REVIEW OF LITERATURE

Short of nuclear war, famine or pestilence, tobacco is the greatest single threat to the health of world’s people. Tobacco is probably the single greatest contributing factor in upsurge of non-communicable disease. About 2.5 million people die every year from diseases caused by tobacco. The diseases caused by tobacco place an extra burden on developing countries already beset by malnutrition and communicable diseases. Tobacco smoking and chewing is an epidemic growing at 2.1% per year, a faster rate than that of world’s population growth.

Tobacco has been smoked/chewed for centuries and possibly used for millennia. At first it was smoked/chewed only by the native populations of America; but, subsequently, after tobacco was brought to Europe in the middle of the sixteenth century, smoking/chewing became widespread throughout the world. Its use must, therefore, satisfy some common needs. What these are is still imperfectly understood, but they are probably partly psychosocial and partly pharmacological. The former include the use of tobacco as a social activity that helps to break down personal reserve and as a distraction that is provided by filling and lighting a pipe, holding a cigarette and watching the smoke, or chewing. The latter are complicated and include, in different circumstances, both cerebral stimulation and sedation, as smokers/chewers sometimes find that tobacco helps them to concentrate and at other times that it helps them to relax.

What is incontrovertible is that once smokers/chewers have become accustomed to its effects, prolonged abstention is distressing, and the feeling of
distress can be relieved by further use\textsuperscript{47}.

The pattern of tobacco usage in Western countries like United States, Sweden and Third World countries like India, Pakistan has changed dramatically in the past two decades. While the number of cigarette smokers has declined, smokeless tobacco use (chewing tobacco) has increased, particularly among male adolescents\textsuperscript{43,48,100}. This increase is largely due to the gain in popularity of commercially available moist snuff, a finely ground tobacco packaged in small tins or packets in United States of America and in India due to heavy promotion/advertising through mass media/sporting events of commercially available polythene pouches containing chewing tobacco preparations combined with arecanut, lime, catechu and flavouring agents\textsuperscript{46,47}. It is found that these preparations (snuff and pouches) foster nicotine addiction far more stronger than cigarette smoking\textsuperscript{100}.

Knowledge on the relationship between tobacco usage and variety of gingival and periodontal pathosis depends primarily on epidemiological evidence\textsuperscript{22,46,47}. An immense amount of such evidence has been obtained\textsuperscript{97}, and of necessity, only a small proportion can be referred to here. It will be beyond the scope of this limited edition to entirely review literature on periodontal and mucosal effects of smoking and tobacco chewing along with studies of immuno-toxicity in experimental animals and humans. Nevertheless, care is taken to ensure reviewing of all existing data as related to objectives and experimental parameters of this study.
Smoking and Periodontal Disease

The effect of tobacco smoking on the periodontium has been the subject of many studies\textsuperscript{10,22,26,51}. The clinical appreciation of differences in the periodontal status and the tissue response to treatment in smokers and non-smokers has stimulated extensive research activity. Further interest has been sparked by the elucidation of immunological interactions in periodontal disease\textsuperscript{56,58,103}.

By today's standards, many of the early studies suffered from inadequate research design. Lack of uniformity in the classification of disease and in the way measurements were made limits comparisons among studies\textsuperscript{32}. However, those studies have provided valuable information and set the tone for many research initiatives that followed.

The questions asked in the early studies dealt with the role of several factors such as diet, calculus, caries, restorations and smoking in the etiology and prevalence of gingivitis. The findings seemed to indicate that gingivitis was associated with smoking although not at a statistically significant level\textsuperscript{101}.

A group of studies conducted by Pindborg and co-workers during the latter part of the 1940s and by others during the 1950s examining large groups of subjects (over 1400 subjects in one experiment and over 5600 in another) concluded that there existed a relationship between the consumption of tobacco and calculus deposition; smoking was a factor in necrotizing ulcerative gingivitis; there were increased calculus deposition and gingivitis; and apparently, tobacco had an effect "per se" on the tissues of smokers\textsuperscript{82,84}.

Arno and co-workers in 1958 studied a sample of 1346 employees 25 to 55
years old and found that there was a significant correlation between tobacco consumption and the presence of gingivitis after adjustment for hygiene and age.

Brandtzaeg and Jamision, in 1964, studied 200 recruits 19 to 25 years old and determined that with increased use of tobacco, there was a trend for increased Russell's Periodontal Index (PI) scores accompanied by increased calculus, debris and oral hygiene indexes (Green and Vermillion). On further analysis the changes in PI could be accounted for by changes in the oral hygiene index.

