ROLE OF ALLERGY AND MUCOSAL INFLAMMATION IN NASAL POLYPS AND CHRONIC SINUSITIS

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ROLE OF ALLERGY AND MUCOSAL INFLAMMATION
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Conclusion

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Summary

Background: Nasal polyps and chronic sinusitis are closely related diseases commonly identified worldwide. Their etiology and pathogenesis are still incompletely understood.

Objective: To investigate the association between allergy and type of cellular inflammation in Asian patients with chronic sinusitis and/or nasal polyps.

Methods: Immunohistochemical staining with a panel of antibodies against CD4+ and CD8+ T cells, B cells, Langerhans cells, mast cells, eosinophils, neutrophils, and natural killer (NK) cells was performed to investigate the pattern of cell present in nasal polyp tissue/inflamed sinus mucosa and the paired middle turbinate from the same side, as well as in middle turbinate from allergic rhinitis and control patients. Serum specific IgE (sIgE) levels to common local allergens were tested using the ImmunoCAP system. A self-developed immunoarray dot blot system was used to evaluate the presence of sIgE against a total of 185 allergens in nasal polyp, chronic sinusitis, allergic rhinitis and nonallergic rhinitis patients. Western blot experiments on the most important antigen source identified using sera nasal polyps and chronic sinusitis patients, *Trichophyton rubrum*, was carried out. Proteins with the strongest antigenicity were characterized by Q-TOF™-MS/MS. The proteins were further purified by HPLC and sent for N-terminal sequencing. Sequence alignment to the NCBI Genebank was performed by using the BLAST algorithm.

Results: Cell scores were strongly correlated between the paired samples from nasal polyp patients. Nasal polyp and inflamed sinus mucosa showed a mixed cell pattern with significantly higher CD8+ T cells, eosinophils and neutrophils, a relatively
higher percentage of NK cell, and an inverse median ratio of CD4+ and CD8+ T cells, as compared to the middle turbinate from control patients. The dot blot system revealed that *Trichophyton rubrum* was the most important allergen in nasal polyp and chronic sinusitis patients. A 15 kD and 60 kD of *Trichophyton rubrum* IgE reaction was shown to have the strongest allergenicity by western blot. These proteins showed homology to a 35 kD heat shock protein (sti35) and 1, 3-β-glucanosyltransferase of *Fusarium spp*.

