150

THE GUT AS AN IMMUNE ORGAN

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PREFACE

The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) is an autonomous, international, philanthropic and non-profit centre for research, education and training as well as clinical service. The Centre is derived from the Cholera Research Laboratory (CRL). The activities of the institution are to undertake and promote study, research and dissemination of knowledge in diarrhoeal diseases and directly related subjects of nutrition and fertility with a view to develop improved methods of health care and for the prevention and control of diarrhoeal diseases and improvement of public health programmes with special relevance to developing countries. ICDDR,B issues two types of papers: scientific reports and working papers which demonstrate the type of research activity currently in progress at ICDDR,B. The views expressed in these papers are those of authors and do not necessarily represent views of International Centre for Diarrhoeal Disease Research, Bangladesh. They should not be quoted without the permission of the authors.

ABSTRACT

After birth a human baby coming out of a sterile intra-uterine environment into a potentially pathogenic environment is protected by the defence mechanisms or immune system of the body. This immune systems are of two types - cellular immunity mediated by small or T. Lymphocytes and humoral immunity mediated by antibodies. There are five classes of immunoglobulins such as IgA, IgM, IgG, IgD and IgE. IgA, IgG and IgM carry out the humoral immunity and IgE mediate the allergic reactions. Function of IgD is not clear. IgG is the only one capable of crossing the placenta. Like other mucosal surfaces, the intestine is endowed with a local secretory immunoglobulin system functionally different from the circulatory antibody system. Protection to the Gut is mainly provided through secretory IgA. Secretory IgA consist of two IgA monomers joined by 'J' chain and a secretory component, which protects the IgA molecule from proteolytic changes in the intestinal lumen. Any deficiency of this system not only makes an individual susceptible to bacterial and viral infections but also leads to increased absorption of undesirable antigens which gaining excess into the body start series of complex antigen and antibody reactions resulting in auto immune diseases.

1. THE IMMUNE SYSTEM

Every human baby emerges from its nine months sojourn in the normally sterile intrauterine environment into a world swarming with potentially pathogenic micro-organisms. Most miraculous is that, in most instances he is able to adapt himself to his new environment. This is due to a series of inherited defensive mechanisms which have developed with the evolution of the vertebrates. This defense mechanism or immunity is conferred mainly to the lymphocytes.

Classically two major forms of immune systems are described; the humoral immune system mediated by the antibodies and the cellular immune system mediated by the small lymphocytes (42, 50). Both systems depend upon the precursor cells called stem cells, derived from the bone marrow (38, 51). Some stem cells reach the thymus via blood stream and under the influence of thymic hormone they are transformed into immunocompetent cells called T lymphocytes. The T lymphocytes when meet an appropriate antigen are specifically stimulated to proliferate and differentiate into immunoblast cells which release several soluble factors, like lymphocyte transformation factor, cytotoxins, migration inhibition factor and transfer factor. In addition, they give rise to immunocompetent small lymphocytes which are the memory cells. They react more quickly to the specific antigens during subsequent infection. Some stem cells at least in birds pass through the bursa of fabricious to become immunocompetent cells. These cells because of an immunoglobulin on their surface are capable of recognising a specific antigen and interact with it to produce plasma cells which synthesize antibodies and thus forms the humoral immune system (9,10,29,35,36, 48). Since these cells are independent of thymus they are called bursa equivalent or B-lymphocytes. Recently it has been postulated that probably bone marrow or the lymphoid structure of the gastrointestinal tract represent mammalian equivalent of bursa in a diffuse form (1,43,70).

The whole sequence of events in the formation of T and B lymphocytes are shown in Fig. 1, 2, 3 and 4. The T and B-lymphocytes occupy also distinct anatomical compartment within the secondary lymphoid organs (21,22,30,75). In lymph node primary nodules and medulla are populated by B-lymphocytes and T-lymphocytes occupy paracortical area (Fig. 5). This specific homing mechanism is termed "Ecotaxis" (21,22). For some antigen, the B-cells alone are not enough to initiate the antibody production and work in cooperation with T-cells (59).

Structure of immunoglobulins

World Health Organisation designated the presently existing five classes of immunoglobulins as IgG, IgM, IgA, IgD and IgE (72). The characteristics of the different immunoglobulins are summarized in Table 1. Shortly after antibodies were identified as γ-globulins, Heidelberger and Pedersen had shown that some purified antibodies sedimented rapidly in the ultra-centrifuge (18S to 23S) and others more slowly (7S). All antibody classes have the same fundamental structure consisting of four polypeptide chains connected by disulfide bonds as first proposed by Porter (54). There are two light and two heavy chains in each immunoglobulin molecule as schematically represented in Fig. 6. The light chains contain about 200 amino acids and the heavy chains consist of approximately 450 amino acids. The light chains are of two types, Kappa (K) and Lambda (λ) and an individual immunoglobulin has either two Kappa or two lambda chains, never one of each kinds. The heavy chains are specific and determines the class of immunoglobulin. They are known as gamma (γ), alpha (α), mu (μ), delta (δ), epsilon (Ε) for IgG, IgA, IgM, IgD and IgE respectively. The molecular weight range from about 50,000 for gamma to about 80,000 for epsilon chains. Each immunoglobulin class has its own characteristic carbohydrate content varying from about 22 monosaccharide residues in IgG to about 82 in monomeric IgM. Papain digestion (55) splits the immunoglobulin molecules e.g. IgG into two identical fragments called Fab fragment, because they bind antigen and a third crystallizable fragment called Fc fragment (Fig. 6). FC fragment does not bind antigen but has the biological activity like placental transfer in the foetus and complement fixation at least in IgG, 1, 2 and 3.

Out of five classes of immunoglobulins, IgG, IgA and IgM are responsible for carrying out the humoral immunity and IgE is important for its role in allergic reactions. The functions of IgD is not yet known. Among all the immunoglobulins IgG can pass the placental barrier and is responsible for maintaining its level in the newborn till the baby starts forming its own IgG (12,31,45,52) which is 2-3 months for the human infants. At 7 years IgG value reaches the adult level as shown in Fig. 7 and 8. In breast-fed infants maternal IgA and IgM provide a local antiseptic paint (11,12). It has been proved that IgA cannot pass the placental barrier (70). As shown in Fig. 9 and 10 IgA produced by the newborn baby was recorded at about 20 days and reaches the adult value only at 12 years of age. IgM is recorded to be synthesized by the foetus as early as (24,60,61, 71a) 20 weeks of intrauterine life but its level at birth is not significant. In the infants it develops faster than IgG or IgA and by 1-2 years adult value is reached.

2. EVIDENCE OF IMMUNE FUNCTION OF THE GUT

The extensive absorptive surface area of the gastro-intestinal tract exposed to extraneous antigens like invading micro-organisms, dietary proteins, drugs and food contaminants, is at constant threat. However, efficient defense mechanism of the host produces a barrier to these potentially harmful factors. Among many other defense systems, the local immune system of the mucosa plays an important role in giving a continuous protection to the body. Intestinal mucosa is well endowed with immunocytes, which may exist as collections of lymphoid cells like Peyer's patches, appendix or as a diffuse populations of lymphocytes, and plasma cells in the lamina propria. There are ample evidences to suggest that intestine is capable of mounting a local immune response independent of systemic immunity. Besredka (4) in 1919 showed that oral immunization of rabbits with killed shigella bacilli provided protection against re-infection irrespective of the serum agglutination titre. Davis (19) in 1922 further showed that in patients suffering from bacillary dysentery, antibodies appear in the stools several days before serum antibodies are detectable. The copro antibodies of cholera appear in the stool earlier than the equivalent rise of titre in the serum. Parenteral immunization of cholera was shown to produce local IgA response in the gut and it has been thought to be due to leakage of some antigens into the mucosa. According to Tomasi (67) local plasma cells are sufficient to respond to any kinds of antigens taken up by the gut from the antigen pool within the intestinal lumen. Antibodies produced under these conditions are IgA and when the antigen is too strong or persistent, additional 7S IgA produced by the plasma cells enter the lymphatics and gives a systemic response (shown in Fig. 13) as it happens in case of sabine vaccine against Polio virus (25). As will be shown later, an unique immunoglobulin secretory IgA, the major antibody of the mucosa, is responsible for providing local immune system. The synthesis of IgA in the mucosa and its transport towards the external surface may be called the "first line of defense system". In some cases of chronic inflammation, IgG comes to play a role which is then called the "second line of defense".

