufacturers' recommendations for initiation of therapy in immunoglobulin deficiencies are 100 to 200 mg/kg as monthly infusions. This minimum effective schedule has support in the literature⁹¹ but is an area of intense debate. Successful therapy is evinced by the prevention of infection, which is usually coupled with some definite increase in the deficient antibody. If it is necessary,

the amount infused or the interval between infusions may be altered. Doses larger than 600 mg/kg or intervals shorter than every 3 weeks have been used infrequently, primarily because of costs that may approach \$10,000 a year.

Side effects from IV immunoglobulin administration are common, occurring in approximately 10% of infusions.^{84, 89} Side effects are usually mild, typically consisting of fever, chills, headache, dizziness, myalgias, nausea, and dyspnea. It has been noted that they occur more frequently at the initiation of therapy or when there has been a hiatus of 8 weeks or longer between infusions. Since there is a direct correlation between infusion rate and adverse reactions, many side effects can be controlled or obviated by slowing

the rate of infusion. Some investigators have had variable success in preventing reactions by premedicating with acetaminophen, nonsteroidal anti-inflammatory drugs, or antihistamines. The latter carry the hypothetical risk of masking the early symptoms of anaphylaxis. Although reactions are uncommon, anaphylactic reactions, which occur predominantly in IgA-deficient patients, represent the most serious adverse reaction to IV immunoglobulin administration. Antibodies to IgA can be detected in 22% of patients with CVID, 29% of isolated IgA-deficient patients, and 60% of patients with a combined IgA-IgG2 deficiency.⁷⁸ No antibodies to IgA were detected in patients whose IgA was >5 mg/dl. Although the anti-IgA antibodies detected were IgG, it has been suggested that there is a correlation between the development of IgG and reaginic IgE antibodies to IgA.⁹² Since the latter can be detected only in a few research laboratories, screening for the former is more practical. For the patients with suspected or proved anti-IgA antibodies, a preparation very low in IgA should be used, and vigilance should be heightened during therapy.

Immunoglobulin replacement therapy has also been reportedly beneficial in the treatment of secondary antibody deficiency from a variety of causes. These causes include the nephrotic syndrome, protein-losing enteropathy, severe burns, chronic lymphocytic leukemia, multiple myeloma, pediatric human immunodeficiency virus infection, bone marrow transplantation, and for severe bacterial infections in premature and newborn infants.⁸⁴ Passive immunization has also long been used for the prophylaxis or therapy of a variety of viral infections in both normal and immunodeficient hosts. IV immunoglobulin and a hyperimmune globulin preparation have been efficacious in modifying the severity of cytomegalovirus infection in patients with bone marrow transplant.⁸⁴ Recently, gammaglobulin therapy has been effective in the treatment of chronic bone marrow failure with pure red cell aplasia of 10-year duration caused by persistent parvovirus B19 infection.⁹³ Innovative use of immunoglobulin therapy includes home treatment in selected patients, which avoids some of the costs of hospital administration, intraventricular injection for enterovirus encephalitis, and oral administration of various preparations to prevent necrotizing enterocolitis or rotavirus infection in low birth weight infants. However, these uses are investigational, and their use should be limited to research protocols until their efficacy has been adequately proved.

We appreciate the critical review of the manuscript by Drs. W. T. Shearer, R. R. Rich, and R. B. Bressler, and the expert secretarial assistance of Mrs. Sarah Petrash and Mrs. Kathy Jolivet.