**Conclusion:** The similarity between the immunohistochemical cell pattern observed in nasal polyps and the paired middle turbinate suggested a diffuse mucosal inflammation. This is the first study that showed a combined inflammatory cell pattern in nasal polyps/inflamed sinus mucosa and adjacent middle turbinate, especially in Asian patients. This could explain the high recurrence rate of nasal polyps/chronic sinusitis, suggesting anti-inflammatory treatment of the adjacent mucosal is necessary in combination with a surgical removal of polyps/inflamed sinus mucosa. In addition to the well-recognized eosinophilic and neutrophilic inflammation in Caucasian studies, our study show for the first time that predominant infiltration of lymphocytes, especially CD8+ T cells and NK cells, may play a key role in the pathogenesis of nasal polyps and chronic sinusitis. Our study using the immunoarray system and western blot suggested that commercial allergen extracts, particularly fungi, need a much larger degree of standardization. Proteins from *Trichophyton rubrum*, i.e. proteins homologous to sti35 and 1, 3-β-glucanosyltransferase of *Fusarium spp.*, were for the first time shown to be highly
allergenic to nasal polyp and chronic sinusitis patients. Further studies on the interaction between these antigens and hosts with nasal polyps and chronic sinusitis will provide important information towards a better understand of the underlying pathogenesis. Vaccine development based on the recombinant proteins may be promising potential in the treatment of nasal polyps and chronic sinusitis.
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List of Abbreviations
AA: arachidonic acid
ABC: avidin-biotin complex
ABPA: allergic bronchopulmonary Aspergillosis
AD: atopic dermatitis
ADCC: antibody-dependent cellular cytotoxicity
AFS: allergic fungal sinusitis
AIDS: acquired immunodeficiency syndrome
AmphoB: amphotericin B
APCs: antigen presenting cells
AR: allergic rhinitis
ATPase: Adenosine triphosphate synthase
BAT: basophil activation test
bFGF: basic fibroblast growth factor
BFP: bombesin-flanking peptide
BLAST: Basic Local Alignment Search Tool
cAMP: cyclic adenosine monophosphate
CA: Candida albicans
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
CGRP: calcitonin gene related peptides
CHS/NP: chronic hyperplastic sinusitis with nasal polyposis
CO: Carbon oxide
COX: cyclooxygenase
CT: computed tomography
CTL: cytotoxic T lymphocytes
CRS: chronic rhinosinusitis
CS: chronic sinusitis
CSS: Churg-Strauss syndrome
Cys-LTs: cysteinyl leukotrienes
DAB: diaminobenzidine tetrahydrochloride
DCs: dendritic cells
DC-SIGN: dendritic cell-specific ICAM-grabbing non-integrin
DTH: delayed-type hypersensitivity
EAACI: European Academy of Allergology and Clinical Immunology
ECP: eosinophil cationic protein
ECRSH: European Community Respiratory Health Survey
EGF: epidermal growth factor
ER: oestrogen receptors
ESS: endoscopic sinus surgery
FESS: functional endoscopic sinus surgery
GM-CSF: granulocyte-macrophage colony-stimulating factor
GRO-α: growth-related oncogene-α
GPI: glycosylphosphatidylinositol
KGF: keratinocyte growth factor
kDa: kilo Dalton
HETES: hydroxyeicosatetraenoic acids
HLA: human leukocyte antigen
H2O2: hydrogen peroxide
HPLC: high-performance liquid chromatography
HRT: histamine release test
Hsps: heat shock proteins
ICAM-1: intercellular adhesion molecule-1
ICR: International Consensus Report
IDT: intradermal dilutional testing
Ig: immunoglobulin
IH: immediate hypersensitivity
IL: interleukin
IMS: Intercontinental Marketing Services
INF-γ: interferon gamma
iNOS: inducible nitric oxide synthase
IP-10: INF-γ inducible protein 10
ISAAC: International Study of Asthma and Allergies in Childhood
IU: international unit
LT: leukotriene
LPR: late phase reaction
LPS: lipopolysaccharide
LRT: leukotriene release test
MA: Malassezia furfur
MBP: major basic protein
MCP: monocyte chemotactic protein
MCS: modified specific IgE class system
MHC: major histocompatibility complex
MIP: macrophage inflammatory protein
MMP: matrix metalloproteinase
MRI: magnetic resonance images
Multi-CSF: multilineage colony-stimulating factor
MT-MMP: membrane type- matrix metalloproteinase
NARES: nonallergic rhinitis with eosinophilia
NCA: neutrophil chemotactic activity
NCBI, NIH: National Center for Biotechnology Information at the National Institutes of Health
NCF: neutrophil chemotactic factor
NF-kappa B: nuclear factor-kappa B
NK cell: natural killer cell
NO: nitric oxide
NOS: nitric oxide synthases
NPY: neuropeptide Y
OMC: ostiomeatal complex
OMU: ostiomeatal unit
ORs: odds ratios
PA: platelet factor
PAF: platelet-activating factor
PAR: persistent allergic rhinitis
PBS-TX: phosphate-buffered saline with 0.1% Triton X-100, pH7.4
PBS-T: phosphate-buffered saline with 0.05% Tween 20, pH7.4
PBMC: peripheral blood mononuclear cells
PCD: primary ciliary dyskinesia
PDGF: platelet-derived growth factor
PGE2: prostaglandin E2
PKC: protein kinase C
PMN: polymorphonuclear neutrophils
PNML: polymorphonuclear leukocytes
PR: progesterone receptors
Q-TOF™- MS/MS: Micromass Q-ToF Tandem Mass Spectrometer
RAST: radioallergosorbent test
sCD4: soluble CD4 receptor
sCD8: soluble CD8 receptor
SCF: stem cell factor
SEA: Staphylococcus enterotoxin A
SEB: Staphylococcus enterotoxin B
SI: leucocyte stimulation index
sICAM-1: soluble intercellular adhesion molecule-1
SP: substance P
SPECT: single photon emission computed tomography
SPSS: statistical package for the social sciences
SPT: skin prick test
TCR: T cell receptor
TFR: Task Force on Rhinosinusitis
TGF-α: transforming growth factor-α
TGF-β: transforming growth factor-β
Th1: T helper 1
Th2: T helper 2
TNF-α: tumor necrosis factor α
TRM: Trichophyton rubrum cell wall
Txs: thromboxanes
TSST-1: toxic shock syndrome toxin 1
VCAM-1: vascular adhesion molecular-1
VEGF: vascular endothelial growth factor
VIP: vasoactive intestinal peptide
VPF: vascular permeability factor
URI: upper airway infection
NP\(^1\), nasal polyp. CRS\(^2\), chronic sinusitis. NK\(^3\), natural killer cell.
Publications and Presentations at Conferences


Papers Submitted and in Preparation


(The results of the above studies have been presented at the American Academy of Otolaryngologic Allergy Foundation (AAOAF) Annual Meeting in September 2003. It received the Sam Sanders basic science award for 2003.)


Chapter 1. Nasal Polyps and Chronic Sinusitis: State of the Art

1.1 Anatomy and Physiology of the Nose

Paranasal sinuses and the nose cavity have important functions: olfaction, sensation, immunity, mucociliary clearance, filtration, warming and humidifying, nasal cycle and airflow dynamics. Understanding the anatomy of the nose is important for us in examining its physiology and related diseases, since the normal structure of the nose is important for proper ventilation and drainage.

The nasal cavity is divided into two parts by the nasal spectrum. The cribriform plate is the roof of the nasal cavity and separates it from the anterior cranial cavity. The inferior wall is the palate which separates the nasal cavity from the oral cavity. The superior, middle and inferior turbinates are bone projections lined with mucus membrane, and they form the lateral wall of the nose. They are considered to be the main nasal passages. Below the turbinates are the superior, middle and inferior meatus which are the openings beneath and lateral to the corresponding turbinate.

There are altogether four paranasal sinuses: the frontal, sphenoidal, maxillary and ethmoidal sinuses. Their anatomy is quite variable in a given population. The ethmoid sinus is the most complex one and is considered to be the center of paranasal sinuses. The ostiomeatal complex (OMC) is the area via which the maxillary sinus, anterior ethmoidal and frontal sinuses drain into the middle meatus. It consists of the maxillary infundibulum, frontal recess, ethmoidal bulla and middle meatus.
The protection role of the sinus is played by the mucociliary apparatus. The nasal cavity is efficient in the filtration of particles which are larger than 10 µm. However, those with a size of about 1 to 2 µm can pass through this filter. A microorganism entering into the sinuses will be propelled through the ostium and out in a mucuous blanket transported by the ciliary epithelium. The mucus is a watery secretion from epithelium goblet cell and mucosal glands. IgA is the major antibody present, together with also IgG and proteins. Anatomic abnormalities or inflammation in this area will cause obstruction of the drainage from the sinuses.