3. IgA: THE FIRST LINE OF DEFENSE

First noted by Chodirker and Tomasi (11), IgA is the predominant immunoglobulin of the gut and other secretory organs. Most (80-90%) of the secretory IgA is structurally and antigenically different from the 7S IgA in the serum. Fig. 11 represents a schematic model of native 11S secretory IgA with bound secretory component. The secretory 11S IgA molecule is a dimer of two 7S IgA monomer synthesized by the same plasma cells, plus two additional components. These are (1) secretory component, a derivative of epithelial cells found throughout the body, and (2) the 'J' chain a structural component of polymeric immunoglobulins present within the plasma cells (65,39,40). The secretory IgA dimers have a mol. weight of 390,000 and the mol. weight of 7S IgA monomer is 160,000 and this comprises less than 15% of the total IgA content in secretory fluid like saliva and colostrum (6) 'J' stands for joining and it joins two 7S IgA monomers to form the 11S secretory IgA dimers and also five 7S monomers in polymeric IgM molecules. 'J' chain has a mol. weight of 20,000 and contains 10% carbohydrates. One mol. of 'J' chain is present per mol. of IgM or secretory IgA. The high cysteine content of 'J' chain lends support to the view that it may have a role in covalent linkage of the polypeptide chains. Secretory component becomes integrated with secretory IgA dimers after the 'J' chain has joined the two monomers. 'J' chain stabilizes 11S IgA molecules and secretory component confers the additional antigenic properties which are lacking in 7S serum IgA. Addition of these two components provides biological advantages to secretory IgA, like resistance to proteolytic enzymes and enhanced ability to adhere to the epithelial cells. Secretory component contains about 6 percent carbohydrate and has a mol. weight of 60,000. It is specifically linked to the heavy chain(α) of the secretory IgA by disulfide bonds. Free secretory components are secreted independent of IgA molecules (56,62). In newborn babies IgA concentration is negligible, but their external secretions contains enough free secretory component. Free secretory components diminish as the baby produces more IgA which bind the free secretory components. Reconstitution of secretory IgA *in vitro* can only result when 11S IgA is incubated with secretory component, suggesting that 'J' chain is necessary to bind secretory components.

Two subclasses of IgA, IgA_1 and IgA_2 have been described and antisera has also been produced (33,56). In IgA_1 the disulfide bridge links one light chain to a heavy chain (L-H) and in IgA_2 a light chain is joined to another light chain by the disulfide bridge (L-L). Only 10% of the human serum IgA are of IgA_2 type

and 50% of the secretory IgA are of IgA_2 variety. Nearly all mouse IgA are IgA_2 subtype, suggesting that this subclass is of more primitive phylogenic origin.

3.1. Source of IgA

Immunofluorescent studies reveal that approximately 85% of the lamina propria plasma cells contain IgA. Few IgG producers have been detected and IgG primarily exists in the interstitial spaces suggesting that the local IgG molecules are derived from extravasation. The density of the IgA producing cells varies in different parts of the intestine with the highest number found in the colon (12) Table 2. IgD and IgE containing cells are specially found in the proximity of the mucus gland (37, 41). In human gastrointestinal tract there are about 20 IgA cells for one IgG cell, contrary to the ratio of 3 to 4 in favour of IgG in the spleen and peripheral lymphnodes. The immunoglobulin content of the secretions gives a rough idea about the immunoglobulin producing cells in the mucosa. Table 3 shows the immunoglobulin content of different external secretions and fig. 12 represents the same in a diagrammatic way. The intestinal lymphoid structures like Peyer's patches, appendix or discrete theliolymphocytes are responsible for the synthesis of immunoglobulin in man. These are suggested to be equivalent to bursa of fabricius which plays a central role in the production of immunoglobulin in the birds. An important mechanism for the initiation of secretory IgA production is the antigenic stimulation coincident to bacterial colonization of the gut. A germfree animal shows few immunocytes in the lamina propria and has only 5% serum IgA level in comparison to the conventional one (15). On exposure to the normal environment, the intestine of these germfree animals become endowed with all the defensive mechanisms like their conventional counterparts in less than two months time. This is called awakening or physiological inflammation of the gut (46,57,58). Similarly in a newborn baby there is a complete lack of immunoglobulin producing cells and they appear within 15 days after birth. Few possibilities have been advanced regarding the origin of the plasma cells in the lamina propria. (a) The precursors of plasma cells are probably derived from the primitive gut like other central lymphoid organs such as bursa of fabricius. Fichtelus in his study suggested that the lymphocytes are bursal equivalent in man and may be the precursor cells of the plasma cells. (b) These cells are of bone marrow origin, still uncomitted to immunoglobulin class, seed the submucosal areas and differentiate into precursors of IgA producing cells under local influence of the gut. After bone marrow transplantation, production of normal secretory IgA is an evidence in favour of this. (c) Or, the lymphoid cells in the Peyer's patches under the influence of

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antigenic stimulation differentiate into secretory IgA producing plasma cells. Lymphoid cells from Peyer's patches after injection into lethally irradiated rabbits, successfully re-populated the lamina propria and differentiated into IgA producing plasma cells. On the contrary, cells from the peripheral lymph nodes homed primarily to the spleen and gave rise to IgG producing cells. (d) Brandtzaeg (7) suggested that some of the excess secretory components due to concentration gradient are released to the lamina propria and some pass into the circulation and influence the B-lymphocytes through selective immunoglobulin affinity. The latter are then attracted to take a juxtaposition to the epithelium producing secretory components.

3.2. Synthesis and external transport of secretory IgA

Immunofluorescent studies showed the secretory component to be localized to the apical portion of the epithelial cells, attached to the plasma membranes and in the intercellular spaces of the epithelium (41, 65). Local synthesis of the secretory IgA has been demonstrated by *in vitro* organ culture and fluorescent antibody technique. The formation of dimer IgA and their transportation are schematically shown in fig. 13, 14 and 15. Various studies suggest that 10S IgA dimers with J chain synthesized by the plasma cells are secreted into the interstinal space. Its further passage is blocked by the zona occludens i.e. tight epithelial upper junctions and it then passes inside the upper one third of the epithelium. The integration with secretory components according to many, occurs within the enterocytes and the secretory IgA is then transported from the cell into the lumen (68). The 10S IgA dimer formed inside the plasma cells of the lamina propria could be transported into two directions (Fig. 13), across the mucous membrane into the lumen or backward into the lymphatics and eventually into the circulation. But combination with secretory component and 'J' chain favours its transport to the luminal side. That serum IgA are derived from the mucosal IgA has been proved by many workers. Paul Crabbe (13) has shown that oral immunization with ferritin produces IgA cells containing antiferritin antibodies essentially restricted the gastrointestinal tract and the majority of the circulating antiferritin antibodies are of IgA type. Total irradiation of the gut causes fall in serum IgA and it can be prevented by shielding the gut. In both dog and the mouse the predominant species of IgA in the serum is 10S dimer and is consistent with intestinal origin (72). In man 85% of the serum IgA are of 7S monomer and only about 15% are 10S IgA dimer suggesting that the secretory cells contribute only a minor fraction of the serum IgA. In IgA-deficient subject IgM producing cells increase in number as a compensatory mechanism (14). Although secretory component normally does not combine with a IgM-immunoglobulin, but in IgA-deficient subjects it does so. The passage of IgM

in such subjects though not known, is speculated to be the same as IgA.

3.3. Biological functions of IgA

Secretory IgA have antibody activity against a wide variety of antigens. They have been demonstrated in the mucus layer covering the microvilli of the gastrointestinal and respiratory tract along with micro-organisms and rendering a protective surface to the epithelia (Fig. 16). To lyse bacteria an antibody usually should have the ability to fix complement, and both serum and secretory IgA lack this property. But recently an alternate pathway for the activation of the components of the complements has been described (34,53). Accordingly IgA has the capacity to trigger a complex mechanism that leads to the cleavage of the third component which activates the subsequent components through to C'9. This indirect pathway of complement activation has been called "complement shunt" (56). The activation of C'3 and later components results in the biological products which mediate the features of the inflammatory response like chemotaxis, histamine release, vascular permeability factors and phagocytosis. Secretory antibodies have also been shown to interfere with the attachment of the micro-organisms to the mucosa, thereby preventing its penetration and rendering it more susceptible to the intestinal clearing mechanism (26). Studies with cholera have shown that coproantibodies are produced locally in the intestinal mucosa and the peak rise of coproantibody preceded the development of serum agglutininin. Studies by Fubura *et al.*, (28) shown in Table 4 have proved that secretory IgA could protect mouse intestinal loops against infection by *Vibrio cholerae bacilli*. Some viruses as represented in Fig. 17, replicate at the portal of entry in the respiratory or gastrointestinal mucosa. Where as the other group of virus like polio, measles, Echo and possibly hepatitis viruses, proceeds further to cause a stage of viraemia and the disease may be caused in tissues distant from the portal of entry. Evidence shows that (27) oral immunization is more effective in the first group and in the second group systemic immunization is probably more effective. If adequate serum not secretory antibody is present, immunity to systemic infection will cause the organisms to persist at the portal of entry resulting in a carrier state. Such a situation may be encountered in cases of salk technic of poliomyelitis vaccination (16).

Macromolecules like gammaglobulin, Egg albumin, bovine serum albumin, insulin etc. are absorbed through the intestinal mucosa (20,35,47). They are absorbed as represented in Fig. 18

by pinocytosis. After absorption, macromolecules may be broken down by lysosomes or they may pass intact and taken up by the lymphatics. Studies suggest that secretory IgA prevents the uptake of intraluminal macromolecular antigens. Walker *et al.*, (73) showed that oral immunization inhibits the rate of absorption of antigens as shown in Fig. 19. An association of IgA-deficiency and variety of diseases like respiratory tract infection, a topic allergy, coeliac disease and rheumatoid arthritis has been suggested (34,37). Patients with IgA-deficiency have higher antibodies against food and milk proteins (5, 38) antigens, indicating that resistance to extraneous antigens is decreased. Jos *et al.*, (44) showed that in cow milk protein intolerance the IgA producing plasmocytes increase from normal number of 280,000 to 500.000/mm3. This is well in agreement with one of our own studies on cow milk protein intolerance (23) which showed high IgA and IgM as shown in Fig. 20. Savilahti (64) also reported increase serum IgA in active phase of coeliac disease and it came down after gluten with rawal from the diet, Figs.21, 22. Normally large quantities of secretory IgA in colostrum and human milk probably protects the mucosa of the breast fed infants, and the lack of this in bottle fed infants is likely to cause cows milk protein intolerance.