REFERENCES

1. Croce CM, Shander M, Martinis J, et al. Chromosomal locations of the human genes for immunoglobulin heavy chains. *Proc Natl Acad Sci USA* 1979;76:3416-9.
2. McBride OW, Hieter PA, Hollis GF, Swan D, Otey MC, Leder P. Chromosomal location of human kappa and lambda immunoglobulin light chain constant region genes. *J Exp Med* 1982;155:1480-90.
3. Max EE. Immunoglobulins: molecular genetics. In: Paul WE, ed. *Fundamental immunology*. New York: Raven Press, 1984:167-204.
4. Alt FW, Blackwell TK, Yancopoulos GD. Development of the primary antibody repertoire. *Science* 1987;238:1079-87.
5. Taussig MJ, Sims MJ, Krawinkel U. Regulation of immunoglobulin gene rearrangement and expression. *Immunology Today* 1989;10:143-6.
6. Haluska FG, Tsujimoto Y, Croce CM. The t(8;14) chromosome translocation of the Burkitt lymphoma cell line Daudi occurred during immunoglobulin gene rearrangement and involved the heavy chain diversity region. *Proc Natl Acad Sci USA* 1987;84:6835-9.
7. Tsujimoto Y, Gorham J, Cossman J, et al. The t(14;18) chromosome translocations involved in B cell neoplasia result from mistakes in VDJ joining. *Science* 1985;229:1390-3.
8. Korsmeyer SJ. Antigen receptor genes as molecular markers of lymphoid neoplasms. *J Clin Invest* 1987;79:1291-5.
9. Yunis JJ, Frizzera G, Oken MM, McKenna J, Theologides A, Arnesen M. Multiple recurrent genomic defects in follicular lymphoma: a possible model for cancer. *N Engl J Med* 1987;316:79-84.
10. Luken MR, Shah VO, Dattilio KL, Civin CI. Flow cytometric analysis of human bone marrow. II. Normal B-lymphocyte development. *Blood* 1987;70:1316-24.
11. Zola H. The surface antigens of human B-lymphocytes. *Immunol Today* 1987;8:308-15.
12. Delespesse G, Sarfati M, Hofstetter H. Human IgE-binding factors. *Immunol Today* 1989;10:159-64.
13. W Paul, Ohara J. B cell stimulatory factor-1/interleukin 4. *Annu Rev Immunol* 1987;5:429-59.
14. Jandl R, Flanagan R, Schur P. Interleukin-1 stimulation of human B-lymphocyte differentiation. *Clin Immunol Immunopathol* 1988; 46:115-21.
15. Nakagawa N, Nakagawa T, Volkman D, Ambrus JL, Fauci AS. The role of interleukin-2 in inducing Ig production in a pokeweed mitogen-stimulated mononuclear cell system. *J Immunol* 1987;138(3):795-801.
16. Jelinek DF, Lipsky PE. Regulation of human B-lymphocyte activation, proliferation, and differentiation. *Adv Immunol* 1987;40:1-58.
17. Pene J, Rousset F, Briere F, Chretien I, Bonnefoy J, Spits H. IgE production by normal human lymphocytes is induced by interleukin-4 and suppressed by interferons and prostaglandin E₂. *Proc Natl Acad Sci USA* 1988;85:6880-4.
18. Vercelli D, Jabara HH, Arai K, Geha RS. Induction of human IgE synthesis requires interleukin-4 and T/B cell interactions involving the T cell receptor/CD3 complex and MHC class II antigens. *J Exp Med* 1989; 169:1295-1307.
19. Pene J, Rousset F, Briere F, et al. Interleukin-5 enhances interleukin-4-induced IgE production by normal human B cells: the role of soluble CD23 antigen. *Eur J Immunol* 1988;18:929-35.
20. Hirano T, Yasukawa K, Harada H, et al. Complementary DNA for a novel human interleukin (BSF-2) that induces B-lymphocytes to produce immunoglobulins. *Nature* 1986; 324:73-6.
21. Goodwin RG, Lupton S, Schmierer A, et al. Human