![Figure 1. Lateral wall of the nose. Sphenoid, middle and inferior turbinates are shown in the figure.](Adjusted from Jones N. et al. The nose and paranasal sinuses physiology and anatomy. Advanced Drug Delivery Reviews, 51 (2001); 5-19.)

From the view of the ultrastructure, the nostrils are covered by skin whereas one third of the anterior nasal cavity is covered by the epithelium which has a typical airway structure. The pseudostratified columnar ciliated mucus membrane is continuous with the sinuses and the pharynx. The function of sinonasal mucosa is considered to be a physical-chemical barrier which plays an important role in the defense of the nasal airway. Under the epithelium is the basement membrane which is a layer of
collagen fibrils. The submucosa (lamina propria) is loose connective tissue which consists of blood vessels, submucosal glands and various types of cells, such as macrophages, fibroblasts, lymphocytes, plasma cells. Lymphocytes are the major type of cells. In normal conditions, T cells exist with B cells in a ratio of 3:1, and there are two to three times as many CD4+ T cells as there are CD8+ T cells.\(^5\) The mast cell is also considered a residential inflammatory cell in normal nasal mucosa.\(^6\) In a pathological condition, the number and status of the host cells may change, as well as the infiltration of neutrophils and eosinophils in nasal mucosa.

1.2 Prevalence of Nasal Polyps and Chronic Sinusitis

Chronic sinusitis is one of the most common chronic diseases reported worldwide. It is closely related to nasal polyps, as 20% of the patients with chronic sinusitis have nasal polyps while the incidence rate of chronic sinusitis in nasal polyps varies from 65% to 90%.\(^7\)-\(^9\) The multitude of factors underlying these conditions and their high recurrence rate makes the treatment of chronic sinusitis and nasal polyps complicated. Understanding the pathogenesis of nasal polyps and chronic sinusitis is critical for treatment.

1.2.1 Nasal Polyps, a Disease with a Long History

Nasal polyps represent one of the most common mass lesions of the nose. It is an outgrowth of nasal mucosa whose appearance is smooth, semitranslucent, gelatinous and pale (\textit{Figure 2}). Polyps with more blood vessels appear to be more pink. Most of
them are benign, inflammatory tissues\textsuperscript{10} and they were first described 4000 years ago in ancient Egypt.\textsuperscript{11} A rhinologist named Ni-Ankh Sekhmet in ancient Egypt treated King Sahura’s nostril disease for what appears to be nasal polyps. In ancient Egypt people described nasal polyps as ‘grapes coming down from the nose’.\textsuperscript{12} They treated them with medicine containing alcohol and surgical instruments were used to remove nasal polyps.

\textbf{Figure 2.} Left nasal polyps.\textsuperscript{13} They are smooth, semitranslucent, gelatinous and pale. (From http://home.hawaii.rr.com/dochazenfield/images/nasal_polyposis2.jpg).

There were some very interesting cases and theories in the history of nasal polyps. Forestus recorded in 1591 the case of a woman who had huge nasal polyps caused by frequently carrying heavy goods on her head.\textsuperscript{14} He thought it was the weight that forced the mucus downwards. Later it was realized that nasal polyps were mainly benign tumors although some of them were malignant. Paget first classified nasal polyps as fibrocellular tumors in 1854. Then in 1863 Virchow considered them as a kind of myxoma. With the increased numbers of neoplastic surgeries, people were
able to look into the pathology of nasal polyps. Zuckerkandl reported in 1882 that the nasal polyps of all of the 39 patients in his study had originated from the middle meatus and were mainly found around the edges of the hiatus semilunaris. The polyps were characterized as ‘catarrhal inflammation’ and he suggested that the edematous mucosa hung down due to its weight and its own blood supply caused it to increase further.

As endoscopy became a popular method for the investigation and treatment of nasal polyps, it became possible to more accurately establish the origins of nasal polyps. There is disagreement on whether nasal polyps originate from the nasal mucosa or from the ethmoid cells. Most studies reported that they originate from the nasal mucosa, especially the middle meatus.\textsuperscript{15,16} The inferior turbinate is not considered to be the origin of nasal polyps. The unique structure of the nose may contribute to this phenomenon. Messerklinger et al. suggested that in the place where two mucosa were in direct contact, disruption of the mucociliary clearance occurred, leading to infection and inflammation.\textsuperscript{3} In the anatomy of the nose, the narrow cleft of the middle meatus and ethmoids are the most probable areas of mucosa contact. It has been suggested that they are the most common places from which nasal polyps originate.

1.2.2 Prevalence of Nasal Polyps

Studies have reported that the prevalence of nasal polyps in the Caucasian population
varies from 1% to 4.3%.\textsuperscript{15,17-20} The incidence ratio of males to females is in the range of 1.2 to 3.\textsuperscript{18,21-23} The incidence rate of nasal polyps in the population may increase with age and the peak is at 50 to 60 years old.\textsuperscript{21,22} Compared to the prevalence in adults, childhood nasal polyps are relatively rare and have a close relationship with asthma and cystic fibrosis.\textsuperscript{24,25} The highest incidence of 4.3% was reported by Hedman et al.\textsuperscript{17} who did a survey in Finland in 1999 on 4300 randomly selected patients from 18 to 65 years old. The latest survey was reported by Johansson et al.\textsuperscript{18} involving 1900 randomly selected residents over 20 years old in Sweden in 2003. Nasal polyps were found in 2.7% of them. The ratio of males to females was 2.2:1 and 5% of patients were over 60 years old. Epidemiology data are lacking in Asian populations. Min et al.\textsuperscript{26} reported that the incidence of nasal polyps in Korea was 0.5%, based on a nationwide survey of 10,054 subjects. Whether the great difference in the prevalence is due to the various populations studied is unknown. Diagnosis may play a partial role as many nasal polyp patients do not have symptoms. Diagnosis can only be made after endoscopic examination.