3.4. Deficiency of IgA and disease

An isolated IgA-deficiency has been reported in approximately one in 500 persons in normal population surveys. But why some persons lead normal life and the others become sick is not clear. Consideration of the following facts are important in this context.

a. Normally in persons with IgA-deficiency, IgM cells are replacing the IgA producing cells quantitatively (17, 63) in the intestinal mucosa.

b. Along with IgA-deficiency, often there may be cellular immunity deficiency explaining the reasons for recurrent infection.

c. There may be concomitant disease such as hereditary telangiectasis, disseminated lupus or cancers.

4. SECOND LINE OF DEFENSE

(Local Synthesis of Immunoglobulins in Chronic Inflammation)

Brandtzaeg *et al.*, (8) found a predominant IgG-response in chronic inflammatory lesions of the gingiva, chronic atrophic gastritis and in ulcerative colitis. They thought the IgG was supplied by exudation and by local synthesis. The precursors of the IgG-cells were probably derived from the recirculating lymphocytic pool and their proliferation into lymphoblasts were related to some persistent antigenic stimulus. IgG is a potent protein both for neutralization and complement fixation. So the local formation of IgG constitute a "second line of defense" against antigens which are not efficiently handled by secretory immunoglobulin system. This requires penetration of extraneous agents deep through the epithelial barrier. Demonstration of IgG antibody production locally against anaerobic faecal bacteria in ulcerative colitis (49) is an evidence in favour of this concept. Such a second line of defense may be initially beneficial to the host, but ultimately it may be hazardous. The effective complement activation system by the IgG-antibody may produce continuous immune complexes and this may give rise to arthus type of reaction. Both first and second line of defense is schematically represented in Fig. 23. Table 5 summarizes the protective and deleterious consequences of local immune systems.

CONCLUSION

It is clear that in common with other mucosal surfaces, the intestine possesses a local secretory immunoglobulin system functionally different from the circulating antibody system. Secretory antibody is predominantly IgA, comprising of two 7S IgA molecules joined by 'J' chain and secretory component which protect the molecules from proteolysis in the intestinal lumen. The local IgA-system protects the body against all kinds of harmful external antigens. The deficiency of this system makes an individual not only susceptible to bacterial and viral infections but also leads to increased absorption of undesirable antigens which gaining excess to the body start series of antigen antibody reactions resulting in auto-immune diseases. In the early months of life insufficient IgA-production may produce the condition known as cow milk protein allergy. Breast feeding can avoid or decrease the incidence of this condition to a significant extent.

TABLE 1

Properties of human immunoglobulins

IMMUNOGLOBULIN CLASSIFICATION

Class	IgG	IgA	IgM	IgD	IgE
Spoken name (pronounced gamma)	γG	γA	γM	γD	γE
Heavy chain name	γ	α	μ	δ	ε
Light chain name	λ or κ in all classes	(Actually there are now two λ classes known.)			
Heavy chain Molecular weight	50,000	64,500	70,000	?50,000	?60,000
% Carbohydrate	2.5%	8%	10%	?	11%
Structure	$\gamma_2\lambda_2$ or $\gamma_2\kappa_2$	$\alpha_2\gamma_2$ or $\alpha_2\kappa_2$ *	$(\mu_2\lambda_2)_5$ or $(\mu_2\kappa_2)_5$	$\delta_2\lambda_2$ or $\delta_2\kappa_2$	$\epsilon_2\lambda_2$ or $\epsilon_2\kappa_2$
Functions	Fixes complement, crosses placenta, 70% of human IgG, secondary response	Bodily secretions, immune response to pathogens entering by respiratory or gastrointestinal tracts, isohemagglutinins	Early antibody, common antibody to blood group substances, powerful agglutinin and hemolysin	?	Allergic responses
Normal serum Concentration (Mg%)	700 – 1500	150 – 250	60 – 170	0.3	0.003

*IgA in serum tends to polymerize to form dimers and larger molecular weight polymers.

Robert S. SCHWARTZ Monograph on immunology. Published by Upjohn Company, Kalamazoo, Michigan

TABLE 2

Respective values for the population densities of plasma cells containing γA-, γM-, and γG-immunoglobulin, in the upper small intestine, colon, and rectum

Tissue	Specimen no.	Population density[a]		
		γA-cells	γM-cells	γG-cells
Duodenum-jejunum[b]		352,000	52,000	16,000
Rectum	1	119,000	25,000	23,000
	2	191,000	11,000	5,000
	3	143,000	18,000	17,000
	4	135,000	24,000	5,000
	5	192,000	8,000	1,000
Mean		156,000	17,000	10,000
Colon	1	444,000	32,000	32,000
	2	306,000	7,000	7,000
	3	289,000	11,000	6,000
Mean		346,000	17,000	15,000

[a] The figures indicate the numbers of specifically fluorescent cells per cubic millimeter of interstitial area.

[b] Mean from 10 tissues.[a]

P.A.CRABBE et al.Gastroenterology,51 : 305,1966

TABLE 3

— Immunoglobulin concentrations (mg/100 ml) in serum and external secretions.

Sample	Nos	Immunoglobulin			Ratio		References
		IgG	IgA	IgM	IgG:IgA	IgG:IgM	
Serum	100	1 230	328	132	3.8	9.3	[17]
Colostrum	15	10	1 234	61	0.008	0.16	[17]
Stimulated parotid saliva	9	0.036	3.95	0.043	0.009	0.84	[17]
« Unstimulated » whole saliva N (*)	8	1.44	19.40	0.21	0.07	6.86	[17]
P (*)	13	6.97	37.14	0.76	0.19	9.17	
Duodenal secretion	40	10.4	31.3	20.7	0.33	0.50	[26]
Jejunal secretion	5	34.0	27.6	ND (**)	1.23	ND	[21]
Colonic secretion	3	86.0	82.7	ND	1.04	ND	[21]

(*) N = normal individuals; P = patients with periodontitis.
(**) ND = not determined.

P. BRANDTZAEG. Ann. Immunol.(Inst.Pasteur)

124 C : 417, 1973

TABLE 4

PROTECTION AGAINST EXPERIMENTAL CHOLERA BY INTESTINAL IgA ANTIBODY IN ISOLATED INTESTINAL LOOPS OF MICE

Experiment no.	Immunizing preparation	Positive loops [a]
1	Intestinal IgA from non immunized mice	14/32
1	Saline	13/31
2	Intestinal IgA from immunized mice	4/15
2	Saline	12/15

[a] number of positive loops over total number tested.

Positieve loops were defined as containing $>$50 mg fluid/cm intestine

E.S. FUBURA et al., Amer. J. Clin. Nutr. 25: 1357, 1972

TABLE 5

. — Postulated protective and deleterious consequences of local immune responses (*).

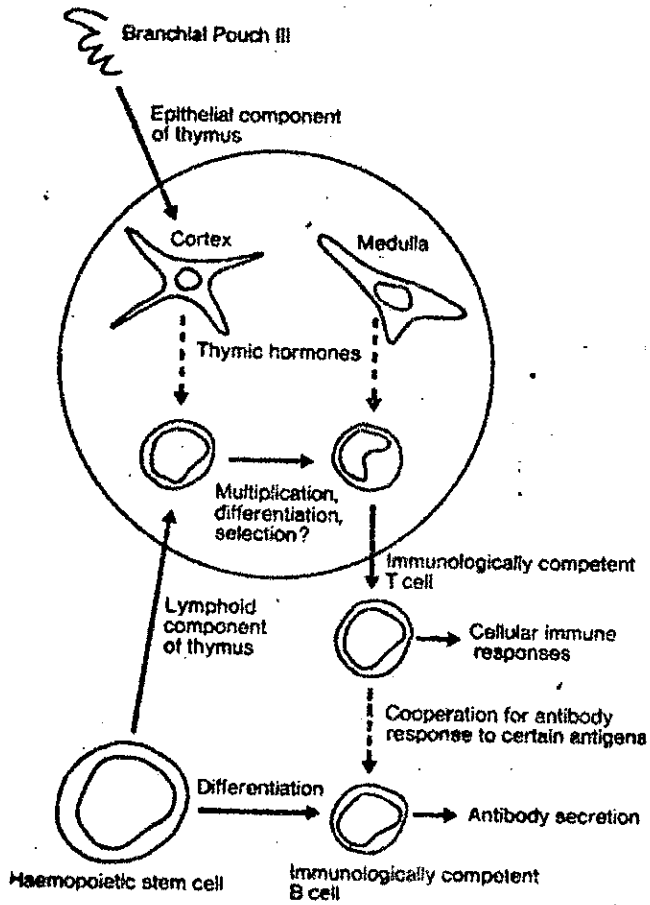
First line of defense (IgA response)	Second line of defense (IgG response)
Protective Antigen trapping in mucous coat Allergen blocking Virus neutralization Bacterial coating and aggregation Opsonization (?) Bacteriolysis (?)	*Protective* Virus and toxin neutralization Enzyme inhibition Allergen blocking Bacteriolysis Chemotaxis and opsonization Inflammation due to immune complexes
Deleterious Participation in dental plaque formation (?) Enhancement of cancer (?)	*Deleterious* Release of pharmacologically active substances from bacteria and host cells Inflammation due to immune complexes (Arthus-type reaction)

(*) From [13].