- interleukin-7: molecular cloning and growth factor activity on human and murine B-lineage cells. *Proc Natl Acad Sci USA* 1989; 86:302-6.
22. Henney CS. Interleukin-7: effects on early events in lymphopoiesis. *Immunol Today* 1989;10:170-3.
 23. Rosen FS, Wedgwood RJ, Eibl M, Aiuti F, Cooper MD, Good RA. Primary immunodeficiency diseases. *Clin Immunol Immunopathol* 1986;40:166-96.
 24. Rosen F, Cooper M, Wedgwood R. The primary immunodeficiencies. Part 1. *N Engl J Med* 1984;311(4):235-42.
 25. Rosen F, Cooper M, Wedgwood R. The primary immunodeficiencies. Part 2. *N Engl J Med* 1984;311(5):300-10.
 26. Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. *Medicine* 1985;64:145-56.
 27. Waldman TA. Immunodeficiency diseases: primary and acquired. In: Samter M, Talmage DW, Frank MM, Austen KF, Claman HN, eds. *Immunological diseases*. 4th ed. Boston: Little, Brown, 1988:430-1.
 28. Cooper MD, Lawton AR. Circulating B cells in patients with immunodeficiency. *Am J Pathol* 1972;69:513-28.
 29. Conley ME, Puck JM. Carrier detection in typical and atypical X-linked agammaglobulinemia. *J Pediatr* 1988;112:688-94.
 30. Stiehm E, Chin T, Haas A, Peerless A. Infectious complications of the primary immunodeficiencies. *Clin Immunol Immunopathol* 1986;40:69-86.
 31. Wright PF, Hatch MH, Kasselberg AG, Lowry SP, Wadlington WB, Karzon DT. Vaccine-associated poliomyelitis in a child with sex-linked agammaglobulinemia. *J Pediatr* 1977;91:408-12.
 32. Buckley RH. Humoral immunodeficiency. *Clin Immunol Immunopathol* 1986;40:13-24.
 33. Schwaber J, Chen RH. Premature termination of variable gene rearrangement in B-lymphocytes from X-linked agammaglobulinemia. *J Clin Invest* 1988; 81:2004-9.
 34. Schwaber J, Payne J, Chen R. B-lymphocytes from X-linked agammaglobulinemia. *J Clin Invest* 1988;81:514-22.
 35. Anker R, Conley ME, Pollok BA. Clonal diversity in the B cell repertoire of patients with X-linked agammaglobulinemia. *J Exp Med* 1989; 169A:2109-19.
 36. Schwaber J, Koenig H, Girard J. Correction of the molecular defect in B-lymphocytes from X-linked agammaglobulinemia by cell fusion. *J Clin Invest* 1988;82:1471-6.
 37. Kwan SP, Kunkel L, Bruns G, et al. Mapping of the X-linked agammaglobulin locus by use of restriction fragment length polymorphism. *J Clin Invest* 1986;77:649-52.
 38. Conley ME, Brown P, Pickard AR, et al. Expression of the genetic defect in X-linked agammaglobulinemia. *N Engl J Med* 1986;315:564-7.
 39. Fearon ER, Winkelstein JA, Civin CI, Pardoll DM, Vogelstein B. Carrier detection in X-linked agammaglobulinemia by analysis of X-chromosome inactivation. *N Engl J Med* 1987; 316:427-31.
 40. Handzel ZT, Buckner VC. Immunodeficiency conditions and their effect on the gastrointestinal tract. *Immunol Allergy Pract* 1988;10:17-27.
 41. Geha RS, Schneeberger E, Merler E, Rosen F. Heterogeneity of acquired or common variable agammaglobulinemia. *N Engl J Med* 1974;291:1-6.
 42. Dosch H-M, Jason J, Gelfand EW. Transient antibody deficiency and abnormal T suppressor cells induced by phenytoin. *N Engl J Med* 1982;306:406-9.
 43. Perri R, Weisdorf D. Impaired responsiveness to B cell growth factor in a patient with common variable hypogammaglobulinemia. *Blood* 1985;66(2):345-9.
 44. Matheson D, Green B. Defect in production of B cell differentiation factor-like activity by mononuclear cells from a boy with hypogammaglobulinemia. *J Immunol* 1987;138(8):2469-72.