Nasal polyposis is a multifactorial disease which relates to many other diseases such as sinusitis, asthma, aspirin intolerance and cystic fibrosis. The epidemiology of nasal polyps will be discussed further in \textbf{chapter 1.3}.

\textbf{1.2.3 Prevalence of Chronic Sinusitis}

Generally speaking, sinusitis is inflammation of paranasal sinuses. Because of the
high frequency of coexistence of inflammation of the nasal cavity, it has also been suggested that the term “rhinosinusitis” should replace the term “sinusitis”. Lanza et al. in 1997 suggested a broader definition of sinusitis, including inflammation of the nasal cavity and paranasal sinuses and of the fluid within these cavities and/or the underlying bone. Sinusitis can be classified into acute, recurrent, subacute and chronic sinusitis which will be briefly introduced in chapter 1.4.

Chronic sinusitis is one of the most common chronic diseases reported worldwide although its prevalence may vary from region to region. Its prevalence and incidence rate keeps on increasing, thus accounting for high medical expenditures and absence from work. Adams et al. reported in 1995 that 15% of Americans under 45 years old had symptoms of chronic sinusitis. The estimated prevalence of sinusitis in Europe varies from 10% to 40%. Kaniler et al. reported that compared to 50 million restricted activity days per year because of sinusitis from 1986 to 1988, the rate increased almost half to 73 million restricted activity days per year from 1990 to 1992. Intercontinental Marketing Services (IMS) reported that acute sinusitis was diagnosed 6.3 million times, whereas chronic sinusitis was diagnosed 2.6 million times from July 2000 to June 2001 in Germany. The prevalence of sinusitis in children is relatively higher than in adults because they are prone to have more upper airway infection (URI) which is the initiation of acute sinusitis. Gordts et al. reported in 1997 that in 100 non-ENT children, the prevalence of sinusitis signs on magnetic resonance images (MRI) was 45%. In addition to the reports in Caucasians, Min et
al.\textsuperscript{26} reported in 1996 that the incidence of chronic sinusitis in Korea was 1.01% and there was no difference between age groups or between sexes. Goh et al.\textsuperscript{33} reported that the incidence of sinusitis in primary school children in Singapore was 4.3%. Because of the limited information coming from epidemiology in Asian populations, whether the various incidence rates indicate genetic contribution or are due to other factors such as the environment, is unknown. The standard of diagnosis may also affect the estimated prevalence.

1.3 Nasal Polyps and Chronic Sinusitis: Multi-factorial Diseases

Nasal polyps and chronic sinusitis are both multi-factor diseases and are associated with many other diseases. The etiology factors of nasal polyps and chronic sinusitis are similar, such as correlations with asthma, rhinitis, cystic fibrosis, Kartagener’s syndrome, Young’s syndrome etc. For diagnosis and treatment, special attention must be paid to the underlying etiology factors.

1.3.1 Diseases Related with Nasal Polyps

Diseases and syndromes reported to be related with nasal polyps are shown in Table 1. In summary, diseases related with nasal polyps are: upper airway diseases, such as sinusitis, allergic fungal sinusitis (AFS) and rhinitis; lower airway diseases, such as asthma, cystic fibrosis and Kartagener’s syndrome; systemic diseases, such as aspirin intolerance and immunodeficiency. In this section, diseases related to the presence of nasal polyps will be reviewed with a special attention to incidence rates and proposed
mechanisms.

### Table 1. Diseases related with the presence of nasal polyps.\(^{34}\)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency (%)</th>
</tr>
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<tbody>
<tr>
<td>Aspirin intolerance</td>
<td>36</td>
</tr>
<tr>
<td>Adult asthma</td>
<td>7</td>
</tr>
<tr>
<td><strong>Intrinsic asthma</strong></td>
<td>13</td>
</tr>
<tr>
<td><strong>Atopic asthma</strong></td>
<td>5</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>2</td>
</tr>
<tr>
<td><strong>Nonallergic rhinitis</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>Allergic rhinitis</strong></td>
<td>1.5</td>
</tr>
<tr>
<td>Childhood asthma/rhinitis</td>
<td>0.1</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>20</td>
</tr>
<tr>
<td>Churg-Strass Syndrome</td>
<td>50</td>
</tr>
<tr>
<td><em>(Asthma, fever, eosinophilia vasculitis and granuloma)</em></td>
<td></td>
</tr>
<tr>
<td>Allergic fungal sinusitis</td>
<td>85</td>
</tr>
<tr>
<td>Kartagener’s syndrome</td>
<td>?</td>
</tr>
<tr>
<td><em>(Bronchiectasis, sinusitis, situs inversus)</em></td>
<td></td>
</tr>
<tr>
<td>Young’s syndrome</td>
<td>?</td>
</tr>
<tr>
<td><em>(Sinopulmonary disease, azoospermia)</em></td>
<td></td>
</tr>
</tbody>
</table>


### I. Asthma

Asthma is characterized by enhanced responsiveness which is also known as bronchial hyperresponsiveness to various stimuli, including cold air, exercise and irritants such as methacholine or histamine. A hyperresponsiveness test is important for the diagnosis. The presence of airway inflammation is another criterion.
Asthma is a common chronic respiratory disease. The incidence of asthma has risen worldwide since the 1970’s, especially in developed countries. The European Community Respiratory Health Survey (ECRSH) defines asthma as the situation of “having an attack of asthma in the last 12 months and/or currently taking medicine for asthma”. According to the report of ECRSH in 2001, the prevalence of asthma in 22 countries ranges from 2% to 11.9% with the highest prevalence in developed countries such as Australia, New Zealand, United States, Ireland and the United Kingdom. In Singapore, the prevalence of asthma was 3% to 5.5% in children from 4 to 17 years old in 1967. In 1994, the incidence in the age group between 6 to 14 years old rose to 19.5%. The incidence of adult asthma was reported to be 2.4% among males and 2.0% among females. Besides genetic predisposition, environmental exposure, as well as the situation of medical care may be important factors contributing to asthma. For example, in Singapore, asthma is more common among Malaysians and Indians than among Chinese. The higher incidence may be due to the habit of keeping carpets and reluctance to receive medication.