In the course of evaluating the relationship of several varieties with the Oral Debris Index of Greene and Vermillion (1960), McKendrick and co-workers, in 1970, determined that smokers had almost twice as much staining as nonsmokers but that the difference in the mean number of stained teeth was not statistically significant.

Sheiham, in 1971, examined over 3000 persons and determined that smokers had more debris and calculus than nonsmokers. When persons with the same level of oral cleanliness were compared for severity of periodontal disease, significant differences between smokers and nonsmokers were not found. These findings agree with those of Kristoferssen. Preber and Kant, in 1973, evaluated 193 15-year-olds and determined that oral hygiene and gingival status was worse among smokers.

Preber and co-workers, in 1980, in a study of young adults (mean age 21.9 years) comparing oral hygiene and periodontal status in smokers versus nonsmokers, reported that smokers have a greater severity of gingivitis and a
higher plaque index than nonsmokers but the same amount of pocket depth and bone loss as nonsmokers. In 1980, Modeer and co-workers examined a group of 232 school children aged 13 to 14 years and concluded that smokers had increased gingival inflammation and plaque accumulation when compared to nonsmokers.

In the evaluation of a representative sample of the United States population as part of the National Health and Nutrition Examination Surveys, Ismail and co-workers evaluated the relationship of smoking to periodontal disease in 3,326 individuals. All mean values obtained were adjusted for potential confounding variables such as age, sex, race, socioeconomic status, oral hygiene and frequency of toothbrushing by using a multiple linear regression model. In the study, smokers had significantly higher mean PI scores in all age groups (25 to 74 years) and significantly higher scores in the debris, calculus and oral hygiene indices. The data suggests that smoking has an independent direct association with periodontal disease, although less strong than the association of oral hygiene and age with periodontal disease.

These studies attempt to determine the effect of smoking on the periodontal status of patients in two ways: first, a direct effect on the individuals by measuring health parameters, and secondly an indirect effect by measuring the oral hygiene status. Although the findings are inconsistent, variables measured and methods of measure are not comparable, and some reviewed clinical reports were not well controlled, it is apparent that smoking worsens the oral hygiene status of the individual and that it acts as a co-factor, together with poor oral hygiene, in
gingivitis and periodontitis\textsuperscript{22}.

These studies indicate that clinical indices of periodontal health such as bleeding and gingival inflammation are altered in smokers when compared to nonsmokers\textsuperscript{25}.

**Tobacco Chewing and Dental Effects**

The relationship between smokeless tobacco use and the health of gingival and periodontal tissue has been little studied. Furthermore, because of variations in study design and diagnostic criteria, comparisons between such reports as are available are often impossible. Thus the effects of smokeless tobacco in relation to gingivitis are not clearly established\textsuperscript{100}. However, gingival recession at the site of placement is a common finding among teenage users of smokeless tobacco between 26\% and 60\% of them having such lesions\textsuperscript{100}. In addition, 77-87\% of those who had gingival recession also had evidence of related oral mucosal pathology. Such soft-tissue changes were also found at the site of tobacco placement\textsuperscript{31,85}.

Evidence that smokeless tobacco has adverse effects on the teeth has been provided by several cross-sectional studies, a limited number of case reports, and a number of investigations of the possibility that smokeless tobacco constituents may serve as predisposing or etiological agents in the development of dental caries\textsuperscript{15,97}. Some studies, however, have suggested a potential protective effect\textsuperscript{65,115}, since the increased salivary flow resulting from tobacco use could provide increased salivary buffering, and hence reduce caries. It is also known that
various forms of smokeless tobacco contain fluoride, which could well offer some protection against caries\(^27\), both directly to the teeth and also via the dental plaque. While some products contain caries-promoting fermentable carbohydrates\(^43\), others use non-fermentable artificial sweeteners which would not increase the plaque's potential to produce caries-inducing acids. In view of all these differences between the different products, it is not surprising that inconsistent results have been obtained by different investigators\(^27,43,100\). However, since gingival recession occurs prematurely in young users of smokeless tobacco, premature root caries seem likely to occur, whether as a result of lesions induced by fermentable carbohydrate or simply of premature root dentine exposure within the oral cavity\(^100\).