P. BRANDTZAEG. Ann. Immunol.(Inst.Pasteur)

124 C : 417, 1973

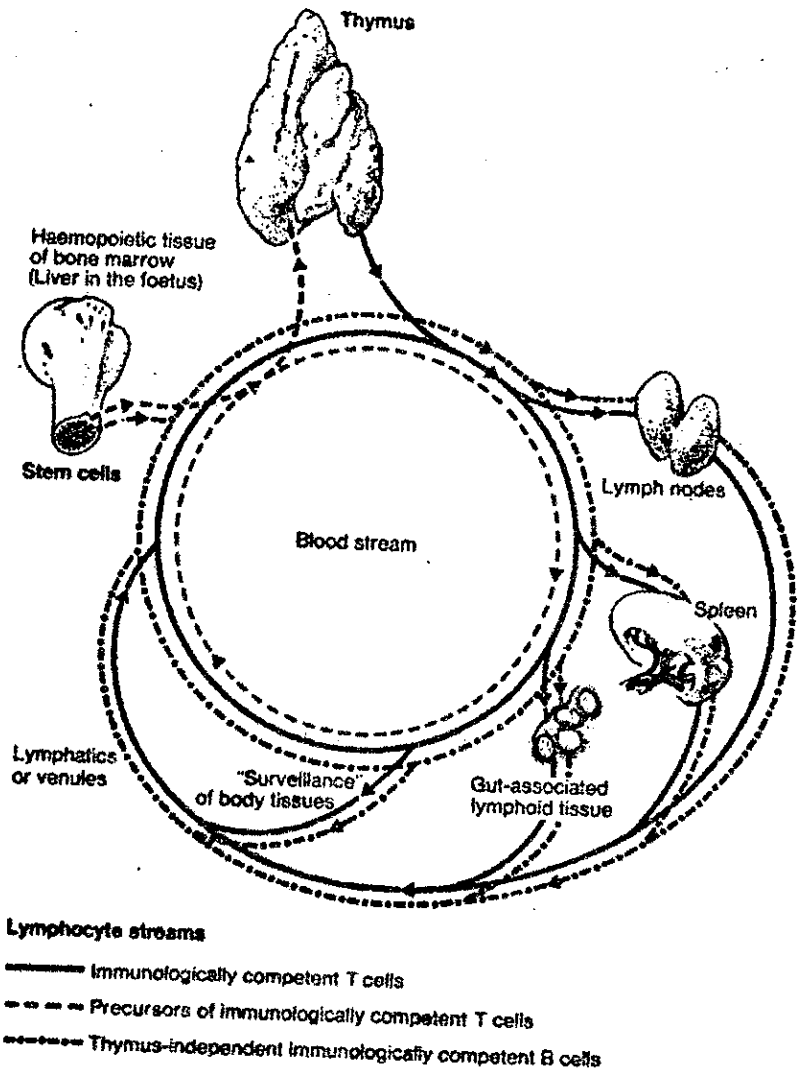
FIG. 1



Differentiation of haemopoietic stem cells under the influence of thymic hormones

G. GOLDSTEIN Triangle 11 : 7, 1972

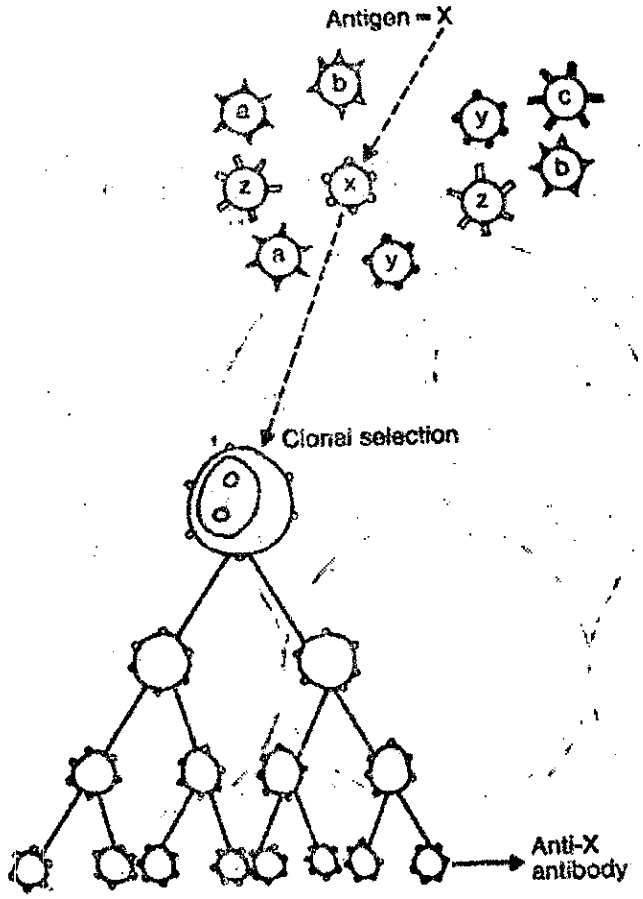
FIG. 2



Circulation of lymphocytes in the body

G. GOLDSTEIN. Triangle 11 : 7, 1972

FIG. 3



Burnet's clonal selection theory

of antibodyformation

G.J.V.NOSSAL. Triangle 11: 1,1972

FIG. 4

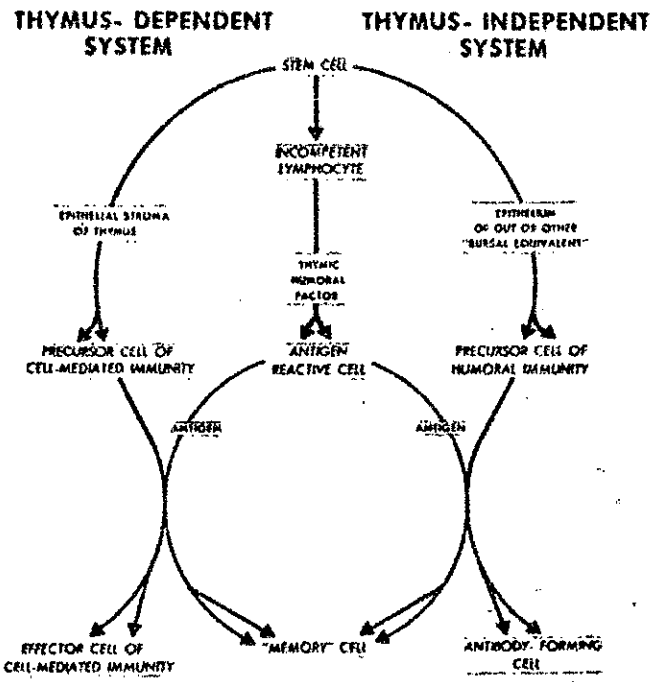
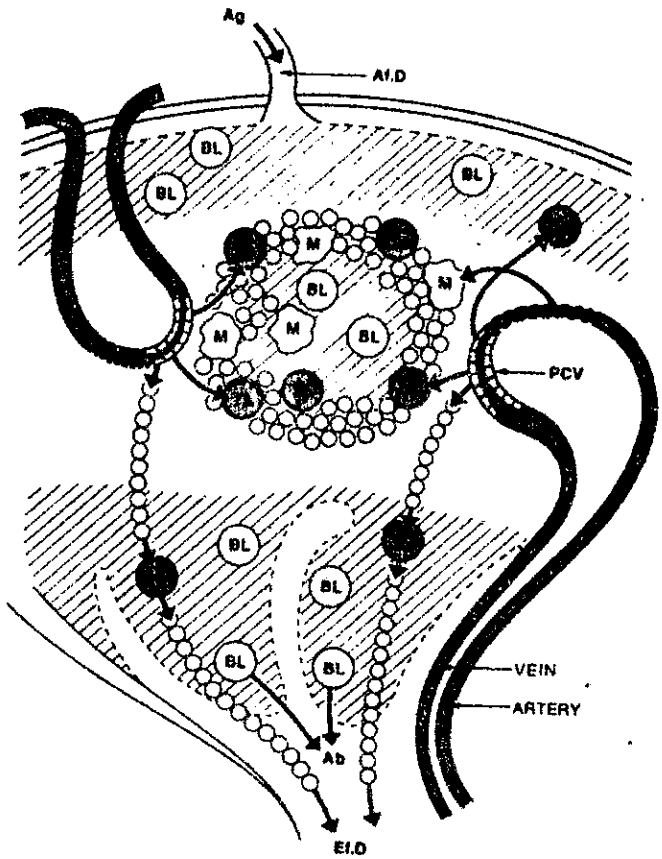


Diagram of two-component concept of differentiation of immunologically competent cells.

