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# Immunology of human nasal mucosa

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## INTRODUCTION

The nasal mucosa consists of a predominantly pseudostratified columnar epithelial layer covering a highly vascular connective tissue stroma. The latter contains serous and seromucous glands and various types of white blood cells, especially lymphocytes and plasma cells. The lymphoid cells are found both superficially in the stroma and around the acini and ducts of the glands.

Nonspecific protection of the nasal mucosa is afforded by various mechanisms that are detailed elsewhere in this symposium. This article will focus on specific protection afforded by the immune system with emphasis on the function of B cells since little is known about the role of T cells in mucous membranes. We will consider in some detail the secretory immune system and the immunological mechanisms giving rise to tissue damage and inflammation, including allergic reactions of the nasal mucosa. Selective IgA deficiency and its local consequences will also be discussed.

## T AND B CELLS

The efficiency of specific immunity depends on the immune system's ability to acquire enhanced capacity for protection. Foreign soluble substances or microorganisms are recognized as antigens when reintroduced into the body and will then elicit a more powerful and long-lasting immune response than on the first encounter. Thus immunological memory is a crucial functional characteristic of the immune system.

The specificity of immunological recognition and reaction depends on two sets of functionally different but morphologically indistinguishable lymphocytes. T cells afford so-called cellular or cell-mediated immunity and B cells are responsible for humoral immunity (Figure 1). T- and B-cell precursors develop from a common stem cell in the bone marrow and migrate, respectively, to the thymus and the Bursa equivalent, which may be fetal liver of peripheral lymphoid organs in mammals. At these sites the lymphoid cells mature and are subsequently seeded to the circulation and peripheral lymphoid organs throughout the body as small T and B lymphocytes. The T cells become distributed mainly to the extra-

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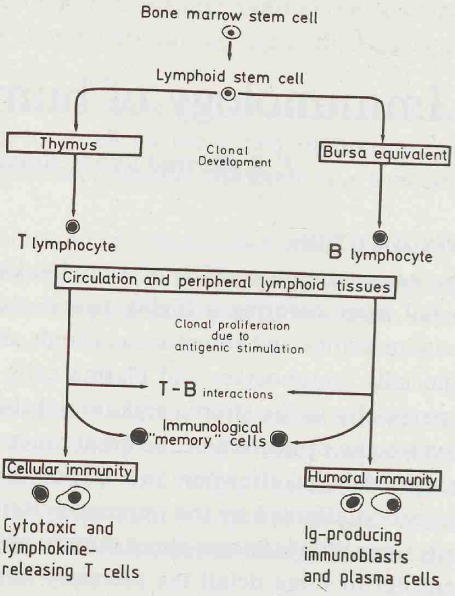


Figure 1. Schematic representation of the T- and B-cell limbs of the immune apparatus giving rise to cellular (or cell-mediated) and humoral immunity, respectively. Modified from Brandtzaeg, P. (1975), Immunoglobulin systems of oral mucosa and saliva, in *Oral Mucosa in Health and Disease.* Edited by Dolby, A. E., Blackwell Scientific Publications, Oxford, pp. 137–213.

follicular so-called paracortical areas of lymph nodes, whereas the B cells aggregate in lymphoid follicles.

On contact with antigen presented by specialized cells, such as macrophages, T and B cells are stimulated to clonal proliferation and differentiation (Figure 1). Activated T cells release lymphokines or become cytotoxic and divide to generate memory T cells. Some B cells undergo terminal differentiation to antibody-producing plasma cells whereas others generate memory B cells. The memory cells are collectively the basis for the body's capacity to mount rapid and long-lasting secondary immune responses. Interaction between certain T-cell subsets and the B cell are important for several aspects of immunoregulation but will not be discussed in this short survey.