 45. Adelman D, Hirano T, Kishimoto T, Saxon A. Elevated serum interleukin-6 (IL-6) levels in patients with common variable immunodeficiency (CVI) [Abstract]. *J ALLERGY CLIN IMMUNOL* 1989;83:299.
 46. Mangan K, Volkin R, Winkelstein A. Autoreactive erythroid progenitor—T suppressor cells in the pure red cell aplasia associated with thymoma and panhypogammaglobulinemia. *Am J Hematol* 1986;23:167-73.
 47. Fujimura S, Kondo T, Yamauchi A, Handa M, Nakada T. Experience with surgery for thymoma associated with pure red blood cell aplasia. *Chest* 1985;88(2):221-5.
 48. Schur PH, Borel H, Gelfand EW, Alper CA, Rosen FS. Selective gamma G globulin deficiencies in patients with recurrent pyogenic infections. *N Engl J Med* 1970;283:631-3.
 49. LeFranc MP, LeFranc G. Human immunoglobulin heavy-chain multigene deletions in healthy individuals. *FEBS Lett* 1987;213:231-7.
 50. Burton DR, Gregory L, Jefferis R. Aspects of the molecular structure of IgG subclasses. *Monogr Allergy* 1986;19:7-35.
 51. Siber GR, Schur PH, Aisenberg AC, Weitzman SA, Schiffman G. Correlation between serum IgG2 concentrations and antibody response to bacterial polysaccharide. *N Engl J Med* 1980;303:178-82.
 52. Hamilton RG. Human IgG subclass measurements in the clinical laboratory. *Clin Chem* 1987;33:1707-25.
 53. Lee SI, Heiner DC, Wara D. Development of serum IgG subclass levels in children. *Monogr Allergy* 1986;19:108-21.
 54. Soderstrom T, Soderstrom R, Avanzini A, Brandtze P, Karlsson G, Hanson LA. Immunoglobulin G subclass deficiencies. *Int Arch Allergy Appl Immunol* 1987;82:476-80.
 55. Plebani A, Monafa V, Avanzini M, Ugazio AG, Burgio GR. Relationship between IgA and IgG subclass deficiencies: a reappraisal. *Monogr Allergy* 1986;20:171-8.
 56. Umetsu DT, Ambrosino DM, Quinti I, Siber GR, Geha RS. Recurrent sinopulmonary infections and impaired antibody response to bacterial capsular polysaccharide antigen in children with selective IgG subclass deficiency. *N Engl J Med* 1985;313:1247-51.
 57. Hammarstrom L, Carbonara AO, DeMarch M, et al. Subclass restriction pattern of antigen-specific antibodies in donors with defective expression of IgG or IgA subclass heavy chain constant region genes. *Clin Immunol Immunopathol* 1987;45:461-70.
 58. Insel RA, Anderson PW. Response to oligosaccharide-protein conjugate vaccine against *Haemophilus influenzae* b in two patients with IgG2 deficiency unresponsive to capsular polysaccharide vaccine. *N Engl J Med* 1986;315:499-509.
 59. Oxelius VA, Hanson LA, Bjorkander J, Hammarstrom U, Sioholm A. IgG3 deficiency is common in obstructive lung disease. *Monogr Allergy* 1986; 20:106-15.
 60. French MAH, Harrison G. Serum IgG subclass concentrations in healthy adults: a study using monoclonal antigens. *Clin Exp Immunol* 1984;56:473-5.
 61. Ambrosino CM, Umetsu DT, Siber GR, et al. Selective defect in the antibody response to *Haemophilus influenzae* type b in children with recurrent infections and normal serum IgG subclass levels. *J ALLERGY CLIN IMMUNOL* 1988;81:1175-9.
 62. Kavanaugh AF, Huston DP. Immunoglobulin G subclass deficiency. *Insights in Allergy* 1989; 4:1-5.
 63. Klemola T. Deficiency of immunoglobulin A. *Ann Clin Res* 1987;19:248-57.
 64. Kuhn LC, Kraehenbuhl J-P. The sacrificial receptor-