H.W. LISCHNER et al. Lancet 2 : 1044, 1969

FIG. 5



Specific homing of T and B lymphocytes

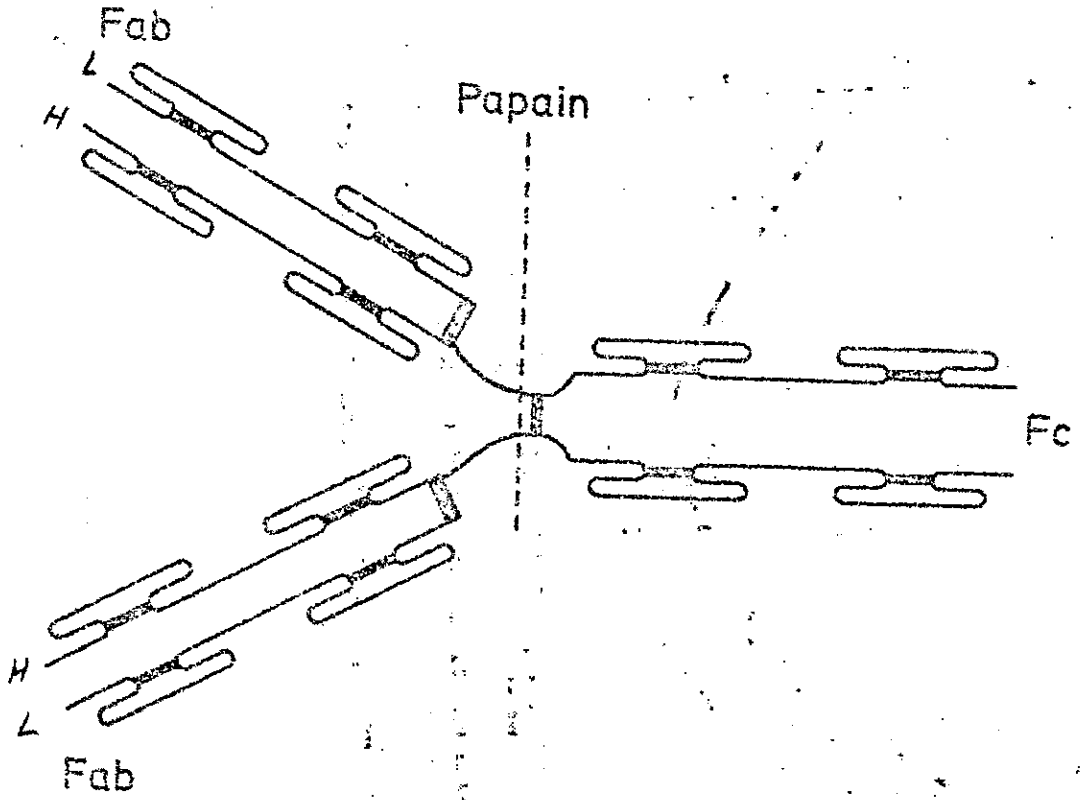
C.G. Craddock et al., New.Eng.J.Med.285 :378, 1971.

Abbreviations - Please see ..... p. 21.

ABBREVIATIONS FOR FIGURE 5

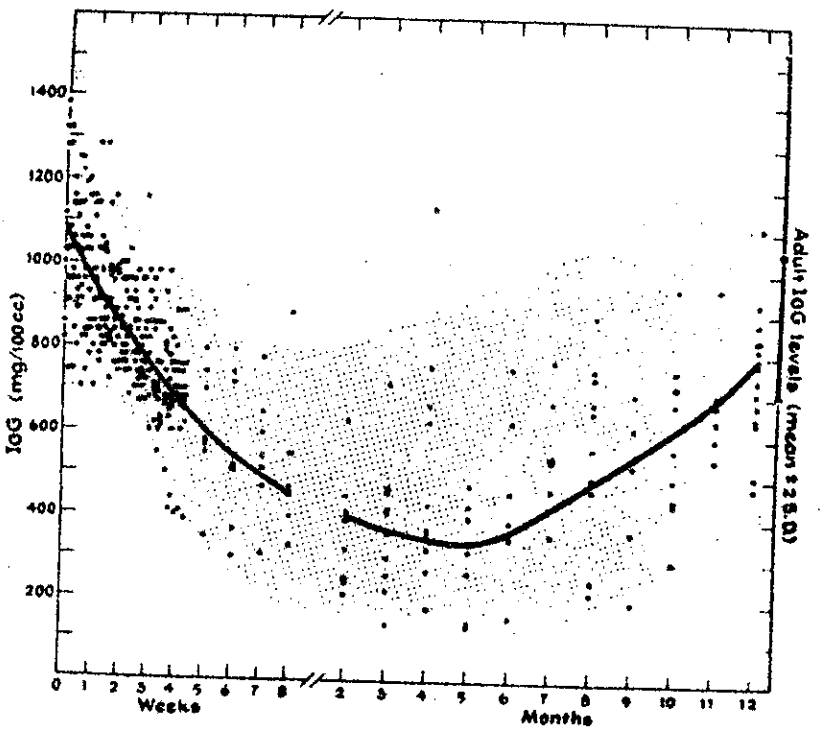
TL	-	Thymus dependent Lymphocyte
BL	-	Bursa dependent Lymphocyte
M	-	Monocyte macrophage
Ag	-	Antigen
Ab	-	Antibody
Af.D	-	Affarent Lymphatic duct
Ef.D	-	Efferent Lymphatic duct
PCV	-	Post-capillary vanule
SA	-	Splenic vein
AS	-	Terminal arteriolar sphincter
P.ALS	-	Periarteriolar Lymphocytic sheath

FIG. 6



Schematic representation of an IgG molecule showing the point of cleavage by papain (- - - -) in the hinge region and the origin of the various fragments

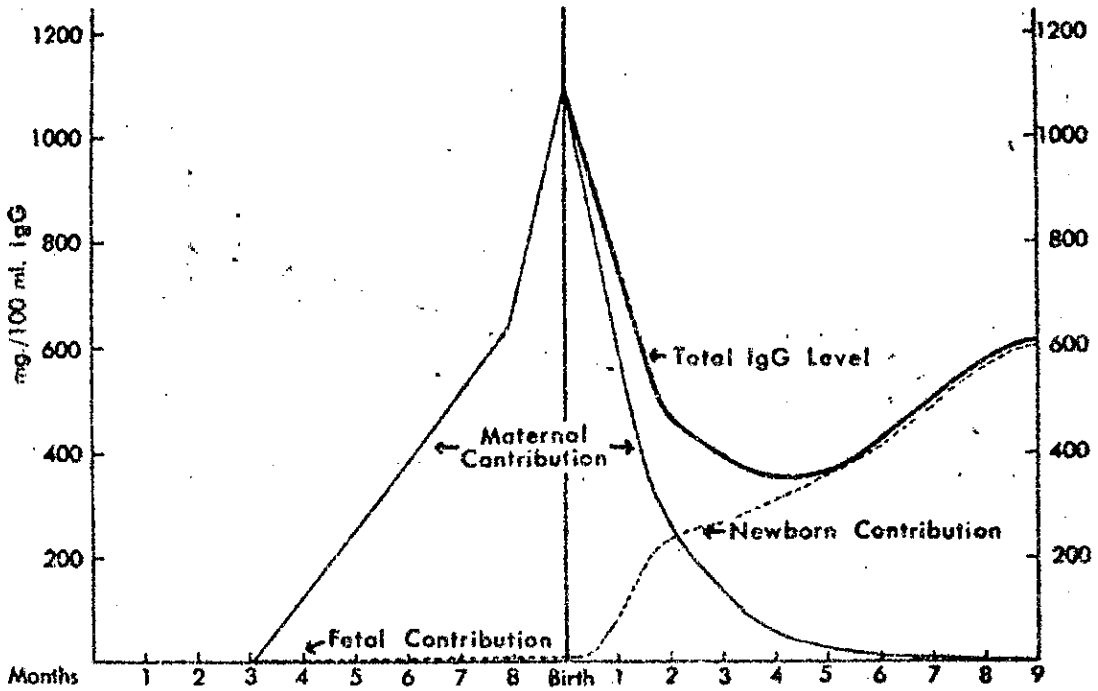
FIG. 7



IgG-values of infants and children

M. ALLANSMITH et al. J. Pediat. 72: 276, 1968

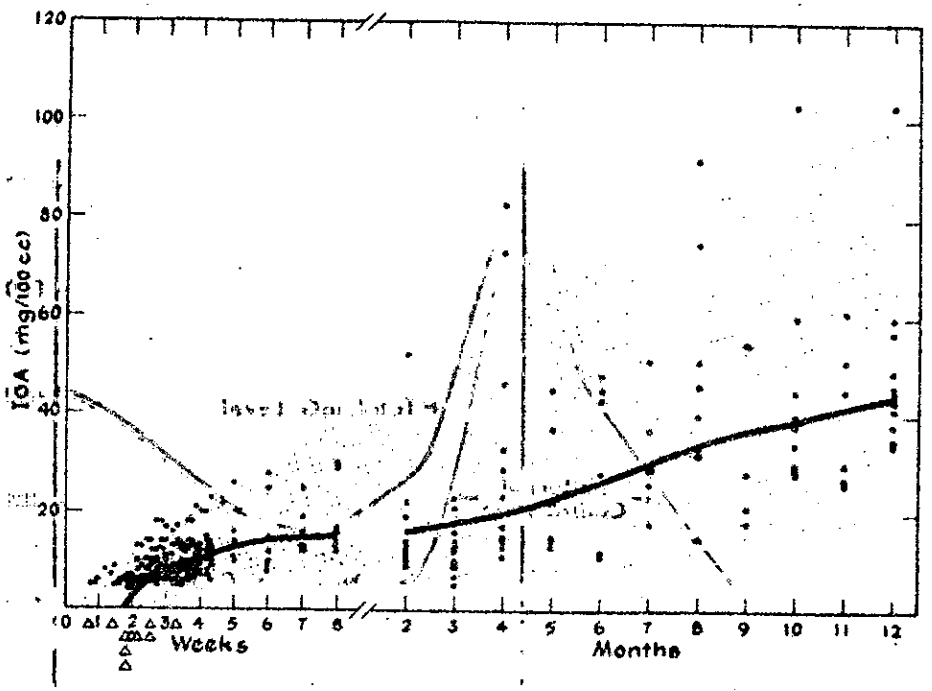
FIG. 8



Schematic representation of probable development of IgG levels in the fetus and newborn.