It has also been suggested that smokeless tobacco, or some of its components, may contribute to degenerative changes (and even to more severe damage) in human salivary glands\(^40,92\). However, the data are inconclusive, and it has been suggested that salivary gland fibrosis and degenerative changes may be associated only with particular tobacco brands, and are thus not a generalized reaction to all tobaccos\(^102\). Furthermore, it has been shown that snuff users have a significantly higher resting salivary flow than non-snuff-taking controls\(^57\). In view of the above, salivary gland data should be interpreted with caution and it should be remembered that any reduction in salivary flow will result in a decrease in protective factors for the oral epithelium, as well as for the exposed crown and root surfaces\(^102\).

Finally, it has also been suggested that excessive tooth surface wear may occur at the site of tobacco use\(^100\). However, such evidence as exists is related
mainly to tobacco chewers rather than snuff takers, and surface wear is probably
the result of the mechanical abrasion caused by the chewing action rather than of
any chemical effect of the tobacco or its by-products. Firm evidence from
controlled studies on calculus and staining in tobacco users, as compared with
non-users, is also lacking, only case reports being available102.

Effects on Periodontal Tissues and Teeth

The first study demonstrating a detrimental influence of betel chewing upon
the periodontal tissues was carried out by Mehta et al (1955), who found a higher
prevalence of periodontal disease among betel chewers than among non-chewers
in a group of 1023 individuals from Bombay79. Gupta (1964), who examined 1673
persons in Trivandrum, Kerala, in South India, found that the mean periodontal
index (PI) for those who chewed betel was consistently greater than for those did
not chew, suggesting worse periodontal status in chewers32.

In 1960, Waerhaug (1967) carried out a comprehensive survey among 8217
persons in Sri Lanka aged 13-60 years and over, 30% of whom had the habit of
betel chewing108. It was found that betel chewers over the age of 20 years had a
very much higher PI (indicating periodontal breakdown) than non-chewers, even
when subgroups of equivalent oral hygiene were compared.

Tobacco Chewing and Oral Mucosal Effects

Oral leukoplakia and other oral lesions have been commonly found at the
habitual sites of placement of smokeless tobacco, including the buccal mucosa and
groove, labial mucosa and groover, gingivae, anterior two-thirds of the tongue and floor of the mouth.

In the study by Gupta et al., the annual rates of oral lesions were 3.9 per 1000 men and 6.01 per 1000 women. Such observations gave rise to a number of epidemiological studies, especially in Asia, Scandinavia and the U.S.A. aimed at investigating the association of oral leukoplakia and other mucosal pathology with smokeless tobacco use by examining the prevalence, incidence, and malignant transformation of these lesions. The results of these studies support the conclusion that smokeless tobacco use plays a causal role in the development and malignant transformation of oral leukoplakia, as discussed in an IARC monograph and the Surgeon General's Report on the Health Consequences of Smokeless Tobacco Use. Some of the studies are discussed below.

In cross-sectional surveys of more than 50,000 individuals in five districts of India, the prevalence of oral leukoplakia ranged from 0.4% to 1.8% among users of smokeless tobacco as compared with almost zero prevalence in non-users. In another survey of 100,000 individuals, the age-adjusted prevalence of leukoplakia was 1.2% among men and 1.8% among women users of smokeless tobacco as compared with 0.05% in non-users. The existence of a dose-response relationship was confirmed in two cross-sectional studies.

In a cohort study of 10,000 individuals followed over a period of 10 years, the incidence of leukoplakia was 2.5 per 1000 among men and 3 per 1000 among women, as compared with zero among those who did not use smokeless tobacco.
In several studies on the oral effects of discontinuation of smokeless tobacco use, it was found that oral leukoplakia apparently regressed. There was a significant decline in the incidence of oral leukoplakia in a group given special health education on the harmful effects of tobacco use as compared with that in the control cohort.

Finally, malignant transformation of leukoplakia induced by smokeless tobacco has been reported by Silverman et al. Gupta et al in 2- and 10-year follow-up studies respectively.

Tobacco and Immunotoxicity

Exposure to cigarette smoke causes both short- and long-term effects on the immune system of animals. The effects may be either localized to pulmonary tissues or may be systemic.

The cellular components of the pulmonary defense system consist of several cell types that are present on and in the airway epithelium. Cells on the surface are studied by means of bronchial lavage and comprise pulmonary alveolar macrophages, lymphocytes and various polymorphonuclear cells. These cells play a vital role in the defense of the lung against inhaled particles by taking up particulates, functioning in the development of an immune response, and secreting tissue-destroying enzymes. Exposure to cigarette smoke causes a prompt decrease in the numbers of pulmonary alveolar macrophages and polymorphonuclear neutrophils. The new alveolar macrophages usually have an
increased capacity for phagocytosis\textsuperscript{21}, a decreased capacity for phagolysosome fusion\textsuperscript{38} and quite different morphometry compared to cells from control animals\textsuperscript{63}. In-vitro exposure of alveolar and peritoneal macrophages to tobacco smoke also resulted in impaired phagocytic function, metabolism and viability\textsuperscript{42}.