Nasal polyp is a common disease related to asthma. It has been reported that 7-15% of asthmatic patients had nasal polyps, most commonly those above 50 years old. Another study reported a much lower incidence of 4.8%. Among nasal polyp patients visiting allergy clinics, the incidence rate of asthma is about 71% to 72%. Generally, nasal polyp patients visiting ENT departments had an incidence rate of asthma of 29.9%. According to reports, 22% to 33% of the patients developed nasal
polyps first whereas 53% to 88% of the patients developed asthma first.³⁹ Male nasal polyp patients are less prone to develop asthma than females. Although in a study by Rugina et al.’s²³ of 224 nasal polyp patients, the incidence rate of asthma was 45% without sex differentiation. Females had more major and severe asthma than males.

It was also suggested that nasal polyps were present more frequently in patients with nonallergic respiratory disease than in patients with allergic respiratory disease. Settipane et al.¹² reported in 1977 that the incidence rate of nasal polyps in asthma patients was 6.7%. In addition, nasal polyps were more common in non-atopic patients who had negative skin test. Grigoreas et al.⁴⁰ in 2002 studied 3817 patients in Greece and reported that the prevalence of nasal polyps was 13% in patients with nonallergic asthma and 2.4% in patients with allergic asthma.

The pathological mechanism underlying the correlation of upper and lower airway diseases is not yet clarified. Hypersensitivity to multi stimuli, for example, allergens, virus infection, cold air etc., is taken as the main pathogenesis in asthma. The nasal cavity has the basic function of warming, filtering and humidifying what has been breathed, thereby reducing the irritation to the lower airway significantly. The fact that most patients have onset of asthma earlier than nasal polyps suggests that environmental factors may not be that important in the pathogenesis of asthma. The theory of systematic mediators has arisen, suggesting that asthma may be not a local but a systemic disease.⁴² Asthma, eczema and allergic rhinitis, are classically taken as
Atopic diseases with close association. Almost 40% of the patients with allergic rhinitis have concomitant asthma while 80% to 95% of the asthmatic patients have allergic rhinitis. Atopic dermatitis may initiate a systemic allergic response and lead to asthma and allergic rhinitis. The systemic changes in atopic patients may account for coexistent diseases in the upper and lower airways.

II. Aspirin intolerance

Aspirin intolerance is characterized by acute bronchial spasm, rhinorrhea, ocular injection or acute urticaria/angioedema occurring within three hours after ingesting aspirin. In 1968, Samter and Beers elaborated the symptom with correlated aspirin intolerance, bronchial asthma and nasal polyps (rhinosinusitis), which was subsequently named “Samter’s syndrome”. The symptom was reported to be more common among middle aged women. Settipane et al. in 1977 defined the similarities between nasal polyps and aspirin intolerance which are shown in Table 2.

Table 2. Similarities between nasal polyps and aspirin intolerance.

<table>
<thead>
<tr>
<th></th>
<th>Aspirin Intolerance (ASA Into.)</th>
<th>Nasal Polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with tetrad of ASA Into.,</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Asthma, Nasal Polyps and Sinusitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased freq in older age group</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mediated by IgE</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Familial occurrence</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Eosinophil in nasal smear</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Elevated total eosinophil count</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pathogenetic mechanisms related to leukotrienes</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>Associated with other disease beside asthma and sinusitis</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

A high incidence rate of nasal polyp occurrence in subjects with aspirin intolerance has been suggested, ranging from 36% to 96%. Other studies have reported much lower incidence rates. For example, Moloney et al. reported in 1977 that of the 445 nasal polyp patients, the incidence rate of Samter’s syndrome was 2%. Larsen et al. in 1997 reported that the average incidence rate of aspirin intolerance in nasal polyp patients visiting the ENT department was 12.8%. However, according to a recent study by Johansson et al. in 2003, no correlation between symptoms of subjective aspirin intolerance and nasal polyps could be found in a study of a Swedish population.

Although in reports aspirin intolerance has been correlated with allergy and a local increased IgE level, again, it has been suggested that atopy did not contribute to the development of nasal polyps. Hamilos et al. reported that aspirin sensitivity was strongly correlated with nonallergic chronic hyperplastic sinusitis with nasal polyposis (CHS/NP) in which a nonallergic cytokine profile was identified.

