

O V I D*

Full Text

[Results Display](#) [Main Search Page](#) [Help](#) [LOGOFF](#)
[PayPerView Account](#) [View Cart](#)



J.P.G.N. JOURNAL OF PEDIATRIC
GASTROENTEROLOGY AND NUTRITION

© 2000 Lippincott Williams & Wilkins, Inc. Volume 30(1) Supplement, January 2000, pp S13-S19

[About this Journal](#)

[Find Citing Articles](#)

[Table of Contents](#)

[Browse TOC](#)

[Email Jumpstart](#)

[Save Article Text](#)

[Email Article Text](#)

[Print Preview](#)

Links

[Abstract](#)
[Complete Reference](#)
[Catalogo Biblioteca ISS](#)

Outline

- [Abstract](#)
- [GASTROINTESTINAL IMMUNE SYSTEM](#)
- [B CELLS: ANTIBODIES AND ANTIBODY-SECRETING CELLS](#)
- [T CELLS](#)
- [DEVELOPMENTAL ASPECTS](#)
- [ORAL TOLERANCE](#)
- [CONCLUSIONS](#)
- [Acknowledgment:](#)
- [REFERENCES](#)

Graphics

- [Fig. 1](#)
- [Fig. 2](#)
- [Fig. 3](#)
- [Table 1](#)

Recent History

Normal Immune Responses t...



[Previous Page](#)

Normal Immune Responses to Ingested Foods

[Supplement Contents]

Husby, Steffen

Department of Pediatrics, Odense University Hospital, Odense Denmark
Address correspondence and reprint requests to Dr. Steffen Husby, Department of
Pediatrics, Odense University Hospital, DK-5000 Odense C, Denmark.

Abstract

ABSTRACT: This is a short review of the literature with a bias toward the author's work. Small amounts of dietary antigens are taken up into the circulation. B-cell responses to foods (antibodies and antibody-secreting cells) occur as a physiological event locally and in the circulation in all three major immunoglobulin classes. A low levels of IgE is also a normal phenomenon. IgA anti-gliadin antibodies represent an exception. Antibody titers in general tend to decline with age. T-cell responses specific for foods are low in the circulation of healthy subjects. T-cell cytokines are more frequently produced in the gastrointestinal mucosa compared with the circulation. Results indicate that the phenomenon of oral tolerance takes place in humans. Oral tolerance within the T cell system may represent an important regulatory mechanism for normal immunity.

The ingestion of foods is a basic requirement for sustaining life. Apart from the digestion of nutrients, the gastrointestinal tract with its surface area of 200 to 300 m² in an adult plays an important role in immune defense, with more immunoglobulin-producing cells than any other organ (approximately 5×10^{10} cells in an adult) (1). The gastrointestinal immune system may react to a vast array of dietary components, either as proper antigens or as haptens. This presentation is focused on the normal immune responses in humans toward food proteins and peptides. Dietary proteins such as ovalbumin (OA) from hen's egg have been used frequently as model antigens in experimental animals, and reference will be made to such studies when appropriate. B-cell responses have been studied in detail, in particular as antibody measurements, whereas antigen-specific T-cell activity for methodologic reasons has as yet been studied only sparsely.

A fascinating aspect of the normal immune response to ingested foods is the development of oral tolerance (2). Oral tolerance is a form of peripheral tolerance in which mature lymphocytes are rendered hyporesponsive after prior administration of the antigen. This mechanism allows the immune response to be downregulated toward innocuous dietary components and commensal bacteria and at the same time enables the subject to mount a vigorous immune response to potentially dangerous micro-organisms. The breach of oral tolerance could be a key mechanism for the development of such different clinical disorders as allergic, inflammatory bowel, and autoimmune diseases. Oral tolerance will be discussed as part of the normal immune response.

GASTROINTESTINAL IMMUNE SYSTEM

The gastrointestinal immune system consists of different types of immune cells dispersed within the mucosa and the submucosa. The esophagus and the ventricle contain significant numbers of lymphocytes, eosinophils and mast cells (for review, see reference 3) and have the potential for

generating immunity and allergic reactions. Antigen-specific immunity is predominantly generated in the small intestine, with its huge surface area, and in the colon. The lymphoid cells of the human small intestine are organized in three compartments: 1) lymphoid follicles including the Peyer's patches, the appendix, and solitary lymph nodules; 2) in the epithelium interspersed as single-cell intraepithelial lymphocytes (IELs); and 3) in the lamina propria as single cells.

The induction of the immune response takes place in the lymphoid follicles in particular involving M cells, macrophages, T cells, and B cells. The effector arm includes IELs, B cells, and T cells in the lamina propria and macrophages, plasma cells, eosinophils, and mast cells (Fig. 1).

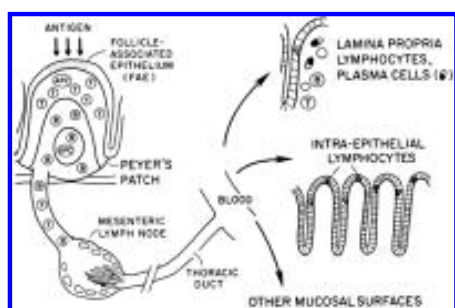


FIG. 1. The organization of gut-associated lymphoid tissue into three major compartments: Peyer's patches, intraepithelial lymphocytes, and lamina propria lymphocytes with indications of lymphocyte migration. (Reprinted with permission from Elson CO. *The immunology of inflammatory bowel disease*. Philadelphia: Lea & Febiger, 1996.)

[\[Help with image viewing\]](#)

[\[Email Jumpstart To Image\]](#)

T cells in the intestinal epithelium and the lamina propria are believed to originate from Peyer's patches or the lymphoid follicles. They come in contact with the antigen, are activated, and mature in the germinal centers of the follicle or Peyer's patches. IgA-committed T cells then leave the mucosa, migrate to the lymph, and move into the blood. The migration of T cells is determined in particular by the integrin $\alpha 4\beta 7$, which reacts with adhesion molecules in the mucosa, predominantly MadCAM1 (4,5). The cells eventually return to the gastrointestinal tract, where they locate within the lamina propria to become lamina propria lymphocytes (LPLs) or within the intestinal epithelium to become IELs (6,7).

B CELLS: ANTIBODIES AND ANTIBODY-SECRETING CELLS

Antibodies to food antigens may be detected in a proportion of the normal population, depending on the method used. In particular, antibodies to milk and egg proteins have been investigated. Forty years ago, measurements with a hemagglutination technique showed that more than 50% of adult blood donors had detectable serum antibodies to cow's milk protein (8). Fewer cord blood sera and sera from infants had detectable antibody and in lower titers (9,10). The radioimmunoassay was introduced, and antibodies to

bovine serum albumin were detected in 75% of normal children and in 8% to 25% of adults, depending on the age of the subject (10). Antibodies to [alpha]-lactalbumin occur at about half this frequency. Not surprisingly, term and preterm infants show development of antibodies in high titers to cow's milk after weaning (11). The antibody titers tend to decline further during the first decade of life for most healthy children, but not in food-allergic children (12). In a limited number of sera using a similar Farr-type radioimmunoassay, we found a high incidence of antibodies to a number of food proteins: OA, [beta]-lactoglobulin (BLG), [alpha]-lactalbumin, bovine serum albumin, and [alpha]-casein (13).