Tobacco smoke affects immune mechanisms, both within the lungs and systematically. These effects on immune function would be relevant to pathogenesis if immune surveillance or other host-immune responses are impaired. Interpretation of the changes in immune function associated with cigarette smoking, however, must be constrained by limitations of current knowledge concerning the immune system and carcinogenesis\textsuperscript{2}.

More extensive data are available concerning systemic immune function and tobacco smoke. Serum immunoglobulin levels differ between smokers and nonsmokers. IgE and IgD tend to be elevated in smokers whereas IgG levels are reduced\textsuperscript{6,33,111}. In experimental models, exposure to tobacco smoke alters humoral antibody responses to administered antigens\textsuperscript{41}. Some, but not all studies suggest impaired humoral immune responsiveness in cigarette smokers\textsuperscript{41,61}.

Impaired cellular immunity has been observed in cigarette smokers. Exposure of lymphocytes in-vitro to cigarette smoke and to nicotine decreases lymphocyte responsiveness to mitogen stimulation (Neher, 1974)\textsuperscript{77}. Corresponding abnormalities in cellular immunity have been demonstrated in some studies. Several recent investigations have characterized T-lymphocyte subsets in smokers and nonsmokers. In heavy smokers, Miller, L.G. et al (1982)\textsuperscript{76} found a diminished ratio of helper to suppressor cells, which returned to normal six weeks following
cessation of smoking. Ginns et al (1982) also found this lowered ratio and reported alterations of T-lymphocyte subsets in persons with lung cancer. Natural killer-cell activity, which may be important for immune surveillance, is also reported to be reduced in smokers.

Bennet, Reade (1982) measured Salivary Immunoglobulin A levels in normal subjects, tobacco smokers, and patients with minor apthous ulceration in Australian population concluding definite decrease in S-IgA concentrations of chronic tobacco smokers compared to matched controls. They discussed the significance of decrease in S-IgA concentrations being due to immuno suppressive effect of the combustion products of tobacco and the possibility of the incidence of intra-oral neoplastic disease being increased in tobacco smokers by this effect.

The author had quantitatively estimated the S-IgA values in cigarette and bidi smokers of Ahmedabad. The study showed significant decrease in S-IgA values with increase in frequency and duration of habitual cigarette or bidi smoking. Bidi smokers had significantly less S-IgA compared to matched cigarette smokers.

The Human IgA System

Immunoglobulin A (IgA) is produced by many species including humans, in quantities exceeding those of all other immunoglobulin classes combined. In humans, most IgA is excreted onto the vast (~400m²) area of mucosal surfaces, becoming the principal mediator of humoral immunity at these sites. At least 66 mg IgA/Kg body weight is produced per day, as compared to 34 mg for
IgE and 7.9 mg for IgM52.53. While serum levels of IgA mature only slowly over 15
years, the concentrations of IgA in external secretions may reach adult levels in
as little as 4 to 6 weeks. In addition to differences in ontogeny and cellular origin,
the secretory and serum IgA systems appear to be independent with respect to the
molecular properties of the IgA produced, the distribution of the IgA subclasses,
antigen specificities and functions53.

IgA destined for either secretory or systemic compartments originates from
plasma cells found in different lymphoid tissues. Secretory IgA (S-IgA) is produced
locally by plasma cells found in remarkable abundance in the intestines (1010
cells/m of intestine) and in salivary, lacrimal and mammary glands. In humans,
these tissues contribute only small quantities of IgA to the intravascular pool. The
primary source of IgA for the latter compartment, but IgA thus produced is rapidly
catabolised resulting in serum levels lower than IgG52.