M. ALLANSMITH et al. J. Pediat. 72 : 276, 1968

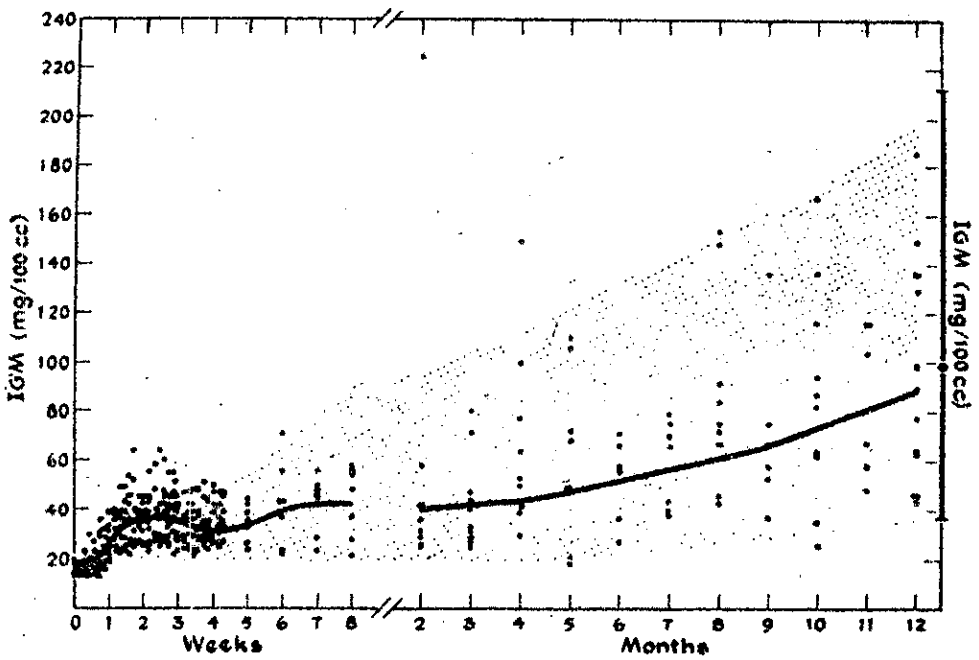
FIG. 9



IgA-values of infants and children

M. ALLANSMITH et al. J. Pediat. 72 : 276, 1968

FIG. 10

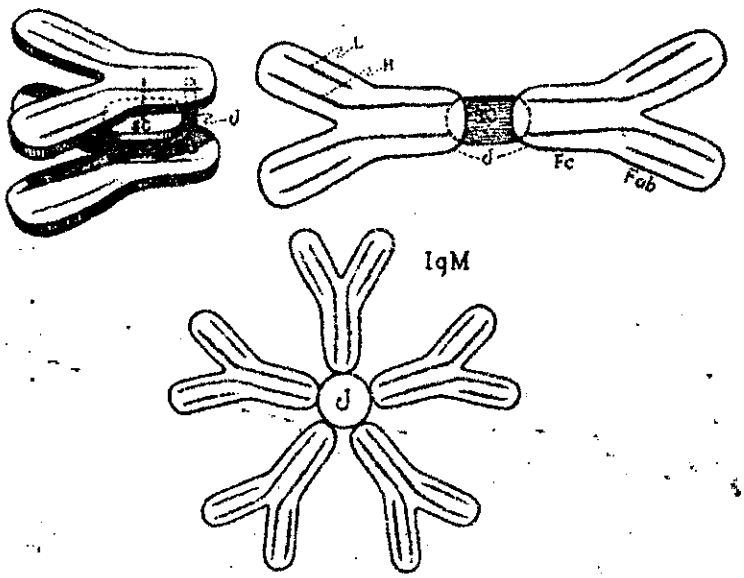


IgM-values of infants and children

M. ALLANSMITH et al. J. Pediat. 72 : 276, 1968

FIG. 11

Secretory IgA

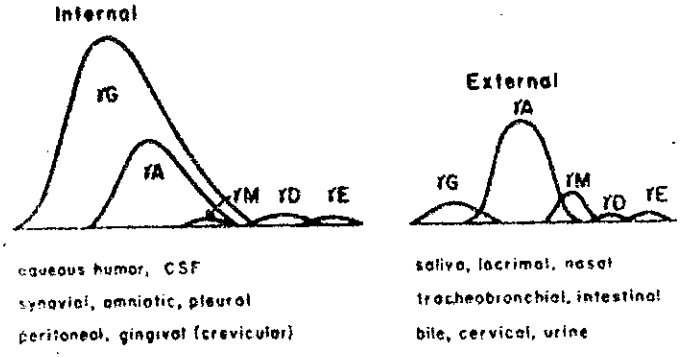


Schematic Representation of Secretory IgA and IgM.

L represents light chain, H heavy chain, J J chain, and SC secretory component. Two forms of secretory IgA, compact (left upper) and extended (right upper) that have been visualized on electron microscopy are shown.

T.B. TOMASI. New Eng. J. Med. 287: 500, 1972

FIG. 12



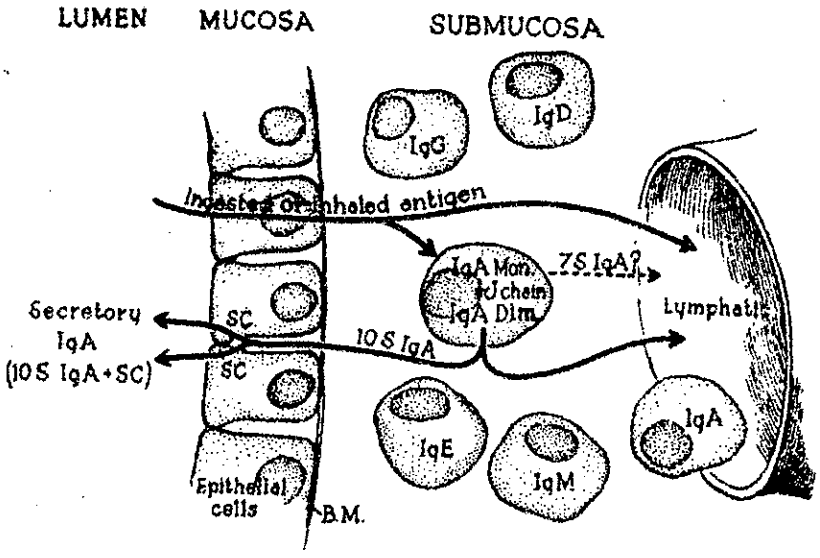
Body Secretions Characterized by Immunoglobulin Content.

Secretions are divided into internal and external. External secretions are derived from mucous membranes having continuity with the external environment. The relative concentrations of various immunoglobulin classes are proportional to the area under their respective curves.