Serum antibodies may be detected in the major immunoglobulin (Ig) classes IgM, IgG, and IgA in most healthy children (14) and adults (13). In a large study in adults, antibodies of the IgA, IgG, and IgM classes were seen to decline during adult age (15), extending the observations made previously in a younger age group (12). We developed sensitive quantitative enzyme-linked immunosorbent assays (ELISAs) for the measurement of IgG antibodies to ovalbumin OA and BLG (16). A high-titered human serum was used for calibration, and the results were expressed metrically as milliunits per milliliter. Controls for assay quality were included by testing for parallelism, by mixing experiments, and by the inclusion of reproducibility controls at different antibody levels. The coefficients of variation were acceptable with between-assay coefficients of variation of 17% to 24%. Serum IgG antibodies to BLG and OA were detectable in 95% of 96 6-to 20-year-old healthy twins, with a log gaussian distribution of antibody levels (17). For these two selected antibodies, no particularly strong association between antibody levels was observed. Based on comparison of antibody levels in monozygotic and dizygotic twins, a significant genetic dependency (heritability estimates of 30–40%) was observed (Fig. 2).

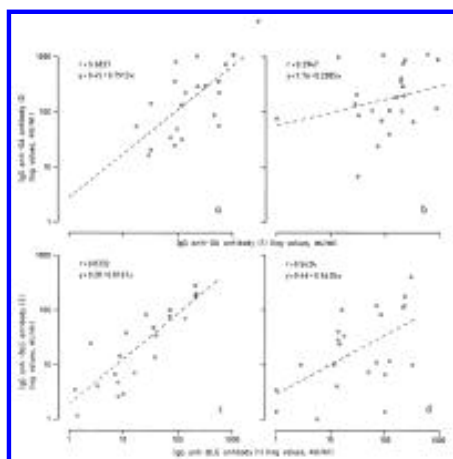


FIG. 2. Within-pair correlations of IgG anti-ovalbumin (OA) and anti-[beta]-lactoglobulin (BLG) antibody levels (log scale) in monozygotic twins (a and c) and dizygotic twins (b and d). Analytical within-assay variation (± 2 SD) indicated by the shaded area around the line of identity (—). Significant differences between monozygotic and dizygotic twins were observed. (Reprinted with permission from Husby et al. *J Immunogenetics* 1987;14:131–42.)

[\[Help with image viewing\]](#)

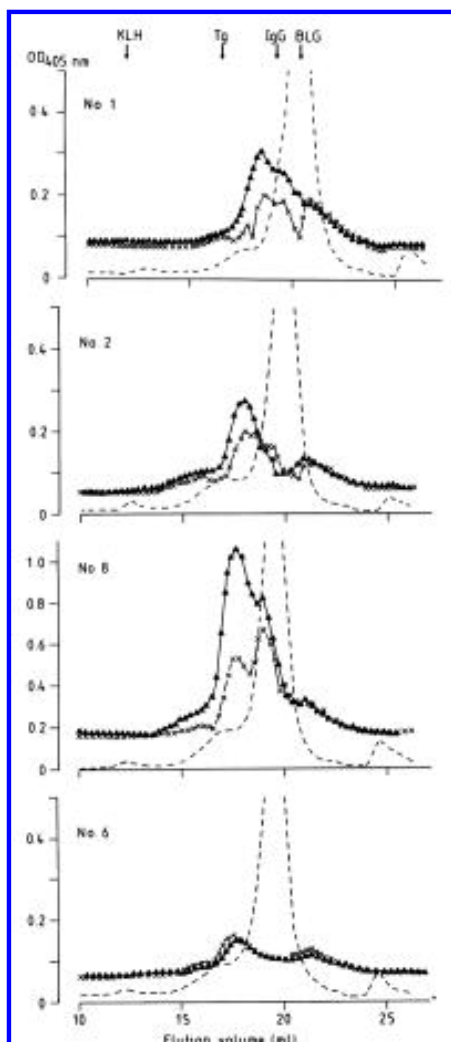
[\[Email Jumpstart To Image\]](#)

Antibody formation against the gliadin fraction of gluten represents an exception from the dogma that dietary protein antibodies of the major immunoglobulin classes occur normally, because the presence of serum IgA antibody to gluten is of diagnostic value in the screening for celiac disease (18,19). However, IgG antibodies to gliadin may be seen in healthy subjects as of limited value for the diagnosis of celiac disease (15).

Human IgG consists of four subclasses (IgG 1–4) and IgA of two subclasses (IgA 1 and 2). The serum antibodies against food antigens seem to reside mainly in IgG1 and IgG4 (20), even though methodologic difficulties are inherent in the quantitation of subclass antibody comparing subclass levels (21). No firm relationship with IgG subclass antibodies to food proteins has been documented between healthy and allergic persons (22). However, IgG1 and IgG4 antibodies tend to be higher in food-allergic infants and tend to predict the later occurrence of inhalant-specific IgE antibodies (23,24). Of note, bottle-fed infants have significantly higher levels of high-affinity IgG1 antibodies to casein compared with breast- or mixed-fed infants (25), indicating antibody affinity maturation. IgA antibodies in serum against foods including gliadin are predominantly of the IgA1 subclass (26).

Dietary protein is taken up from the gastrointestinal tract in small amounts in healthy persons (27,28), seemingly with no deleterious effects. We studied antigen uptake by using ELISA with a detection limit of 0.3 ng/ml. The maximum levels of OA in our study ranged from 1.7 to 10.5 ng/ml. The antigen may be detected in an antigenically intact form or in high-molecular-weight antigen–antibody complexes. Only IgG was detected in immune complex formation with OA (Fig. 3), and the subjects with high IgG antibodies in serum had high-molecular-weight OA in contrast to the subjects with low-IgG anti-OA levels who showed free, intact OA in their sera (29).

FIG. 3. Fractionation by high-performance liquid chromatography in combination with IgG-specific ELISA detection of ovalbumin-containing IgG immune complexes. Sera obtained before (x–x) and 5 hours after a meal. Three subjects (nos. 1, 3, 8) with detectable levels of IgG anti-OA antibody; subject 6 without antibody included as a negative control. (Reprinted with permission from Husby et al. *Scand J Immunol* 1986;23:447–55.)



[\[Help with image viewing\]](#)

[\[Email Jumpstart To Image\]](#)

The uptake of intact dietary antigen into the circulation may stimulate the production of B cells, which subsequently proliferate and secrete antibody. Alternatively, the antibodies may appear in the circulation after local stimulation of lymphocytes in the gastrointestinal mucosa. Such a passage of B cells or plasmablasts was shown for bacterial antigens (30), and an immune response may be detected both in the circulation and in the mucosa (31). In a study in healthy adults of the immune response to keyhole limpet hemocyanin (KLH) after oral challenge, we saw only limited levels of antibodies and of antibody forming cells of the major immunoglobulin classes, but we detected an IgA antibody response within the intestine (32).

In summary, the appearance of serum antibodies to dietary antigens is a normal physiologic response after the ingestion of food. Antibodies to dietary antigens may occur in all three major immunoglobulin classes, and the titers tend to decline with age. Antibody-secreting cells may be detected in the circulation, probably at low levels after oral antigen stimulation.

T CELLS

T-cell responses to foods may be studied by in vivo methods by tests measuring skin reactivity cell-mediated immunity (CMI) and by in vitro methods, including lymphocyte proliferation (^3H -thymidine uptake), cytokine production, and the emergence of cell surface markers—for example, for cellular activation. In animal experiments only minor increases in foot pad thickness are normally seen in response to ingested foods. Increased foot pad thickness in response to dietary antigens was seen in experimental graft-versus-host disease (33). Immune reactivity to food antigens such as OA administered orally may well be influenced by the local bacterial environment (34).