Mechanisms underlying nasal polyp development in aspirin intolerance patients have not been clarified yet. Genetic contribution was suggested in some studies. Mullarkey et al. investigated HLA patterns in patients with Samter’s syndrome as well as those with asthma alone and controls. A significant increase in HLA-DQw2 (relative risk, 4.06) was found only in the Samter’s syndrome group. Another theory suggested is that in aspirin intolerant patients with nasal polyps, aspirin exposure
would increase the release of leukotrienes from nasal polyps and the inhibition of
eosinophil apoptosis.\textsuperscript{57} Settipane et al.\textsuperscript{58} reported in 1991 that in aspirin intolerance
patients with nasal polyps, aspirin inhibited the cyclooxygenase pathway and induced
the lipoxygenase pathway, thus causing an increased production of leukotrienes
including LTC-4, LTD4 and LTE4. These leukotrienes may produce bronchospasm,
airway mucosa edema and increased responsiveness, mucus hypertension and
increased neutrophils and eosinophils in exudates. The overproduction of LTC4-E4,
together with an increased local IgE level and eosinophilia was evidenced in nasal
polyp patients with asthma and aspirin intolerance.\textsuperscript{51} Other mechanisms mentioned in
the association between nasal polyps and aspirin intolerance include low production
of antiinflammatory prostaglandin E2 (PGE2) due to COX-1 and COX-2
inhibition,\textsuperscript{59,60} and a significantly higher level of inducible nitric oxide synthase
(iNOS) activity in Samter’s symptom patients compared with nasal polyp patients
without aspirin intolerance.\textsuperscript{61}

\section*{III. Chronic sinusitis and allergic fungal sinusitis (AFS)}

Chronic sinusitis is a common disease which is closely associated with nasal polyps.
The prevalence and diagnosis of chronic sinusitis are discussed in chapters \textbf{1.2} and
\textbf{1.4}, respectively. Settipane et al.\textsuperscript{9} reported that the incidence rate of nasal polyps in
conjunction with chronic sinusitis was 20\%. On the other hand, the percentage
occurrence of chronic sinusitis in nasal polyp patients is much higher. Bunnag et al.\textsuperscript{7}
reported that 90\% of 57 nasal polyp patients had definite pathological changes on
their sinus X-rays, while another study reported an incidence rate of 65%. It was also suggested that chronic sinusitis had a higher incidence rate of nasal polyps in the Asian than the Caucasian population due to smaller nasal passages.

The terms of ‘purulent’ and ‘hyperplastic’ are used to differentiate between two types of maxillary sinusitis due to infection or inflammation. The former type is caused by bacterial or perhaps a subsequent viral infection. The latter type involves a hypersecretion of mucus and is often found in nasal polyp patients. Hamilos et al. reported that CHS/NP was one of the most common indications for sinus surgery among the 200,000 sinus surgeries done in the US in 1994.

Although the coexistence of nasal polyps and sinusitis is commonly found, it is not clear whether sinusitis predisposes for nasal polyps or results from it. Polyps may block the OMU (ostiomeatal unit) and disrupt normal ventilation, giving rise to a risk factor for the infection of the sinuses. On the other hand, the persistent irritation caused by a sinus infection may contribute to enlargement of the nasal polyps. Araujo et al. reported that 80% out of 114 patients with chronic sinusitis had the same pathogens in the middle meatus and maxillary sinus, suggesting an underlying correlation between diseases in the two locations. Whether the coexistence of the two diseases is due to physical or immunological factors can be established after further studies.
Allergic fungal sinusitis (AFS) is a benign noninvasive sinus disease related to a hypersensitivity reaction to fungus. It accounts for 2% to 10% of the patients with chronic sinusitis who required sinus surgery. Safirstein et al. were the first to note in 1976 the clinical similarity between the combination of nasal polyposis, crust formation, and sinus cultures yielding *Aspergillus* and allergic bronchopulmonary Aspergillosis (ABPA). Then in 1981, AFS was described by Millar as a distinctive clinical and histopathologic entity. Katzenstein et al. reported that 7 (5.9%) out of 119 chronic sinusitis patients had septate fungal hyphae which was identified as the *Aspergillus* species in their specimen, and he named it ‘allergic Aspergillus sinusitis’. In subsequent studies it was found that *Dematiaceous* fungi (*Bipolaris, Exserohilum, Curvularia, and Alternaria* etc.) played a more important role in etiology of AFS than *Aspergillus*. The term ‘allergic Aspergillus sinusitis’ was then renamed ‘allergic fungal sinusitis’.

AFS is more common in adolescents and young adults. Besides chronic sinusitis, AFS correlates with many other diseases. According to reports, more than two thirds of AFS patients have allergic rhinitis. 50% of AFS patients have asthma but no linkage exists with aspirin intolerance. Nasal polyps are frequently found in AFS with a high incidence rate from 75% to 100%. As regards the prevalence of AFS, it is suggested that AFS is more common in temperate regions with high humidity, and there is a remarkable variation in the incidence rates in different locations. Also, there is no sexual or ethnic predilection for the prevalence of AFS.
AFS is difficult to diagnose. Besides many symptoms of the nose and of the adjacent affected areas, typical symptoms of AFS include immunosuppression, atopy and chronic sinusitis refractory to medical therapy. Increased specific IgE to one or more fungal allergens is found in 90% of patients.\textsuperscript{72,75-77} Total IgE levels may also increase to as high as 1000 IU/ml. AFS patients are often allergic to multiple fungal allergens as well as many nonfungal allergens.\textsuperscript{78} However, nowadays, commercial IgG and IgE antibodies are limited to a small number of allergens. Thus, the role of allergy in AFS may be underestimated. The allergy tests will be discussed further in chapter 4.

Histologically, AFS is characterized by thick mucin with dense collections of degenerating eosinophils and Charcot-Leyden crystals (allergic mucin). Although a fungal culture of allergic mucin has been suggested, a variable yield from 6% to 93% has been reported.\textsuperscript{74,79-81} In the diagnosis of AFS, it was suggested that a combination of CT scan with MRI was highly specific for AFS.\textsuperscript{73}

Kupferberg et al.\textsuperscript{82} in 1998 suggested the following criteria for the diagnosis of AFS,

(1) Type I hypersensitivity confirmed by history, skin tests or serology;

(2) Nasal polyposis;

(3) Characteristic CT scan;

(4) Eosinophilic mucus without fungal invasion into the sinus tissue;

(5) Positive fungal stain of sinus contents.