## ANTIBODIES

Antibodies are immunoglobulin (Ig) molecules produced by plasma cells and their immediate precursors, the immunoblasts. There are five major Ig classes (IgG, IgA, IgM, IgD and IgE) and, in addition, various subclasses of IgG and IgA. Each Ig molecule consists of at least one subunit of two identical heavy chains and two identical light chains, either the κ (kappa) or λ (lambda) type. The light chains are common to all Ig classes whereas the heavy chains are unique for each class (Figure 2). Ig molecules are split in three fragments when exposed to papain digestion, two antigen-binding fragments (Fab) and one so-called crystalizable fragment (Fc), which carries the Ig-class or isotype specificity and certain biologi-

Table 1. Mechanisms for nonspecific amplification of immune reactions.

1. COMPLEMENT ACTIVATION
   Induced by antibodies of the IgG or IgM class reacting with soluble or insoluble antigens.
2. HISTAMINE RELEASE
   Induced by antibody (IgE) or mediator effects (e.g. the complement split product C5a) on mast cells or basophilic granulocytes.
3. MACROPHAGE ACCUMULATION AND ACTIVATION
   Induced by lymphokines such as migration inhibition factor (MIF) and macrophage activation factor (MAF) released from activated lymphocytes (mainly T cells).

From Brandtzaeg, P. (1983), Protective immunity and immunopathology, in *Basic Text in General Pathology, Integrated Pathology Audiovisual Learning System,* 3d ed. Edited by Iversen, O. H., Donald, K. J. and de Vries, M. J., Universitetsforlaget, Oslo (in preparation).

cal properties of the molecule such as the capacity for complement activation.

*IgG antibodies.* IgG consists of one subunit and is thus monomeric with a mol. wt. of about 150 000. It is the predominating Ig of serum and interstitial fluid and can activate complement, thereby initiating nonspecific amplification of immune reactions (Table 1).

*IgA antibodies.* This Ig is mainly monomeric (mol. wt. of about 160 000) in serum but it can also be produced in a dimeric form. The dimers consist of two IgA subunits bound together by another plasma cell product, the so-called J (joining) chain with a mol. wt. of about 15 000 (Figure 2). Dimeric IgA is the most impor-

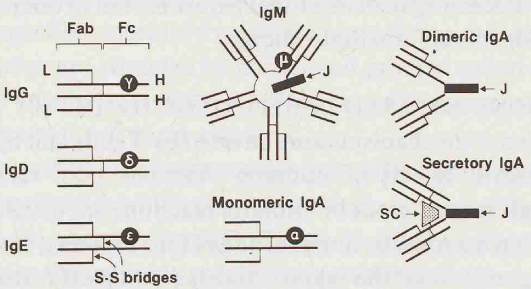


Figure 2. Schematic representation of the five major human Ig classes with their Fab and Fc fragments and their light (L) and heavy (H) chains. The isotype characteristics are located in the H chains as indicated by the different Greek letters used as labels, namely gamma (γ), delta (δ), epsilon (ε), mu (μ) and alpha (α), respectively. The L and H chains are connected by disulphide (S-S) bridges. Pentameric IgM and dimeric IgA contain, in addition, a polypeptide called Joining (J) Chain. Secretory Component (SC) is associated with secretory IgA. From Brandtzaeg, P. (1983), Protective immunity and immunopathology, in *Basic Text in General Pathology, Integrated Pathology Audiovisual Learning System,* 3d ed. Edited by Iversen, O. H., Donald, K. J. and de Vries, M. J., Universitetsforlaget, Oslo (in preparation).

tant antibody protein in exocrine secretions where it occurs bound to an epithelial glycoprotein now called the secretory component (SC), which has a mol. wt. of about 80 000 (Figure 2). Secretory IgA is very stable and resists many types of proteolytic enzymes. It protects mucous surfaces by affording immune exclusion of soluble antigens and microorganisms.

Monomeric IgA has an important function in serum and interstitial tissue fluid because of its agglutinating and neutralizing effect on virus and other particulate antigens. Since IgA lacks complement-activating capacity it may, in addition, be important as a moderator of immune reactions by dampening down harmful effects caused by IgG.