Few studies have investigated T-cell reactivity to foods and dietary antigens in healthy adults. Depending on the methods used, antigen-specific T-cell reactivity to foods seem to be virtually absent in healthy people (35). Along the same line, spontaneous interferon (IFN)-[gamma]–, interleukin (IL)-4–, and IL-5–secreting cells are uncommon in healthy children (36). However, in another study the antigen nonspecific-response T cells from infants and children expressed mRNA of several cytokine genes: IFN-[gamma], IL-4, IL-5, IL-10, and IL-13 (37). Investigating local immunity is of obvious importance. In the duodenal lamina propria of adults (31) and children (36), the frequencies of spontaneous cytokine-secreting cells are high compared with those observed in the peripheral blood.

Cytokine production has been investigated in relation to food allergy and atopic dermatitis. In children with atopy, results indicate an imbalance between T cells producing IFN-[gamma] (T-helper [Th]1-type response) and T cells producing IL-4 and IL-5 (Th2-type response) (38). A very strict partition between Th1 and Th2 responses may, however, in the clinical situation represent an oversimplification. To this end, duodenal lamina propria lymphocytes from children with cow's-milk-sensitive enteropathy compared with those in control subjects show a general increase both in IFN-[gamma]– and IL-4–secreting cells (36).

DEVELOPMENTAL ASPECTS

In the human fetus, a gastrointestinal tract develops with columnar epithelium and villi at 9 to 10 weeks of gestation. At 14 weeks of gestation clusters, of T and B cells with accessory cells appear, and they develop into well-defined Peyer's patches at approximately 19 weeks of gestation. Germinal centers with activated B cells do not appear before birth (39). M-cells at the luminal side of the Peyer's patches function to sample particulate antigens from the lumen (40). The human fetus passively receives IgG from the maternal circulation primarily through the placenta. Very few B cells and plasma cells are seen in the

gut lamina propria before the time of birth at 40 weeks of gestation. Some antigenic stimulation may take place through the amniotic fluid, which has been hypothesized to constitute a low-grade stimulation of the fetal immune system, because secretory-component-associated IgA (sIgA) has been demonstrated in amniotic fluid (41).

The cord blood provides an opportunity to determine the immune responses at birth. Total IgE levels have been measured to look for markers for atopy and high IgE levels related to the later development of atopic disease (42,43). With a refined radioimmunoassay, it was possible to determine cord blood IgE levels in all samples from a population of twins (44). We estimated the genetic determination (heredity) of IgE in such an unselected population to be approximately 80% with the use of new biometric methods for twin data analysis. IgE class antibodies directed to a number of antigens including foods can be detected in a proportion of cord blood samples (45).

After birth, the numbers of B cells and plasma cells increase rapidly, corresponding to stimulation from the external environment, including microbial antigens and dietary antigens. In the human, no clearly demarcated gut closure takes place, even though a decrease in antigen uptake has been demonstrated in comparing premature infants with those born at term (46) and further during the first 2 to 3 months of life (47). sIgA antibodies to BLG have been found in neonatal breast milk from healthy infants fed cow's milk (48). IgG, and more slowly, IgA-and IgM-producing cells, begin to appear after the first few weeks of life. Gradually, secretory IgA becomes the most important immunoglobulin at the mucosal surfaces. In a study of food-allergic infants IgE antibodies during the first months of life tended to decrease or stay at low levels in those infants who were tolerant, but no significant differences were seen (23).

T-cell reactivity toward food antigens has been seen to peak in infancy and then gradually to decline in contrast with reactivity to respiratory allergens, which gradually increases (45,49). In infants who received cow's milk formula during the first 12 months of life, a gradual decrease in T-cell reactivity to bovine BLG was observed in 8 of 10 infants (50). These results are in keeping with those of a study that investigated the production of cytokines from blood mononuclear cells cultured from cord blood and peripheral blood at 6 and 12 months of age. In those infants who were healthy at the age of 3 years, a gradual increase in the production of IFN- γ was observed, whereas those infants in whom asthma with atopy developed later had defective IFN- γ production (38). Infancy may constitute a sensitive window for the development of atopic disease in predisposed persons (49).

ORAL TOLERANCE

Oral tolerance may be observed as part of the normal physiologic response, in particular to soluble antigens, whereas particles and living and multiplying micro-organisms in general induce an active immune response. Oral tolerance has been induced in response to a range of antigens from soluble antigens such as OA from hen's egg (51) to particulate antigens such as sheep red blood cells (52). These results have primarily been obtained in rodents, but species differences exist (e.g., it was not possible to induce oral tolerance in rabbits [53]). Both T- and B-cell immune responses may be involved in the development of oral tolerance. T cells are more easily tolerized than B cells, and the tolerance persists for a longer time (54). Similarly, T-cell tolerance may be obtained as part of oral tolerance without a similar effect on B-cell responses, probably as a form of low-zone T-cell tolerance (55).

Three mechanisms have been implicated for immune tolerance: clonal deletion, clonal anergy, and active suppression. The T-cell response to orally ingested antigens has been related to a Th2-type response (IL-4, IL-5, and IL-10) with the secretion of IL-4 and IL-5 and concomitant downregulation of Th1-like cells producing IFN-[gamma] and IL-2. A further functional subset Th3 has been suggested with production of the suppressive cytokine TGF-[beta] (55). However, suppression may occur by either CD4+ or CD8+ T cells producing TGF-[beta], and in one experimental system both Th1 and Th2 responses were susceptible to oral tolerance induction. Thus, a dichotomy of T cells into cells producing the proinflammatory IFN-[gamma] and cells producing the anti-inflammatory TGF-[beta] may more accurately describe the opposing immune forces at the mucosal surface. The mechanisms of oral tolerance have been investigated to a considerable degree, and comprehensive reviews of oral tolerance have recently been published (56,57).

Few studies have been performed on oral tolerance in humans (58,59). We conducted a study of oral tolerance toward an antigen KLH, which the subjects had not experienced before (35). Eight healthy adults had a daily intake of 50 mg KLH, twice daily for 5 days and together with eight control subjects were parenterally immunized two times with KLH. Antibody responses in serum and saliva and anti-KLH-producing cells were higher in the orally challenged subjects. However, T-cell proliferation and delayed skin test reactivities were diminished, indicating orally induced T-cell tolerance (Table 1). No IgE anti-KLH in serum or IgE anti-KLH-producing cells were detected with ELISA and ELISPOT techniques, respectively (Husby et al., unpublished data, 1994).

	24 Hours		48 Hours	
	Mean (range)	Positive/total	Mean (range)	Positive/total
KLH-fed	1.2 (0-10)	1/8	0.0 (0-0)	0/8
Controls	11.9 (0-23)	7/8	6.6 (0-20)	5/8

Data represent number of positive responses. $P = 0.007$, 24 hours; $P = 0.038$ 48 hours, KLH group versus controls. KLH, keyhole limpet hemocyanin.

TABLE 1. Delayed-type skin test response to KLH in eight subjects fed KLH and subsequently immunized parenterally and eight subjects parenterally immunized only. Data represent number of positive responses. $P = 0.007$, 24 hours; $P = 0.038$ 48 hours, KLH group versus controls. KLH, keyhole limpet hemocyanin.