Body secretions characterized by immunoglobulin content

T.B. TOMASI. New Eng. J. Med. 287 : 500, 1972

FIG. 13

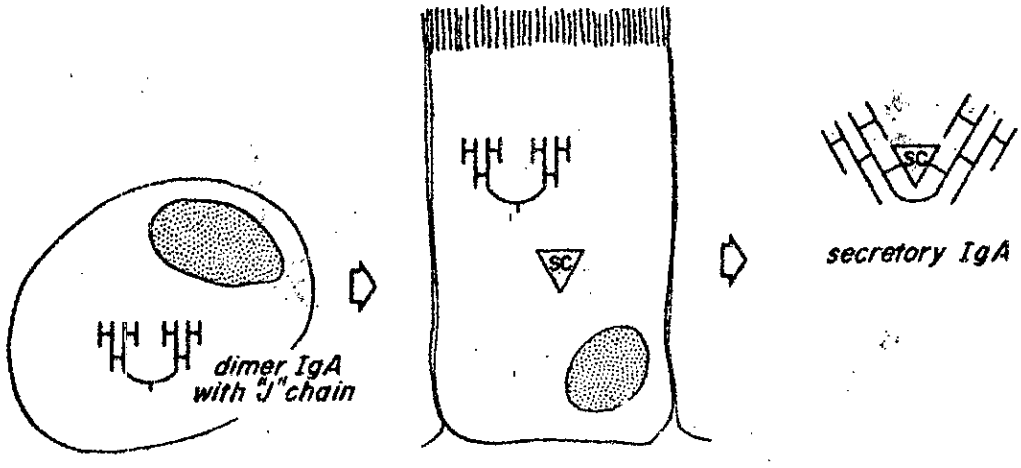


Synthesis and transport of immunoglobulins

from submucosal area

T.B. TOMASI. New Eng. J. Med. 287 : 500,1972

FIG. 14

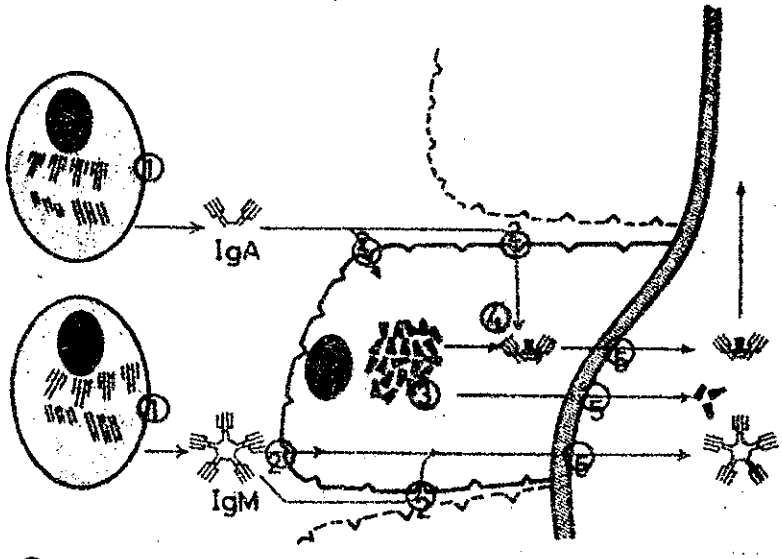


Diagrammatic representation of synthesis and transport of secretory IgA (SIgA) into the intestinal lumen. Dimers of IgA (10SIgA) containing J chain for stability are synthesized by plasma cells in the lamina propria and secreted into the interstitial space. Secretory component combines with IgA in the intercellular space or within the enterocyte and the SIgA is then transported from the cell into the intestinal lumen.

W.A.WALKER et al. J. Pediat. 83: 517, 1973

FIG. 15

SCHEMATIC STEPS OF
GLAND-ASSOCIATED IMMUNE RESPONSES



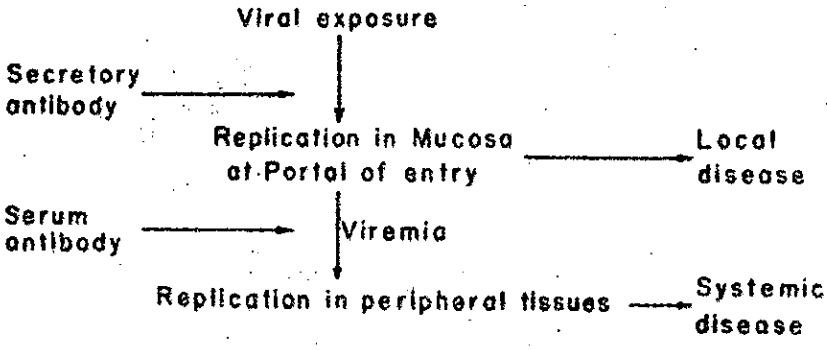
P. BRANDTZAEG. Ann. Immunol.(Inst.Pasteur)

124 C : 417, 1973

FIG. 16

Electron microphotograph of mucus layer on the microvilli of the jejunum containing micro-organisms. S. TABAQCHALI. Scand. J. Gastroenterology 5 : suppl. 6, 139, 1970

FIG. 17

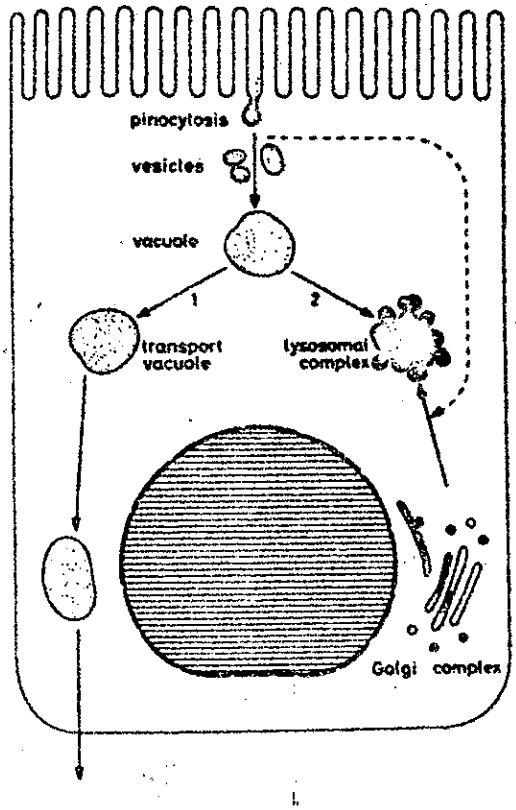


General Scheme for the Sequence of Spread of Viral Infections.

Two types of infection are shown: one producing local disease (e.g., influenza), and the other systemic (poliomyelitis).

T.B. TOMASI. New Eng. J. Med. 287, 500, 1972

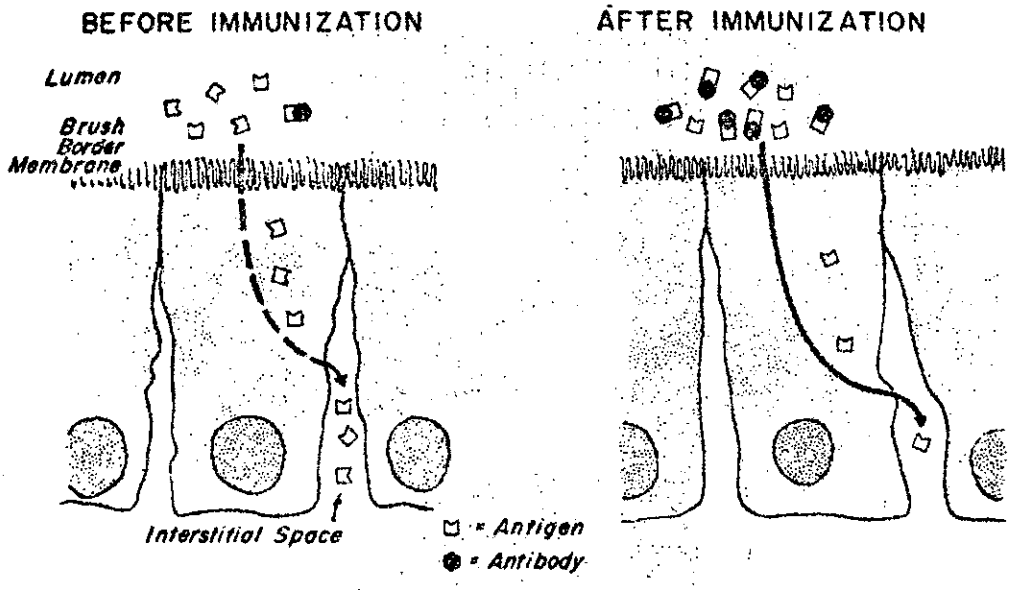
FIG. 18



Macromolecular absorption by jejunalenterocytes of the newborn infant by pinocytosis.

W.A.WALKER et al. J. of Pediat. 83: 517, 1973

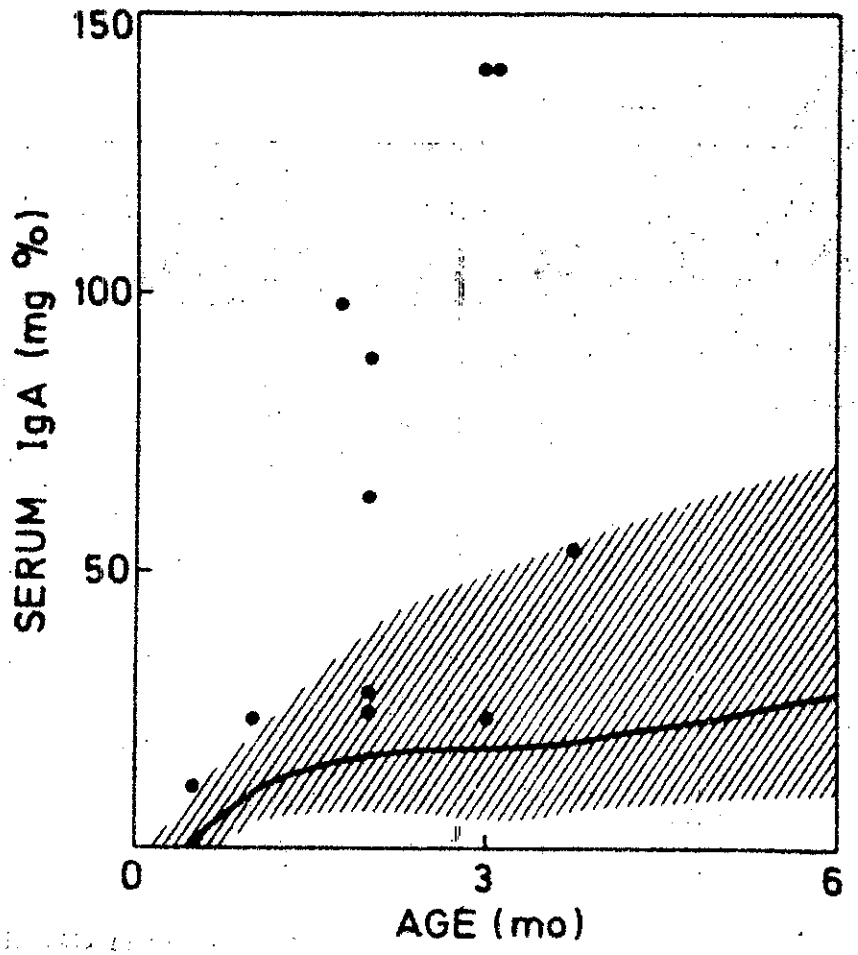
FIG. 19



Antigen absorption in the small intestine before and after oral immunization.