*IgM antibodies.* This is the largest Ig molecule since it normally exists in a pentameric form (mol. wt. of about 900 000). It is a powerful activator of complement and may hence be a better bacteriolytic antibody than IgG. Like dimeric IgA, pentameric IgM contains J chain and, therefore, can combine with SC and act as a secretory Ig.

*IgD antibodies.* IgD is a monomeric molecule (mol. wt. of about 180 000), whose function is largely unknown. Only small amounts of IgD are found in normal human serum. Along with monomeric IgM, it is present as an antigen receptor on the surface of most early memory B lymphocytes and may be involved in propagation of immunological memory.

*IgE antibodies.* IgE antibodies (mol. wt. of about 190 000) are potent inducers of acute inflammatory reactions since they can cause release of histamine from mast cells and basophils which carry Fc receptors for this Ig class (Table 1). IgE is probably important in defence against intestinal parasites; but in our part of the world it is best known for its role in atopic allergy.

## IMMUNE REACTIONS INVOLVED IN HYPERSENSITIVITY

Since different effector mechanisms are activated by T cells and by the various Ig classes, the biological effects of immune reactions may vary considerably (Table 1). Although several types of immune reactions are usually engaged at a given time to combat a particular antigen, one of four principal types is often predominant and responsible for the major clinicopathological features if the reaction persists. When neutralization and elimination of antigen is unsuccessful, a persistent immune reaction may cause inflammatory disease and substantial tissue damage. Such a situation appears clinically as hypersensitivity and is classified according to the underlying type of immune reaction (Figure 3). The four principal types of immune reactions that may have adverse effects will be briefly discussed below.

*Type 1 hypersensitivity.* This type includes atopic allergy and generalized anaphylactic reactions where two adjacent IgE molecules attached to the mast cell or basophil specifically binds an antigen (Figure 3). Less than one hundred IgE

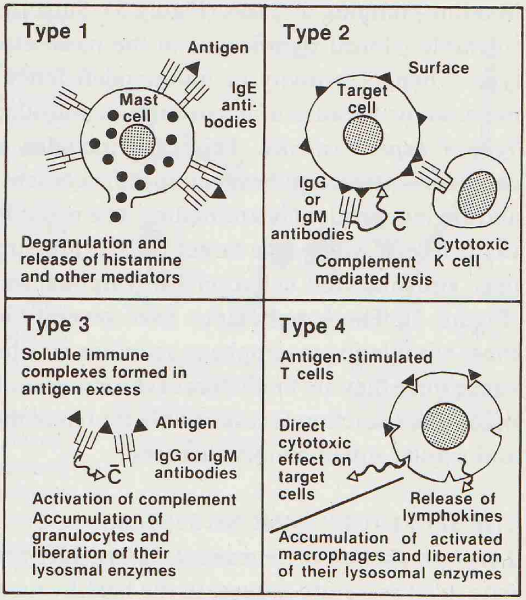


Figure 3. Schematic representation of the four principal types of hypersensitivity induced by immune reactions that may initiate inflammation and cause tissue damage.
From Brandtzaeg, P. (1983), Protective immunity and immunopathology, in *Basic Text in General Pathology, Integrated Pathology Audiovisual Learning System,* 3d ed. Edited by Iversen, O. H., Donald, K. J. and de Vries, M. J., Universitetsforlaget, Oslo (in preparation).

molecules reacting in such a way are necessary for degranulation of the cell. The subsequent liberation of histamine and other vasoactive substances initiates a series of biological events which may induce clinical symptoms such as rapid onset of itching, sneezing, nasal obstruction and hypersecretion. The pathology of the target tissue is characterized by hyperacute inflammation with vascular dilatation, congestion, increased vascular permeability and accumulation of eosinophils; the latter are attracted by a mast-cell product called eosinophil chemotaxic factor of anaphylaxis (ECF-A). This type of hypersensitivity is clearly involved in many cases of nasal allergy.