[\[Help with image viewing\]](#)

[\[Email Jumpstart To Image\]](#)

CONCLUSIONS

It may be concluded that humoral immunity to foods occurs normally in the three major immunoglobulin classes, IgM, IgG, and IgA. Transient and low levels of IgE antibodies may also be seen during infancy and early childhood. The development of immune responses is influenced by the intake of food antigens, in particular in the first year of life. The mode of infant feeding and the timing of weaning is of obvious importance. Furthermore, the infective load during the first months of life could be an important cellular Th1-type activating component that influences the maturation of the infant's immune response. The development of immunologic oral T-cell tolerance to food antigens may represent an important regulatory mechanism for normal immunity. Detailed knowledge of the normal immune responses to foods is advantageous for studies of gastrointestinal allergy and intolerance.

Acknowledgment:

The scientific work of the author was partly supported by the Danish Medical Research Council, The King Christian X Foundation, The Illum Foundation, and the Jacob B. Madsen and Wife Foundation.

REFERENCES

- Brandtzaeg P, Baklien K. Immunohistochemical studies of the formation and epithelial transport of immunoglobulin in normal and diseased human intestinal mucosa. *Scand J Gastroenterol* 1976; 11(suppl 36):1–36. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
- Tomasi TB. Oral tolerance. *Transplantation* 1980; 29:353–6. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
- Miller HRP. *Immunopharmacology of mast cells and basophils*. San Diego, CA: Academic Press, 1993:197–215.
- Roberts K, Kilshaw PJ. The mucosal T cell integrin M2907 recognizes ligand on mucosal epithelial cell lines. *Eur J Immunol* 1993; 23:1630–5. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
- Berlin C, Berg EL, Briskin MJ, et al. 47 integrin mediate lymphocyte binding to the mucosal vascular addressin Mad-CAM1. *Cell* 1993; 74:185–95. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
- Husband AJ, Gowans JL. The origin and antigen-dependent distribution of IgA-containing cells in the intestine. *J Exp Med* 1978; 148:1146–60. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)

7. Dunkley ML, Husband AJ. The induction and migration of antigen-specific helper cells for IgA responses in the intestine. *Immunology* 1986; 57:379–85. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
8. Gunther M, Aschaffenburg R, Matthews RH, Parish WE, Coombs RRA. The level of antibodies to the proteins of cow's milk in the serum of normal human infants. *Immunology* 1960; 3:296–306. [\[Context Link\]](#)
9. Kletter B, Gery I, Freier S, Davies AM. Immune responses of normal infants to cow milk: I. Antibody type and kinetics of production. *Int Arch Allergy* 1971; 40:656–66. [\[Context Link\]](#)
10. Rothberg RM, Farr RS. Anti-bovine serum albumin and anti-alpha lactalbumin in the serum of children and adults. *Pediatrics* 1965; 35:571–88. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
11. Peterson RDA, Good FA. Antibodies to cow's milk proteins: Their presence and significance. *Pediatrics* 1963; 31:209–20. [\[Context Link\]](#)
12. May CD, Remigio L, Feldman J, Bock SH, Carr RI. A study of serum antibodies to isolated milk proteins and ovalbumin in infants and children. *Clin Allergy* 1977; 7:583–95. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
13. Husby S, Oxelius VA, Tesiner B, et al. Humoral immunity to dietary antigens in healthy adults. Occurrence, isotype and IgG subclass distribution of serum antibodies to protein antigens. *Int Arch Allergy Appl Immunol* 1985a;77:416–22. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
14. Firer MA, Hosking CS, Hill DJ. Cow's milk allergy and eczema: Patterns of the antibody response to cow's milk in allergic skin disease. *Clin Allergy* 1982; 12:385–90. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
15. Scott H, Rognum TO, Midtved T, Brandtzaeg P. Age-related changes of human serum antibodies to dietary and colonic bacterial antigens measured by an enzyme-linked immunosorbent assay. *Acta Pathol Microbiol Immunol Scand* 1985; 93:65–70. [\[Context Link\]](#)
16. Husby S, Schultz Larsen F, Hyltoft Petersen P, Svehag SE. Humoral immunity to dietary antigens in atopic dermatitis: I. Biotin-avidin amplified ELISA-analysis of IgG antibodies. *Allergy* 1986; 41:379–86. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
17. Husby S, Schultz Larsen F, Hyltoft Petersen P. Genetic influence of the serum levels of naturally occurring human IgG antibodies to dietary antigens: Quantitative assessment from a twin study. *J Immunogenet* 1987; 14:131–42. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
18. Unsworth DJ, Walker-Smith JA, Holborow EJ. Gliadin and reticulin antibodies in childhood coeliac disease. *Lancet* 1983;i874. [\[Context Link\]](#)
19. Stern M, Teuscher M, Wechmann T. Serologic screening for coeliac disease: methodological standards and quality control. *Acta Paediatr Suppl* 1996; 412:49–51. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
20. Husby S, Jensenius JC, Svehag SE. ELISA quantitation of IgG subclass antibodies to dietary antigens. *J Immunol Methods* 1985b;82:321–31. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
21. Hvatum M, Scott H, Brandtzaeg P. Pitfalls in determining IgG and IgG subclass antibodies to food antigens. *J Immunol Methods* 1992; 148:77–85. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
22. Høst A, Husby S, Gjesing B, Larsen JN, Løwenstein H. Prospective estimation of IgG, IgG subclass, and IgE antibodies to dietary proteins in infants with cow milk allergy: Levels of antibodies to whole milk protein, beta-lactoglobulin and ovalbumin in relation to repeated milk challenge and clinical course of cow milk allergy. *Allergy* 1992; 47:218–29. [Catalogo Biblioteca ISS](#) [\[Context Link\]](#)
23. James JM, Sampson HA. Immunologic changes associated with the development of tolerance in children with cow milk allergy. *J Pediatr* 1992; 121:371–7. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)