The criteria of the AFS diagnosis has been revised by the Mayo Clinic as follows,
chronic sinusitis and the presence of allergic mucin with a fungal organism confirmed by histology or culture.\textsuperscript{83}

The mechanism of AFS remains controversial and will be further discussed in \textbf{chapter 5}. The recurrence rate of AFS ranges from 10\% to 100\% as a consequence of the poorly understood pathogenesis.\textsuperscript{84,85} Long-term treatment and follow-up are necessary.\textsuperscript{73}

\textbf{IV. Nonallergic rhinitis with eosinophilia (NARES)}

Rhinitis is characterized by the inflammation of the membrane lining the nose. Many patients with sinusitis associated with nasal polyps have a long history of perennial rhinitis. Symptoms of rhinitis include nasal itching, rhinorrhea and/or nasal congestion. According to the initiation of allergy, rhinitis is classified into allergic and nonallergic rhinitis. It has been reported that the incidence rate of nasal polyps in allergic rhinitis is only 1.5\%.\textsuperscript{12} Nasal polyps are more commonly found in patients with nonallergic rhinitis. In clinics, skin prick tests and tests of peripheral blood for elevated immunoglobulin E against specific allergens are often used for diagnosis. However, it has been suggested that nonallergic rhinitis patients may have positive results to irrelevant inhalant allergens.\textsuperscript{86}

The incidence rate of chronic rhinitis in the population is at a worldwide high but varies strongly among specific populations. The prevalence of allergic rhinitis ranges
from 9% to 42%. It has been estimated that about 44% of the allergic rhinitis cases coexist with nonallergic rhinitis, the occurrence being named “mixed rhinitis”. In adults and females, nonallergic rhinitis and mixed rhinitis are more common than allergic rhinitis. They are also prone to be perennial rather than seasonal.

Vasomotor rhinitis is the most common form of nonallergic rhinitis, followed by nonallergic rhinitis with eosinophilia (NARES). These patients showed no evidence of immunologic nasal disease, no precipitant antibodies, and no demonstration of associated respiratory pathology. However, nasal eosinophilia could be identified. A skin prick test was negative in these patients with no increased specific serum IgE. There was also a negative history for allergen induced exacerbation. These patients often have nasal polyps and are more refractive to medical therapy. The pathogenesis and etiology of NARES is poorly defined. Moneret-Vautrin et al. reported in his study that 7 (13.5%) out of 42 patients with perennial rhinitis had NARES and four of them had nasal polyps. The author suggested that NARES was a precursor to nasal polyps, asthma and aspirin intolerance. Many factors may increase the risk of recurrent infection which may predispose to nasal polyps. An autonomic nervous system dysregulation with a predominating adrenergic hyperreactivity may play an important role in the pathogenesis. Inflammatory effects of local release of neurotransmitters, and eosinophilia regulation by chemical mediators contributed to the inflammatory state. Toxic substances released by eosinophil, such as major basic protein (MBP) and eosinophil cationic protein (ECP), can cause epithelium damage.
and result in a prolonged mucociliary clearance.\textsuperscript{93-98}

V. \textit{Cystic fibrosis (CF)}

Cystic fibrosis (CF) is the most common lethal genomic dysfunction and an autosomal recessive disease in Caucasian children. The incidence of CF varies among different populations. In Caucasian people, the incidence of cystic fibrosis is about one in 2000 live births. However, this disease is rare in Asian and African people in which the incidence is as low as one in 100,000. Patients have a median survival expectation of 30 years of age.\textsuperscript{99}

CF is associated with a defective gene regulating chloride transport in epithelial cells located in the long arm of chromosome 7. This affects the position of the apical membrane-bound protein-cystic fibrosis transmembrane conductance regulator (CFTR). CFTR plays an important role in electrolyte and water transport through the respiratory epithelial cells. Decreased chloride transport leads to accumulation of mucus secretion primarily in the respiratory and gastrointestinal systems.

The diagnosis of CF includes pancreatic enzyme deficiency with malabortion, chronic progressive obstructive pulmonary disease, chronic pulmonary infection with \textit{Staphylococcus aureus, Pseudomonas aeruginosa} or both, and abnormal electrolyte loss in sweat. Recurrent chest infection and sinusitis are universal symptoms in CF patients, although some studies reported a much lower incidence.\textsuperscript{100} This may be due
to a weakened function of physical protection caused by a thickened mucus blanket. The incidence rate of nasal polyp cases in CF varies from 6% to 48%.\textsuperscript{100} It has been reported that 50% of nasal polyp patients within 4 to 16 years old had CF.\textsuperscript{101} Therefore, children with nasal polyps have to be carefully tested for CF. The incidence rate of nasal polyps in adult CF patients varies from 20% to 37%.\textsuperscript{9,102} Most of these patients have multi or bilateral nasal polyps. In addition, the recurrence of nasal polyps in patients with CF is higher than in those without CF.

The pathogenesis of nasal polyp formation in CF patients is not clear. Besides the factor of decreased local protection, genetic factors have also been suggested. Dotsch et al.\textsuperscript{103} reported a reduction of the neuronal and inducible nitric oxide synthase gene expression in CF patients with nasal polyps. That reduction may disturb the barrier against infective agents already present at the site of the entrance. Jang et al.\textsuperscript{104} suggested that CFTR had a heterogeneous pattern of localization in patients with nasal polyps. However, Cimmino et al.\textsuperscript{105} reported that there were no genotype differences in CF patients with or without nasal polyps. The genetic factors contributing to the occurrence of nasal polyps in CF patients need to be clarified.