*Type 2 hypersensitivity.* This type results from lytic immune reactions caused by IgG (or IgM) antibodies which can activate complement or "arm" cytotoxic killer (K) cells with Fc receptors for IgG (Figure 3). Target cells expressing antigens corresponding to the antibody specificity are ultimately lysed. The clinical significance of this type of immune reaction is well-known from transfusion reactions and other reactions against blood cells such as autoimmune hemolytic anemia. In the nasal mucosa it may be of importance in the elimination of virus-infected epithelial cells.

*Type 3 hypersensitivity.* This type is induced by soluble aggregates of antibodies and antigens (immune complexes) occurring either in the circulation or locally at a tissue site. Only immune complexes involving complement-activating IgG (or IgM) are of importance in this context, and the immunopathological result is chronic inflammation including certain types of vasculitis and other so-called

immune-complex diseases (Figure 3). Such hypersensitivity is probably of considerable clinical significance in the nasal mucosa, either as a consequence of type 1 hypersensitivity or immunodeficiency that enhances influx of foreign material, or because of persistent uncontrolled infections.

*Type 4 hypersensitivity.* This type includes cell-mediated immune reactions caused by interaction between specifically sensitized T lymphocytes and antigen and are independent of antibodies. The reaction is caused either by directly cytotoxic T cells which lyse target cells expressing foreign antigenic determinants (e.g. virus-infected cells), or by lymphokines released from activated T cells (Figure 3). The lymphokines have several biological functions (Table 1); but those stimulating macrophage activities may be of the greatest biological significance since they are mediators of chronic granulomatous inflammation. This type of immune reaction is responsible for tissue damage in tuberculosis, sarcoidosis and similar inflammatory diseases.

## THE SECRETORY IMMUNE SYSTEM

*Local production of immunoglobulins.* IgA-producing cells normally predominate in all secretory tissues; in the healthy nasal mucosa they amount to 70–80% of the gland-associated immunocyte population. In the gastrointestinal tract there is, in addition, a substantial proportion of IgM-producing cells, especially in the proximal small intestine. Such immunocytes are less frequent in the upper aero-alimentary tract where, on the other hand, IgG- and IgD-producing cells are much more frequent than in the gut. IgE-producing immunocytes are extremely rare in normal mucosae and exocrine glands but may be encountered locally in atopic conditions. The local number of IgG-producing cells is significantly increased in inflammatory diseases, both in the gut and in the upper aero-alimentary tract.

*Glandular transport of secretory IgA and IgM.* Most gland-associated IgA immunocytes produce J-chain-containing dimers in contrast to such cells founds in tonsils, lymph nodes, spleen, bone marrow and inflammatory sites, where the IgA product is mainly monomeric. The J chain is mandatory for the SC-binding site of the IgA dimers and thus determines their uptake by the glandular epithelium. Serous-type secretory epithelial cells produce SC and express it on their basolateral surfaces as a receptor. When dimeric IgA combines with this exposed SC, the complexes are taken up by pinocytosis and transported as secretory IgA to the glandular lumen (Figure 4). Since J chain is also incorporated into pentameric IgM, this isotype has also affinity for SC and can be transported through serous glandular cells by the same mechanism as dimeric IgA (Figure 4).

Secretory immunity is hence entirely dependent on the capacity of gland-associated immunocytes to produce J chain. Such capacity is also shown by most IgD cells and by at least half of the IgG cells in nasal mucosa. Nevertheless, since J