24. Calkhoven PG, Aalbers M, Koshte VL, et al. v. Nieop JC, Oranje AP, Aalberse RC. Relationships between IgG1 and IgG4 antibodies to foods and the development of IgE antibodies to inhalant allergens: II. Increased levels of IgG antibodies to foods in children who subsequently develop antibodies to inhalant allergens. *Clin Exp Allergy* 1991;21:99–107. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
25. Devey ME, Beckman S, Kemeney DM. The functional affinities of antibodies of different IgG subclasses to dietary antigens in mothers and their babies. *Clin Exp Immunol* 1993; 94:117–21. [\[Context Link\]](#)
26. Kemp M, Husby S, Larsen ML, Svehag SE. ELISA antibodies of IgA subclass antibodies to dietary antigens. *Int Arch Allergy Appl Immunol* 1988; 87:247–53. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
27. Paganelli R, Levinsky RJ. Solid phase radioimmunoassay for detection of circulating food protein antigens in human serum. *J Immunol Methods* 1980; 37:333–41. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
28. Husby S, Jensenius JC, Svehag SE. Passage of undegraded dietary antigen into the blood of healthy adults. *Scand J Immunol* 1985c;22:83–92. [\[Context Link\]](#)
29. Husby S, Jensenius JC, Svehag SE. Passage of undegraded dietary antigen into the blood of healthy adults: Further characterization of the kinetics of uptake and the size distribution of the antigen. *Scand J Immunol* 1986: 23:447–55. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
30. Czerkinsky C, Prince SJ, Michalek SM, et al. IgA antibody-producing cells in peripheral blood after antigen ingestion: Evidence for a common mucosal immune system in humans. *Proc Natl Acad Sci USA* 1987; 84:2449–53. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
31. Quiding M, Nordström I, Kilander A, et al. Intestinal immune responses in humans. Oral cholera vaccination induces strong intestinal antibody responses and interferon-[gamma] production and evokes local immunological memory. *J Clin Invest* 1991; 88:143–8. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
32. [\[Context Link\]](#)
33. Strobel S, Ferguson A. Modulation of intestinal and systemic immune responses to a fed protein in mice. *Gut* 1986; 27:829–37. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
34. Moreau MC, Corthier G. Effect of gastrointestinal microflora on induction and maintenance of oral tolerance to ovalbumin in C3H/HeJ mice. *Infect Immunol* 1988; 56:266–8. [\[Context Link\]](#)
35. Husby S, Mestecky J, Moldoveanu Z, Elson CO. Oral tolerance in humans: T cell tolerance after antigen feeding. *J Immunol* 1994; 152:4663–70. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
36. Hauer AC, Breese EJ, Walker-Smith JA, MacDonald TT. The frequency of cell secreting interferon-[gamma] and interleukin-4, -5 and -10 in the blood and duodenal mucosa of children with cow's milk hypersensitivity. *Pediatr Res* 1997; 42:629–38. [Catalogo Biblioteca ISS Full text \(pacchetto Ovid\) Bibliographic Links](#) [\[Context Link\]](#)
37. Koning H, Neijens HJ, Baert MR, Oranje AP, Savelkoul HF. T cell subsets and cytokines in allergic and non-allergic children: I. Analysis of IL-4, IFN-gamma and IL-13 mRNA expression and protein production. *Cytokine* 1997; 9:416–26. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
38. Miles EA, Warner JA, Lane AC, Jones AC, Colwell BC, Warner JO. Altered T lymphocyte phenotype at birth in babies born to atopic parents. *Pediatr Allergy Immunol* 1994; 5:202–8. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
39. MacDonald TT, Spencer J. Development of gastrointestinal immune function and its relationship to intestinal disease. *Curr Opin Gastroenterol* 1993; 9:946–52. [Catalogo Biblioteca ISS](#) [\[Context Link\]](#)
40. Owen RL, Pierce NF, Apple RT, Cray WC. M cell transport of *Vibrio cholerae* from the intestinal lumen into Peyer's patches: a mechanism for antigen sampling and for microbial transepithelial migration. *J Infect Dis* 1986;153:1108–18.28. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)

41. Cleveland MG, Bakos M–A, Pyron DL, Rajaraman S, Goldblum RM. Characterization of secretory component in amniotic fluid: Identification of new forms of secretory IgA. *J Immunol* 1991; 147:181–8. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
42. Kjellman NIM, Croner S. Cord blood IgE determination of allergy prediction: a follow-up to seven years of age in 1,651 children. *Ann Allergy* 1984; 53:167–71. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
43. Bousquet J, Menardo J–L, Viala J–L, Michel F–L. Predictive value of cord blood IgE determination in the development of “early-onset” atopy. *Ann Allergy* 1984; 51:291–5. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
44. Husby S, Holm NV, Christensen K, Skov R, Morling N, Petersen PH. Cord blood immunoglobulin E in like-sexed monozygotic and dizygotic twins. *Clin Genet* 1996; 49:332–8. [\[Context Link\]](#)
45. Holt PG, O’Keefe PO, Holt BJ, et al. T cell “priming” against environmental allergens in human neonates: sequential deletion of food antigen specificities during infancy with concomitant expansion of responses to ubiquitous inhalant allergens. *Pediatr Allergy Immunol* 1995; 6:85–90. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
46. Robertson DM, Paganelli R, Dinwiddie R, Levinsky RJ. Milk antigen absorption in the preterm and term neonate. *Arch Dis Child* 1982; 57:369–72. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
47. Axelsson I, Jakobsson I, Lindberg I, Polberger S, Benediktsson B, R  ih   N. Macromolecular absorption in preterm and term infants. *Acta Paediatr Scand* 1989; 7:532–7. [\[Context Link\]](#)
48. Robertson DM, Forrest PJ, Frangoulis E, Jones CL, Mermelsterin N. Early induction of secretory immunity in infancy: Specific antibody in neonatal breast milk. *Arch Dis Child* 1986; 61:489–94. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
49. Prescott SL, Macaubas C, Holt BJ, et al. Transplacental priming of the immune system to environmental allergens: Universal skewing of initial T cell responses toward the Th2 cytokine profile. *J Immunol* 1998; 160:4730–7. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
50. Vaarala O, Saukkonen T, Savilahti E, Klemola T, Akerblom HK. Development of immune response to cow's milk proteins in infants receiving cow's milk or hydrolyzed formula. *J Allergy Clin Immunol* 1995; 96:917–23. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
51. Thomas HC, Parrott DMV. The induction of tolerance to a soluble protein by oral administration. *Immunology* 1974; 27:631–9. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
52. Kagnoff MF. Effects of antigen-feeding on intestinal and systemic immune responses: II. Suppression of delayed-type hypersensitivity reactions. *J Immunol* 1978; 120:1509–13. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
53. Peri B, Rothberg RM. Circulating antitoxin in rabbits after ingestion of diphtheria toxoid. *Infect Immunol* 1981; 32:1148–54. [Catalogo Biblioteca ISS Bibliographic Links](#)
54. Mowat AMI. Depletion of suppressor T cells by 2’-deoxyguanosine abrogates tolerance in mice fed ovalbumin and permits the induction of intestinal delayed-type hypersensitivity. *Immunology* 1986; 58:179–84. [\[Context Link\]](#)
55. Miller A, Lider O, Roberts AB, Sporn M, Weiner HL. Suppressor T cells generated by oral tolerization to myelin basic protein suppress both in vitro and in vivo immune responses by the release of TGF- β following antigen specific triggering. *Proc Natl Acad Sci USA* 1992; 89:421–5. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
56. Strobel S, Mowat AM. Immune responses to dietary antigens: Oral tolerance. *Immunol Today* 1998; 19:173–81. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)

57. Strober W, Kelsall B, Marth T. Oral Tolerance. J Clin Immunol 1998; 18:1–30. [\[Context Link\]](#)

58. Korenblatt PE, Rothberg RM, Minden P, Farr RS. Immune responses of human adults after oral and parenteral exposure to bovine serum albumin. J Allergy 1968; 41:226–35. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)

59. Lowney ED. Suppression of contact sensitization in man by prior feeding of antigen. J Invest Dermatol 1973; 61:90–3. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)

Accession Number: 00005176-200001001-00003

Copyright (c) 2000-2005 [Ovid Technologies, Inc.](#)

Version: rel10.1.0, SourceID 1.11080.2.37

[\[Get TIFF\]](#)

Tables and charts containing text may be unclear or incomplete when printed. To retrieve the best possible version of an image, use the "Get TIFF" link above. For more information, see Help under "Help with Image Viewing."