Appreciation and understanding of the immunological role of the IgA
systems have been hampered by the relatively normal health status of many IgA-
deficient individuals in Western populations. However, this implies unimportance
of IgA in both serum and secretion is rare, and the compensatory role of secretory
IgM in replacing S-IgA in deficient patients is not fully appreciated. Yet, even
without taking the compensatory role of secretory IgM into account, increased
incidences of a number of pathological conditions such as respiratory tract and
autoimmune diseases have been associated with selective IgA deficiency53. In
communities lacking modern standards of hygiene as in India, subnormal mucosal
protection due to IgA deficiency may have much more serious effects52. An
unusual feature of IgA when compared with IgG and IgM, is the distribution of the various molecular forms, namely monomeric IgA (mlgA) and polymeric IgA (plgA), in the two compartments. In serum, IgA occurs predominantly in a monomeric form with two α-heavy (H) and two light (L) chains linked by covalent (disulfide) and noncovalent bonds. In healthy individuals, only a small proportion (-10% or less) of serum IgA is plgA composed of disulfide-linked monomers. An additional small glycoprotein, J chain, is attached to the penultimate cysteine residues of two α-H chains. In contrast, IgA found in external secretions is mostly polymeric with dimers and smaller amounts of tetramers. A large, carbohydrate-rich glycoprotein, secretory component (SC), becomes disulfide-linked to one of the monomers during the selective transport of plgA through epithelial cells, and in some species hepatocytes, into external secretions54.

With respect to plgA and mlgA, the former molecular form is principally produced by plasma cells distributed in the mucosal tissues and glands. Almost all of the IgA-positive cells in these tissues express J chain. In contrast, IgA-positive plasma cells in normal human bone marrow secrete almost exclusively mlgA. Interestingly, the bone marrow cells in IgA myeloma release predominantly plgA, which appears only in small quantities in external secretions55.

Human IgA, like IgG, occurs in multiple genetic forms encoded on chromosome 14 near the genes of IgM, IgD, and IgE heavy chains. Two subclasses, IgA1 and IgA2, have been identified by serologic and structural studies. Primary amino acid and carbohydrate structures of human IgA of both subclasses have been determined in several laboratories. There are surprisingly
few differences in the amino acid sequences in the constant region of α2 chains, except for the hinge region, which in the α1 chain is highly susceptible to unique IgA1-specific protease produced by several bacterial species. Although IgA2 is richer in the total content of carbohydrates than IgA1, the latter subclass contains more oligosaccharide side chains, particularly in the hinge region54.

The cells that produce IgA1 or IgA2 also display a characteristic tissue distribution. In the bone marrow, approximately 90% of the cells are IgA1-positive and thus mirror the intravascular distribution of this subclass; on the other hand, mucosal tissues and glands contain variable proportions of IgA1 and IgA2 cells, depending on the anatomic origin of the tissue (Table-1).53

Although most of the total IgA is selectively transported into external secretions, the fate of the large quantities produced daily for the systemic compartment in humans remains speculative. It has been proposed that extravascular IgA is internally catabolized in the liver and possibly other tissues52.

Effectors Functions of Secretory IgA

Most of the biological properties of antibody molecules of various isotypes are governed by the Fc region which comprises two or three constant domains of the C-terminal portion of heavy chains55. The protective functions of secretory IgA antibodies have been amply documented in a variety of models (Table-2). Although the Fab part of immunoglobulin molecules is capable of neutralizing biologically active antigens such as viruses, enzymes, and toxins, the fate of the complex formed and the mode of its disposal are dependent on the Fc region74. This is particularly pertinent to effector functions in which ancillary humoral factors (e.g.
Table 1
Distribution (%) of plgA, mlgA, IgA1 and IgA2 in Various Body Fluids and in Cells from Different Tissues

<table>
<thead>
<tr>
<th>Body fluids</th>
<th>mlgA</th>
<th>plgA</th>
<th>IgA1</th>
<th>IgA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>External secretions</td>
<td>5-10</td>
<td>90-95</td>
<td>50-67</td>
<td>33-50</td>
</tr>
<tr>
<td>(saliva, tears, colostrum and milk, intestinal and bronchial secretions)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>85-99</td>
<td>-1-15</td>
<td>84</td>
<td>16</td>
</tr>
<tr>
<td>Cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretory tissues</td>
<td>3-13</td>
<td>87-97</td>
<td>35-56</td>
<td>44-65</td>
</tr>
<tr>
<td>(salivary, lacrimal, and mammary glands, lamina propria of the intestinal and respiratory tracts)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow, spleen, tonsils</td>
<td>63-94</td>
<td>6-37</td>
<td>79-88</td>
<td>12-21</td>
</tr>
</tbody>
</table>
Table 2