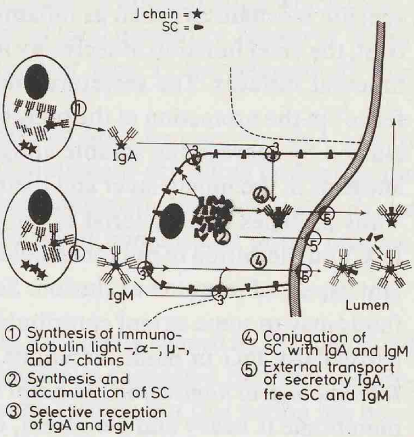


Figure 4. Schematic representation of the various steps involved in gland-associated production and external transport of dimeric IgA and pentameric IgM. SC acts as a receptor for these two immunoglobulins, and SC-IgA and SC-IgM complexes are formed in the basolateral plasma membrane of the serous-type epithelial cell. The secretory immunoglobulins thus formed are taken up by pinocytosis and transported through the cytoplasm outside the Golgi region to the gland lumen (on the right). While the conjugation of dimeric IgA with SC is covalently stabilized, this is so for only a minor fraction of secretory IgM. An excess of free SC in the secretion, therefore, is necessary to avoid release of bound SC from secretory IgM. Modified from Brandtzaeg, P. (1974), Mucosal and glandular distribution of immunoglobulin components. Immunohistochemistry with a cold ethanol-fixation technique. *Immunology 26,* pp. 1101–1114.

chain cannot combine with IgG and IgD, these isotypes are not translocated externally by a specific mechanism but depend on passive diffusion to reach the secretions. This is so also for IgE.

*Origin of IgA-producing cells.* Precursors for the gland-associated immunocytes originate in lymphoepithelial structures localized along the intestinal (Peyer's patches) and respiratory tracts. These gut- and bronchus-associated lymphoid tissues (GALT and BALT) are covered by a specialized epithelium containing so-called membrane (M) cells which transport actively antigens from the lumen to the underlying lymphoid tissue. In this way B lymphocytes receive their "first signal" for proliferation and differentiation and are transformed to IgA-expressing immunoblasts. These cells will migrate through the lymph into the general circulation and subsequently become dissemitated to glandular sites. Here they receive a "second signal" for terminal differentiation to antibody-producing immunocytes. Normally most B-cells generated in lymphoepithelial tissues end up as immunocytes of the IgA isotype.

Experiments in animals have convincingly shown the role of GALT and BALT as precursor sources for the secretory immune system. In man there is indirect evidence that, in addition to GALT and BALT, the tonsils may contribute to the population of B cells migrating to glands of the upper aero-alimentary tract, including the nasal mucosa. It seems that the tonsils have functional features both of lymphoepithelial tissues and peripheral lymph nodes.

*Function of antibodies in secretions.* The principal function of systemic immunity

is to neutralize and eliminate foreign material, often in cooperation with non-specific mechanisms such as inflammation and phagocytosis (Table 1). By contrast, the chief function of secretory immunity is immune exclusion of antigens at mucosal surfaces. The secretory immune system thus acts as a "first line of defence" in the protection of the body (Figure 5). Secretory IgA affords immune exclusion by aggregating soluble antigens and agglutinating bacteria. Trapping of antigens in the mucin layer and their subsequent removal are thereby enhanced. Virus particles and bacterial toxins can, moreover, be neutralized by secretory IgA, and inhibition of microbial colonization on epithelial cells is another important aspect of immune exclusion. Secretory IgM and IgG leaking into exocrine fluids may to some extent contribute to immune exclusion at mucosal surfaces – particularly IgG in nasal secretions.

*Immunological homeostatis in nasal mucosa.* When the antigen load on a mucous membrane is heavy and persistent, or the "first line of defense" is too weak (e.g. IgA deficiency), a substantial influx of foreign material may be expected to take place. A second "line of defense" is then established by local production of IgG (and perhaps some IgE in atopic individuals), combined with exudation of serum