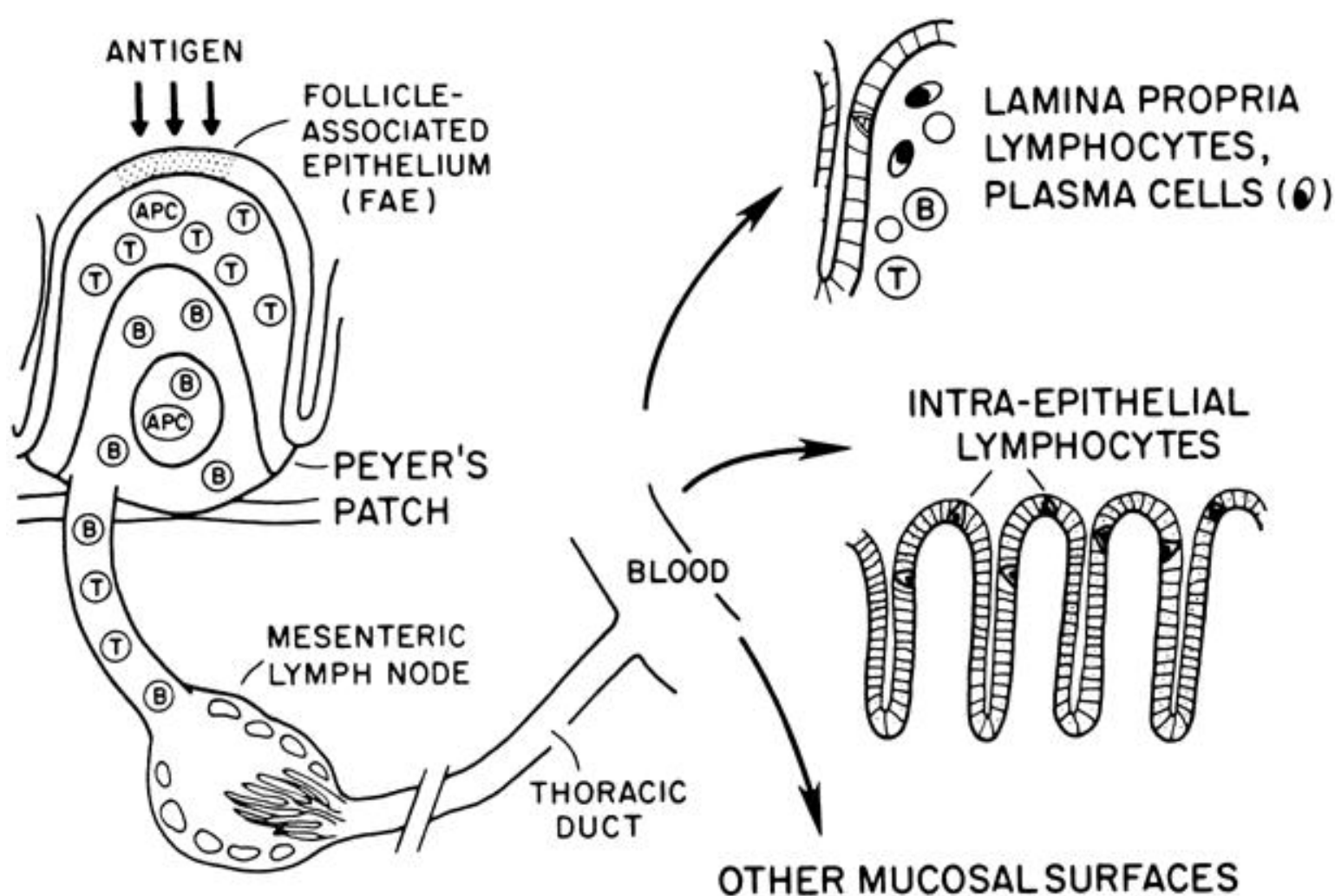
FIG. 1


FIG. 1. The organization of gut-associated lymphoid tissue into three major compartments: Peyer's patches, intraepithelial lymphocytes, and lamina propria lymphocytes with indications of lymphocyte migration. (Reprinted with permission from Elson CO. *The immunology of inflammatory bowel disease*. Philadelphia: Lea & Febiger, 1996.)

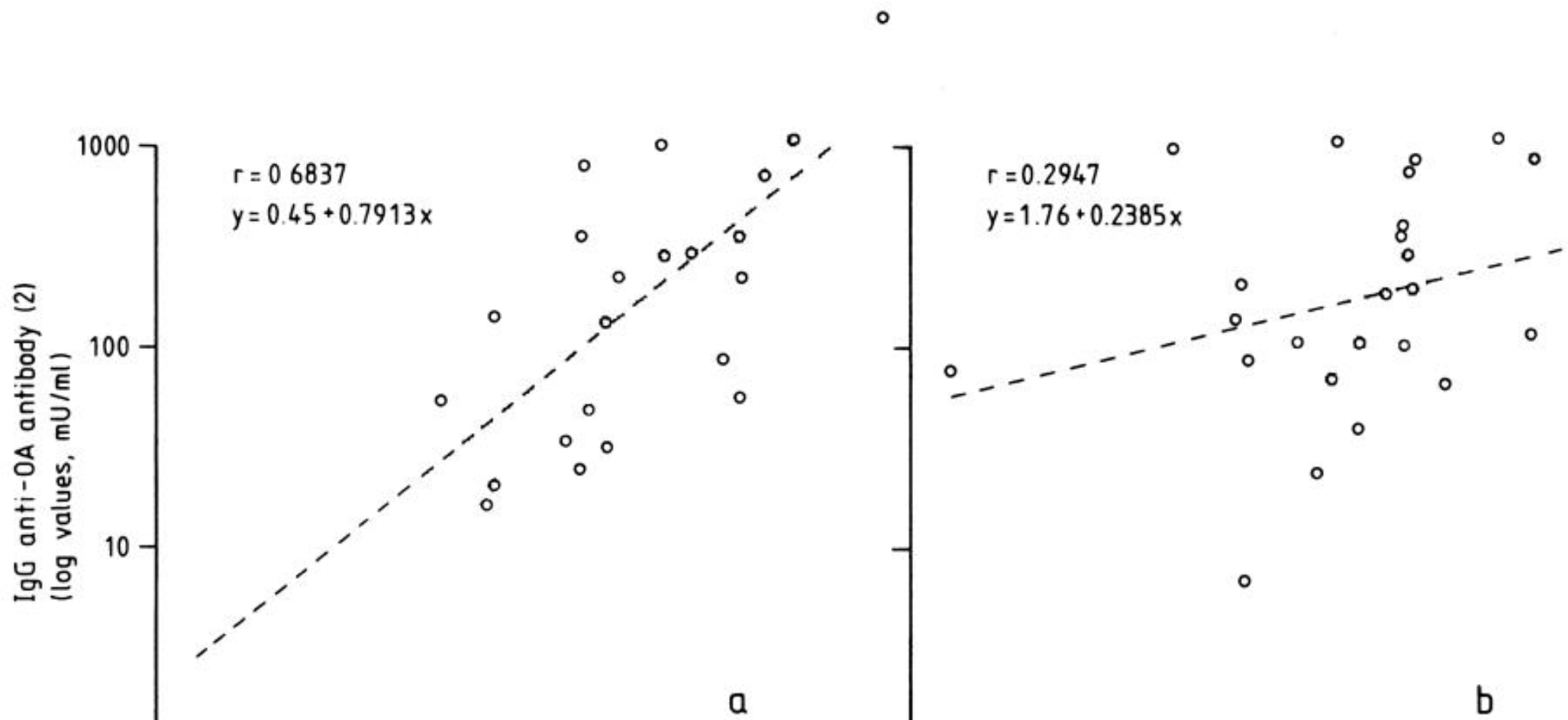
From: Husby: J Pediatr Gastroenterol Nutr, Volume 30(1) Supplement. January 2000. S13-S19

Version: rel10.1.0, SourceID 1.11080.2.37

O V I D*	Full Text
Previous Page Main Search Page Help LOGOFF	

[\[Get TIFF\]](#)

Tables and charts containing text may be unclear or incomplete when printed. To retrieve the best possible version of an image, use the "Get TIFF" link above. For more information, see Help under "Help with Image Viewing."