Effector Functions of Secretory IgA

<table>
<thead>
<tr>
<th>Function</th>
<th>Secretory IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutralization (viruses, toxins, enzymes)</td>
<td>+</td>
</tr>
<tr>
<td>Inhibition of bacterial adherence</td>
<td>+</td>
</tr>
<tr>
<td>Loss of bacterial plasmid (curing effect)</td>
<td>+</td>
</tr>
<tr>
<td>Inhibition of antigen uptake from mucosae</td>
<td>+</td>
</tr>
<tr>
<td>Enhancement of antibacterial effect of innate factors</td>
<td></td>
</tr>
<tr>
<td>Lactoperoxidase</td>
<td>+</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>+</td>
</tr>
<tr>
<td>Suppression of inflammatory effects of C-dependent and C-independent reactions</td>
<td>+</td>
</tr>
<tr>
<td>Polymorphonuclear phagocytosis</td>
<td>+</td>
</tr>
<tr>
<td>Cutaneous anaphylaxis and Arthus reaction</td>
<td>+</td>
</tr>
<tr>
<td>Immune lysis</td>
<td>+</td>
</tr>
<tr>
<td>NK cell activity</td>
<td>+</td>
</tr>
<tr>
<td>Antibody-dependent cellular cytotoxicity</td>
<td>-</td>
</tr>
</tbody>
</table>

complement) and various types of cells (phagocytes and epithelial cells) form an essential component. The presence of the intact Fc with its negative charge also appears to play an important role in inhibition of the adherence of antibody-coated antigens to epithelial cells. Because most external secretions contain low levels of complement components and because some substances present in these
secretions interfere with complement activity, complement-dependent functions at mucosal surfaces may be limited. Effective opsonization by secretory IgA is unlikely due to the low number and impaired function of phagocytic cells in most

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Secretory</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular form</strong></td>
<td>Polymeric</td>
<td>Monomeric</td>
</tr>
<tr>
<td><strong>Subclasses</strong></td>
<td>IgA1 &gt; IgA2</td>
<td>IgA1 &gt; IgA2</td>
</tr>
<tr>
<td><strong>Antibody activity</strong></td>
<td>IgA1 &gt; IgA2</td>
<td>Almost exclusively IgA1</td>
</tr>
<tr>
<td><strong>Protein antigens</strong></td>
<td>IgA1 &gt; IgA2</td>
<td></td>
</tr>
<tr>
<td><strong>Carbohydrate antigens</strong></td>
<td>IgA2 &gt; IgA1</td>
<td></td>
</tr>
<tr>
<td><strong>Lipopolysaccharides</strong></td>
<td>IgA2 &gt; IgA1</td>
<td></td>
</tr>
<tr>
<td><strong>Lipoteichoic acid</strong></td>
<td>IgA2 &gt; IgA1</td>
<td></td>
</tr>
<tr>
<td><strong>Site of production</strong></td>
<td>Secretory tissues</td>
<td>Bone marrow</td>
</tr>
<tr>
<td><strong>Origin of precursors</strong></td>
<td>Gut- and bronchus-associated lymphoid tissues</td>
<td>(Bone marrow)</td>
</tr>
<tr>
<td>of IgA plasma cells</td>
<td>Interacts with epithelial cells of ecto- and endodermal origin</td>
<td>?</td>
</tr>
<tr>
<td><strong>Effector functions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pathological conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IgA myeloma</strong></td>
<td>Not affected</td>
<td>Affected</td>
</tr>
<tr>
<td><strong>IgA deficiency</strong></td>
<td>Affected or may not be affected</td>
<td>Affected</td>
</tr>
<tr>
<td><strong>Cesium irradiation</strong></td>
<td>Affected</td>
<td>Not affected</td>
</tr>
<tr>
<td>of peripheral blood</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

external secretions, with exception of colostrum; furthermore poor opsonization is afforded by IgA. However, secretory IgA operates in an environment which
contains innate humoral defense factors such as lysozyme, lactoferrin, and the lactoperoxidase system. Their anti-microbial activity is, in certain experimental models, potentiated by secretory IgA\textsuperscript{53}.

In humans, where IgA is the immunoglobulin isotype produced in largest quantities, further diversification has occurred with respect to molecular forms, distribution in body fluids, sites of production, antibody activity, and effector function. In these respects, the secretory and serum IgA systems display a considerable degree of independence (Table-3). However, in contrast to IgM, IgG and IgE, as an antibody isotype IgA does not utilize inflammatory pathways of antigen disposal. This is advantageous not only for elimination of exogenous antigens but also for interaction with endogenous antigens. Thus, the serum and secretory IgA systems must be viewed differently from other immunoglobulin isotypes\textsuperscript{53,74}. 