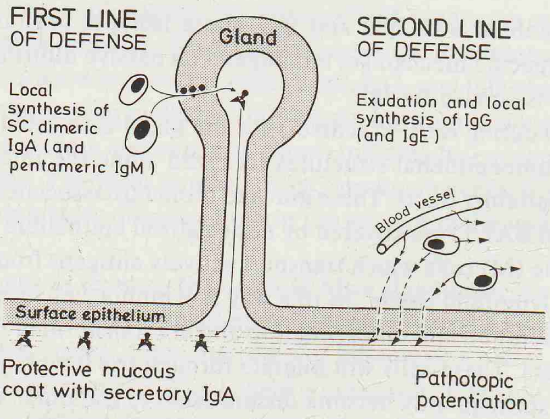


Figure 5. Schematic representation of human respiratory mucosa. Two basic principles of antibody protection are visualized. The "first line of defence" consists primarily of secretory IgA which is produced as dimers by immunocytes adjacent to glandular elements. The dimers are then conjugated with epithelial SC and selectively translocated through the glandular epithelium. Secretory IgA is subsequently included in the protective mucus coat on the mucosal surface. The "second line of defence" is associated with mucosal inflammatory reaction giving rise to passive external diffucion of serum-derived and locally produced IgG (and some IgE in atopy). This represents a mechanism of "pathotopic potentiation" of local immunity but may have adverse effects on the mucosa as explained in the text. From Hanson, L. Å. and Brandtzaeg, P. (1980), The mucosal defence system, in *Immunological Disorders in Infants and Children,* 2nd ed. Edited by Stiehn, R. and Fulginiti, V. A., Saunders Co., London, pp. 137–164.

IgG and complement factors (Figure 5). The result is inflammation which initially affords so-called "pathotopic potentiation" of local immunity. However, if antigen elimination is unsuccessful, type 3 (and/or type 1) hypersensitivity may result in inflammatory mucosal disease.

This adverse development is normally inhibited both by secretory IgA and by IgA within the tissue. IgA antibodies lack complement-activating properties and will, by competition for antigen, dampen down phlogistic immune reactions and thus contribute to maintenance of immunological homeostasis in the mucosa.

## ALLERGY OF NASAL MUCOSA

Atopic allergic reactions of the nasal mucosa are largely caused by IgE-mediated type 1 hypersensitivity (Figure 3). It was originally suggested that the IgE-producing cells belonged to the secretory immune system, but this notion has been refuted by several recent studies. Such cells are indeed very rare in mucous membranes, and no active epithelial transport mechanism has been discovered for this Ig class. IgE-bearing mucosal mast cells may apparently contain additional cytoplasmic IgE and, therefore, have probably been erroneously interpreted as IgE-producing plasma cells in many early studies. The mucosal mast cells most likely acquire their IgE in local lymph nodes where most IgE seems to be produced. After being "armed" with IgE the mast cells migrate to the mucosa where they are found both in the connective tissue and within the surface epithelium. Release of IgE from such mast cells may explain increased concentrations of IgE present in nasal secretions from atopic subjects.

Apart from allergen avoidance, treatment with antihistamines, mast-cell stabilizing drugs (sodium cromo-glycate) and steroids may reduce the clinical symptoms of nasal allergy. The influence of these pharmacologic agents on the local immunological homeostasis is complex and further studies in this field are obviously needed.

## NASAL MUCOSA IN IgA DEFICIENCY

Lack of serum IgA usually reflects a selective deficiency of IgA-producing cells at mucosal sites, spleen, bone marrow, tonsils, and peripheral lymph nodes. For various reasons that are only partly understood there is a partial or complete block in the differentiation of B cells to IgA immunocytes. In the secretory immune system this block results in enhanced local development of immunocytes of other isotypes. Thus, in the gut IgA-deficient subjects have an abundance of IgM- and IgG-producing cells and IgM takes over as a protective antibody in "the first line of defense".

Conversely, this compensation with IgM is less consistent in the upper aero-alimentary tract. In the nasal mucosa, for example, IgA-deficient subjects often have an abundance of IgG- and IgD-producing cells and very few immunocytes of

the IgM isotype. This fact may explain the tendency of such individuals to have recurrent upper-respiratory tract infections and increased frequency of allergy, whereas they usually show few or no symptoms from their intestinal canal. The altered proportions of Ig-producing immunocytes, as revealed by immunohistochemistry in biopsy specimens from the middle or lower turbinate, may aid the diagnosis of IgA deficiency.

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