FIG. 2

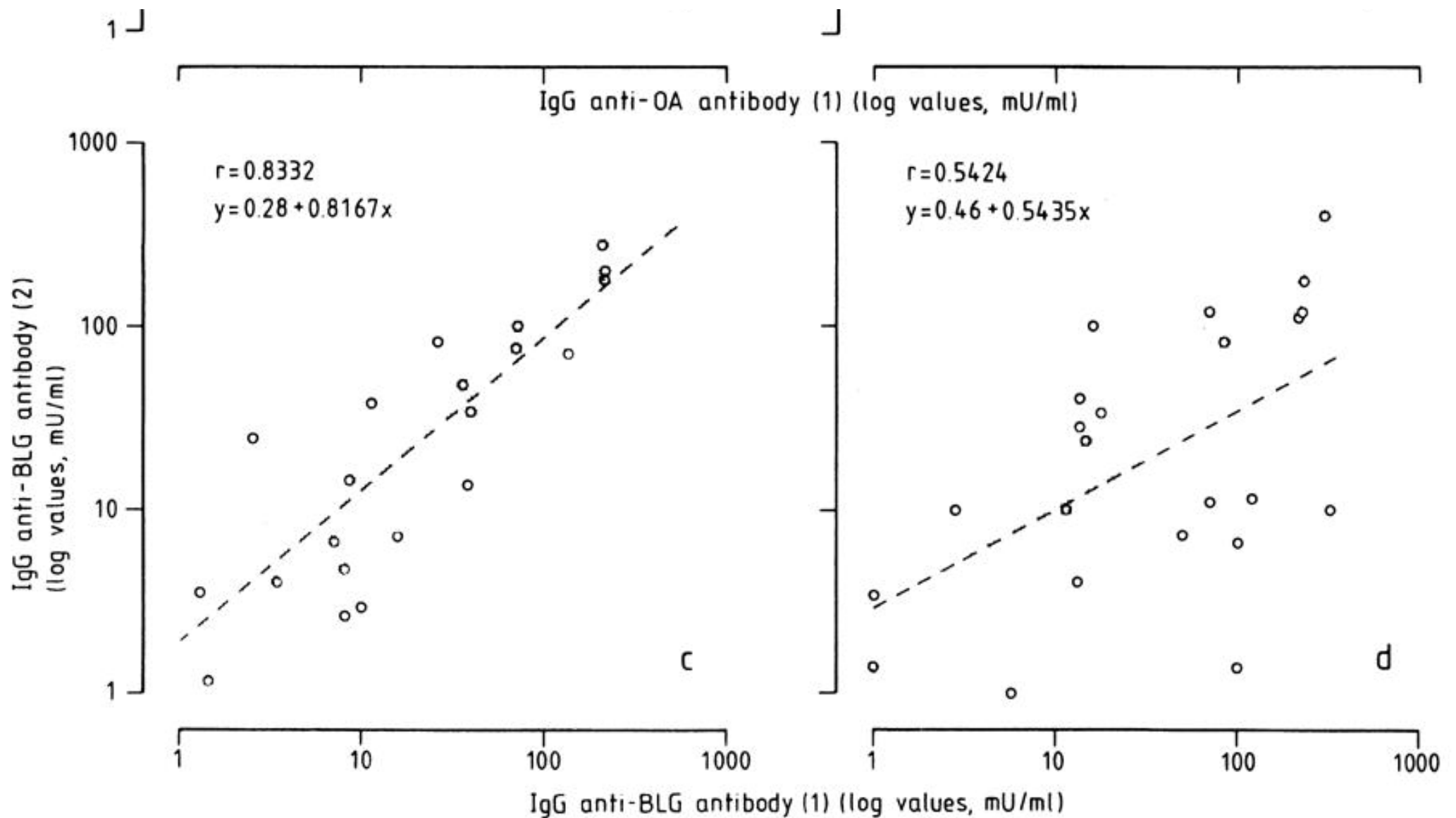
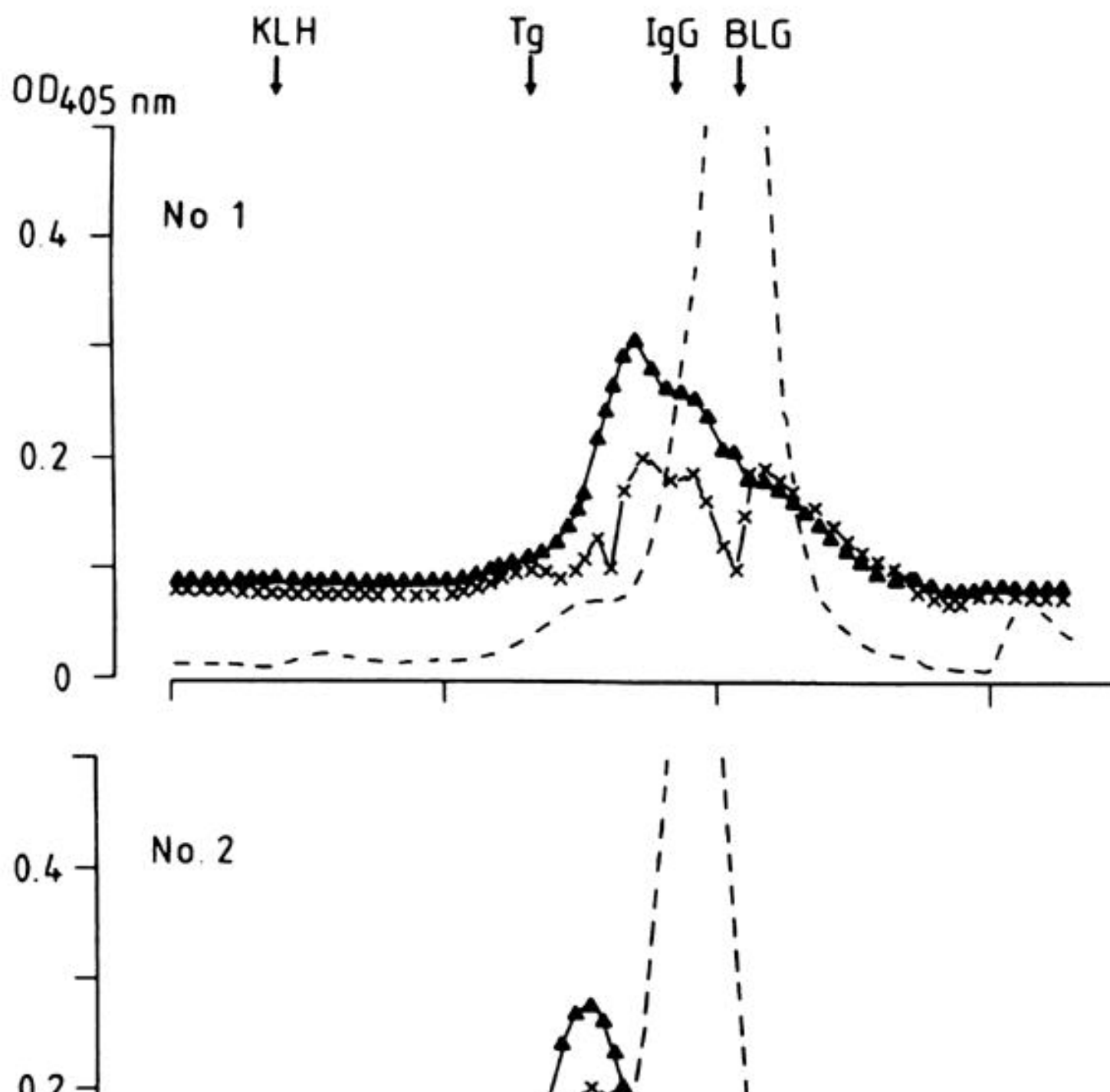