W.A.WALKER et al. J. Pediat. 83: 517, 1973

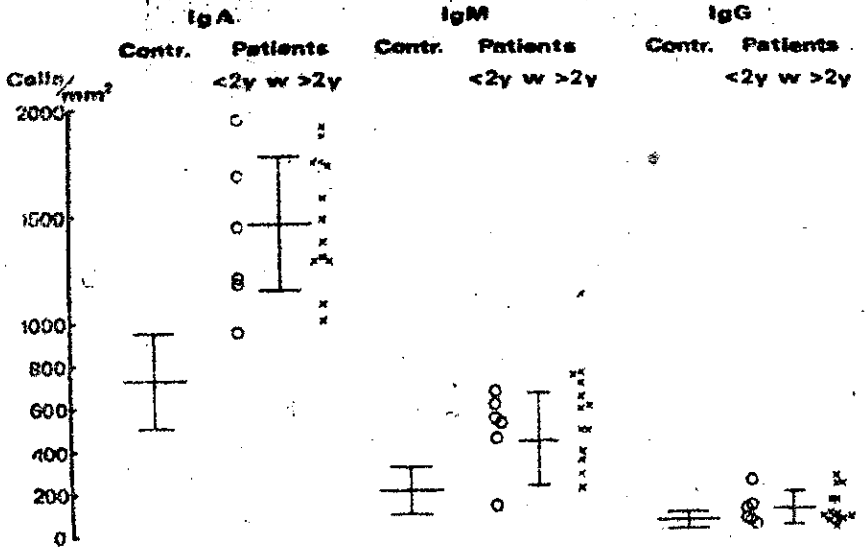
FIG. 20



Serum IgA during the active phase of cow milk protein intolerance.

E.Eggermont et al.,Acta paediat. belg.27 : 233, 1973.

FIG. 21

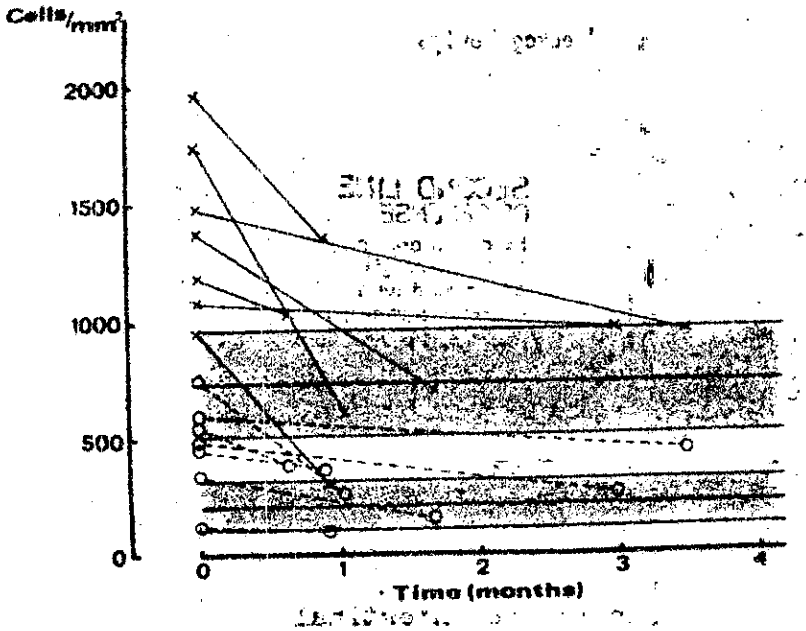


Immunoglobulin-containing cells in the jejunal mucosa of patients and controls (cells/mm³). The mean values ±SD are indicated for the controls and for the whole group of patients (W). ○ = patient under 2 years of age, × = patient over 2 years of age.

Immunoglobulin containing cells in active coeliac patients

E. SAVILAHTI. Gut 13 : 958, 1972

FIG. 22

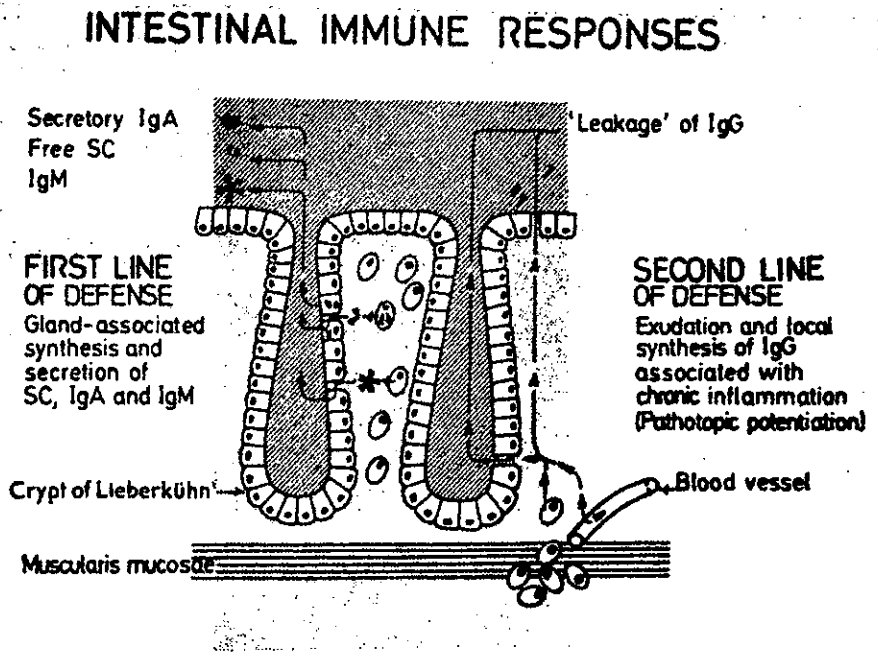


Follow-up results in seven patients treated with a gluten-free diet. × = IgA-containing cells of a patients, ○ = IgM-containing cells. Shaded areas = means of the control group ±SD for IgA-(upper) and IgM-containing (lower) cells.

Immunoglobulin containing cells of coeliac patients after treatment with glutenfree diet.

E. SAVILAHTI. Gut 13 : 958, 1972

FIG. 23



Two major types of immune responses in the intestinal mucosa constituting a first and a second "defense line"

P.BRANDTZAEG. Ann. Immunol.(Inst.Pasteur) 124 C: 417,1973

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ICDDR,B (CRL) publications can be obtained from Publications Unit, International Centre for Diarrhoeal Disease Research, Bangladesh, G.P.O. Box 128, Dacca - 2, Bangladesh.

A. CRL Annual Report 1976.

CRL Annual Report 1977.

CRL Annual Report 1978.

B. Working Paper:

No. 1. The influence of drinking tubewell water on diarrhoea rates in Matlab Thana, Bangladesh by George T. Curlin, K.M.A. Aziz and M.R. Khan. June 1977 (Rep. Sept. 1978). 21 p.

No. 2. Water and the transmission of El Tor cholera in rural Bangladesh by James M. Hughes, John M. Boyce, Richard J. Levine, Moslemuddin Khan, George T. Curlin. Dec 1977. 27 p.

No. 3. Recent trends in fertility and mortality in rural Bangladesh 1966-1975 by A.K.M. Aluddin Chowdhury, George T. Curlin. Jan 1978. 14 p.

No. 4. Assessment of the Matlab contraceptive distribution project - implications for program strategy by T. Osteria, Makhlisur Rahman, R. Langsten, Atiqur R. Khan, Douglas H. Huber and W. Henry Mosley. Apr 1978. 25 p.

No. 5. A study of the field worker performance in the Matlab contraceptive distribution project by Makhlisur Rahman, T. Osteria, J. Chakraborty, Douglas H. Huber and W. Henry Mosley. Jul 1978. 17 p.

No. 6. Constraints on use and impact of contraceptives in rural Bangladesh: Some preliminary speculations by R. Langsten, J. Chakrabory. Aug 1978. 23 p.

No. 7. The demographic impact of the contraceptive distribution project by T. Osteria, W.H. Mosley and A.I. Chowdhury. Sept 1978. 17 p.

No. 8. Development of milk teeth in rural Meheran children of Bangladesh by Moslemuddin Khan and George T. Curlin. Sept.1978. 23 p.

No. 9. A follow-up survey of sterilization acceptors in Matlab, Bangladesh by Makhlisur Rahman, Douglas Huber and J. Chakraborty. Oct 1978. 31 p.

No. 10. The Demographic Impact of Sterilization in the Matlab Village-Based MCH-FP Program by T. Osteria, S. Bhatia, J. Chakraborty and A.I. Chowdhury. Nov 1978. 23 p.

No. 11. Parental dependency on children in Matlab, Bangladesh by Makhlisur Rahman. Dec 1978. 28 p.

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