- translocation of polymeric IgA across epithelia. *Trends Biochem Sci* 1982;7:299-302.
65. Ammann AJ, Hong R. Selective IgA deficiency: presentation of 30 cases and a review of the literature. *Medicine* 1971; 50:223-36.
 66. Brandtzaeg P, Fjellander I, Geruldsen ST. Immunoglobulin M: local synthesis and selective secretion in patients with immunoglobulin A deficiency. *Science* 1968;160:789-91.
 67. Oxelius V, Laurell A, Lindquist B, et al. IgG subclasses in selective IgA deficiency. *N Engl J Med* 1981;304(24):1476-7.
 68. Bjorkander J, Bake B, Oxelius A, Hanson LA. Impaired lung function in patients with IgA deficiency and low levels of IgG2 or IgG3. *N Engl J Med* 1985;313(12):720-8.
 69. Cassidy JT, Burt A, Petty R, Sullivan D. Selective IgA deficiency in connective tissue diseases. *N Engl J Med* 1969; 280:275.
 70. Buckley RB, Fiscus SA. Serum IgD and IgE concentrations in immunodeficiency diseases. *J Clin Invest* 1975;55:157-65.
 71. Wilton AN, Cobain TJ, Dawkins RL. Family studies of IgA deficiency. *Immunogenetics* 1985;21:333-42.
 72. Hammarstrom L, de Lange G, Smith C. IgA2 allotypes determined by restriction fragment length polymorphism in IgA deficiency: reexpression of the silent A2m(2) allotype in the children of IgA-deficient patients. *J Immunogenet* 1987;4:197-201.
 73. Lawton AR, Royal SA, Self KS, Cooper MD. IgA determinants on B-lymphocytes in patients with deficiency of circulating IgA. *J Lab Clin Med* 1972;80:26-33.
 74. Waldmann TA, Broder S, Krakauer R, Durm M, Meade B, Goldman C. Defect in IgA secretion and IgA-specific suppressor cells in patients with IgA deficiency. *Trans Assoc Am Physicians* 1976;89:215-24.
 75. Strober W, Karakauer R, Klaeveman HL, Reynolds HY, Nelson DL. Secretory component deficiency: a disorder of the IgA immune system. *N Engl J Med* 1976;294:351-6.
 76. Roman S, Moore JS, Darby C, Muller JS, Hoover RG. Modulation of Ig gene expression by Ig binding factors. *J Immunol* 1988;140:3622-30.
 77. Buckley RH. Advances in the diagnosis and treatment of immunodeficiency diseases. *Arch Intern Med* 1986;146:377-84.
 78. Bjorkander J, Hammarstrom L, Smith CIE, Buckley RH, Cunningham-Rundles C, Hanson LA. Immunoglobulin prophylaxis in patients with antibody deficiency syndromes and anti-IgA antibodies. *J Clin Immunol* 1987;7:8-15.
 79. Levitt D, Haber P, Rich K, Cooper MD. Hyper IgM immunodeficiency. A primary dysfunction of B-lymphocyte isotype switching. *J Clin Invest* 1983;72:1650-6.
 80. Geha RS, Hyslop N, Alani S, et al. Hyper immunoglobulin M immunodeficiency (dysgammaglobulinemia): presence of immunoglobulin M-secreting plasmacytoid cells in peripheral blood and failure of immunoglobulin M-immunoglobulin G switch in B cell differentiation. *J Clin Invest* 1979;63:385-91.
 81. Mayer L, Kwan S-P, Thompson C, et al. Evidence for a defect in "switch" T cells in patients with immunodeficiency and hyperimmunoglobulin M. *N Engl J Med* 1986;314(7):409-13.
 82. Ohno T, Inaba M, Kuribayashi K, Masuda T, Kanoh T, Uchino H. Selective IgM deficiency in adults: phenotypically and functionally altered profiles of peripheral blood lymphocytes. *Clin Exp Immunol* 1987;68:630-7.
 83. Bruton OC. Agammaglobulinemia. *Pediatrics* 1952;9:722-8.
 84. Stiehm ER, Ashida E, Kim KS, et al. Intravenous immunoglobulins as therapeutic agents [Clinical conference]. *Ann Intern Med* 1987;107:367-82.
 85. Ochs HD, Fischer SH, Wedgewood RJ. Modified immune globulin: its use in the prophylactic treatment of patients with immune deficiency. *J Clin Immunol* 1982;2(suppl 2):22s-30s.
 86. Nolte MT, Pirofsky B, Gerritz GA, Golding B. Intravenous immunoglobulin therapy for antibody deficiency. *Clin Exp Immunol* 1979;36:237-43.
 87. Cunningham-Rundles C, Smithwick EM, Siegal FP, et al. Use of intravenous pH 4.0-treated gamma globulin in humoral immunodeficiency disease. In: Wedgewood RJ, Paul NW, Rosen FS, eds. *Primary immunodeficiency diseases*. New York: Alan R. Liss, 1983:201.
 88. Roifman CM, Gelfand EW. Replacement therapy with high-dose intravenous gamma globulin improves chronic sinopulmonary disease in patients with hypogammaglobulinemia. *Pediatr Infect Dis J* 1988;7:92s-6s.
 89. Ochs HD, Fischer SH, Wedgewood RJ, et al. Comparison of high-dose and low-dose intravenous immunoglobulin therapy in patients with primary immunodeficiency diseases. *Am J Med* 1984;76(3A):78-82.
 90. Pirofsky B, Campbell SM, Montanaro A. Individual patient variations in the kinetics of intravenous immune globulin administration. *J Clin Immunol* 1982;2 (suppl 2):7S-14s.
 91. Pirofsky B. Intravenous immune globulin therapy in hypogammaglobulinemia: a review. *Am J Med* 1984;76(3A):53-60.
 92. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia: detection of IgE antibodies to IgA. *N Engl J Med* 1986;314(9):560-4.
 93. Kurtzman G, Frickhofen N, Kimball J, Jenkins DW, Nieuhuis A, Young NS. Pure red-cell aplasia of 10 years duration due to persistent parvovirus B19 infection and its cure with immunoglobulin therapy. *N Engl J Med* 1989;321(8):519-23.

Correction

Concerning the article by Svensson et al. "Albumin, bradykinins, and eosinophil cationic protein on the nasal mucosal surface in patients with hay fever during natural pollen exposure." *J ALLERGY CLIN IMMUNOL* 1990;85:828-33.

The lavage fluid levels of **albumin** are **micrograms** per milliliter and not **nanograms** per milliliter as incorrectly written throughout the article. This correction does not change any of the conclusions drawn in the article.