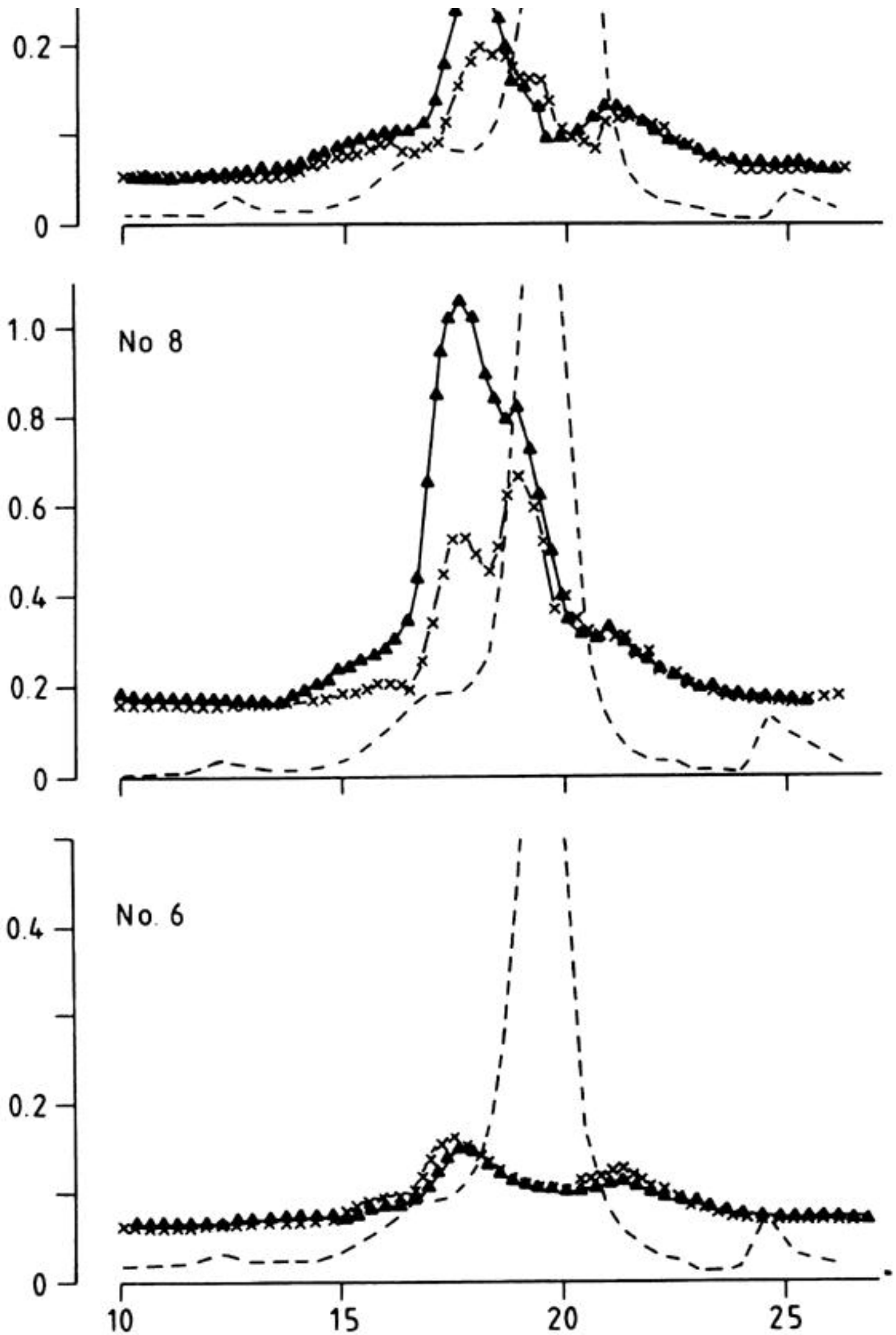
FIG. 2. Within-pair correlations of IgG anti-ovalbumin (OA) and anti-[beta]-lactoglobulin (BLG) antibody levels (log scale) in monozygotic twins (a and c) and dizygotic twins (b and d). Analytical within-assay variation (± 2 SD) indicated by the shaded area around the line of identity (—). Significant differences between monozygotic and dizygotic twins were observed. (Reprinted with permission from Husby et al. *J Immunogenetics* 1987;14:131–42.)

From: Husby: *J Pediatr Gastroenterol Nutr*, Volume 30(1) Supplement, January 2000, S13-S19

[\[Get TIFF\]](#)

Tables and charts containing text may be unclear or incomplete when printed. To retrieve the best possible version of an image, use the "Get TIFF" link above. For more information, see Help under "Help with Image Viewing."

FIG. 3



10

15

20

25

Elution volume (ml)

FIG. 3. Fractionation by high-performance liquid chromatography in combination with IgG-specific ELISA detection of ovalbumin-containing IgG immune complexes. Sera obtained before (x-x) and 5 hours after a meal. Three subjects (nos. 1, 3, 8) with detectable levels of IgG anti-OA antibody; subject 6 without antibody included as a negative control.

(Reprinted with permission from Husby et al. *Scand J Immunol* 1986;23:447-55.)

From: Husby: J Pediatr Gastroenterol Nutr, Volume 30(1) Supplement. January 2000. S13-S19

Copyright (c) 2000-2005 [Ovid Technologies, Inc.](#)

Version: rel10.1.0, SourceID 1.11080.2.37

[\[Get TIFF\]](#)

Tables and charts containing text may be unclear or incomplete when printed. To retrieve the best possible version of an image, use the "Get TIFF" link above. For more information, see Help under "Help with Image Viewing."

TABLE 1

	24 Hours		48 Hours	
	Mean (range)	Positive/total	Mean (range)	Positive/total
KLH-fed	1.2 (0–10)	1/8	0.0 (0–0)	0/8
Controls	11.9 (0–23)	7/8	6.6 (0–20)	5/8

Data represent number of positive responses. $P = 0.007$, 24 hours; $P = 0.038$ 48 hours, KLH group versus controls. KLH, keyhole limpet hemocyanin.

TABLE 1. *Delayed-type skin test response to KLH in eight subjects fed KLH and subsequently immunized parenterally and eight subjects parenterally immunized only* Data represent number of positive responses. $P = 0.007$, 24 hours; $P = 0.038$ 48 hours, KLH group versus controls. KLH, keyhole limpet hemocyanin.

From: Husby: J Pediatr Gastroenterol Nutr, Volume 30(1) Supplement. January 2000. S13-S19

Copyright (c) 2000-2005 [Ovid Technologies, Inc.](#)

Version: rel10.1.0, SourceID 1.11080.2.37