Another theory was suggested by Bernstein et al.\textsuperscript{106} who pointed out three defects in CF patients: first, the classical cyclic adenosine monophosphate (cAMP)–controlled chloride channel due to the defect in the CFTR gene; second, an increased number of open sodium channels; and third, an increased number of ATPase dependent
sodium/potassium pumps at the basal lateral surface of the respiratory epithelial cell. These defects lead to decreased chloride transport and increased sodium absorption. Finally, there is mucus dehydration and water retention in lamina propria. These factors may contribute to the formation of nasal polyps.

**VI. Primary ciliary dyskinesis (Kartagener’s Syndrome)**

Kartagener’s syndrome is a rare primary ciliary dyskinesia (PCD) syndrome with an incidence in 1/20,000 births. Symptoms of Kartagener’s syndrome include bronchiectasis, situs inversus and sinusitis. Nasal polyps have also been reported in these patients. The diagnosis is based on an abnormal ciliary beat frequency, accompanied by specific abnormalities of the ciliary axoneme. It has been suggested that the mode of inheritance of PCD is autosomal recessive.

There may a number of ultrastructural defects responsible for the abnormal ciliary beat patterns in patients with PCD. However, a study in Hong Kong reported that the ultra structure can be normal in the patients. The contribution of nitric oxide has been recently pointed out. Noone et al. investigated 78 patients of primary ciliary dyskinesia and found, besides 100% cilia structure defects, a low nasal nitric oxide production in all patients. In another study by Wodehouse et al., the nasal nitric oxide production was significantly lower in PCD, as compared with that of normal controls, idiopathic bronchiectasis, CF, lone sinusitis and Young's syndrome. These factors may result in an increased susceptibility to infection.
VII. Churg-Strauss Syndrome (CSS)

Churg-Strauss syndrome (CSS) is a vasculitis. The six criteria set in 1990 in the diagnosis of CSS are asthma, neuropathy (mono or poly), 10% peripheral blood eosinophilia, pulmonary infiltrates, paranasal sinus abnormalities, and extravascular eosinophils. Patient is diagnosed as having CSS if at least four of these six criteria are positive.

A survey in a French urban multiethnic population reported a incidence of 10.7 per 1,000,000 adults.\textsuperscript{113} Cases reported in Asian populations are rare.\textsuperscript{114-117} About 50% of CSS patients have nasal polyps.\textsuperscript{9,118} Although eosinophilia of blood and tissues is the common feature in CSS, the underlying mechanism is not clarified yet.\textsuperscript{119} Inhibition of CD95-mediated apoptosis by soluble CD95 may prolong eosinophil survival.\textsuperscript{120} In addition, T lymphocytes derived cytokines may contribute to eosinophil activation. In recent years, with the application of leukotriene-modifiers in the treatment of asthma, there have been reports on the manifestation of CSS through an unknown mechanism when the leukotriene modifiers permit corticosteroid doses to be reduced.\textsuperscript{121,122}

VIII. Young’s Syndrome

Young’s Syndrome is characterized by recurrent respiratory infection, azoospermia due to bilateral epididymal obstruction and nasal polyposis/sinusitis. It is also responsible for 7.4% of male infertility.\textsuperscript{34} Its incidence is higher than that of CF or Kartagener’s syndrome but the disease is less severe than either of them. Although
cases have been reported in Japan, it has been suggested that the syndrome is very rare in Asia, as compared to Caucasian populations.\textsuperscript{123,124} Studies in China have also reported a low incidence.\textsuperscript{125} Young’s syndrome is not a primary ciliary dyskinesia disease. Normal sweat chloride value, pancreatic function and ciliary ultrastructure can differentiate it clearly from CF and primary ciliary dyskinesia which have ciliary dysfunction or abnormality of mucus secretion. Abnormality of mucociliary transport which causes decreased clearance is common in patients with Young’s syndrome.\textsuperscript{126}

\textit{IX. Woakes syndrome}

Woakes syndrome was first mentioned by Edward Woakes in 1885, when he reported nasal polyps associated with ‘necrosing ethmoiditis’. Nowadays, that syndrome is defined as a rare autosomal recessive disorder of bony nasal deformation, associated with recurrent bilateral nasal polyposis, which is found both in adults and children.\textsuperscript{127} However, a genetic mutation in the disorder has not been identified yet.

\textit{X. Sarcoidosis}

Sarcoidosis is a multisystem disease characterized by the presence of granulomas, which are small areas of inflamed cells. It is more common in African Americans than in Caucasians, and with a major age group from 20 to 40 years of age. Most commonly affected areas are lung and lymph nodes. About 1\% of the patients with sarcoidosis had involvement of nasal mucosa also.\textsuperscript{128} There have been several studies reported of nasal polyps with sarcoidosis.\textsuperscript{129-131} However, symptoms in patients may
be so minor, as to go unreported. The mechanism underlying sarcoidosis is not clear yet. It is considered to be a disorder of the immune system or may be also caused by infection of virus, or exposure to toxins or allergens.

1.3.2 Diseases Related with Chronic Sinusitis

Like nasal polyps, chronic sinusitis is not an isolated disease and has been linked to many diseases. Its epidemiological behavior is quite similar to that of nasal polyps, with reported etiology factors like allergic and non allergic rhinitis, asthma, nasal polyps, cystic fibrosis, aspirin sensitivity, immunodeficiency, immotile cilia syndrome, Down syndrome, Young’s syndrome, chronic otitis media, septal deviation, foreign body tumors, trauma, barotraumas, airway infection, dental infection, idiosyncratic reaction to drugs, exposure to smoking, choanal atresia, cleft palate, nasal obstruction, adenotonsillar hypertrophy/infection, etc. In this section, we will review the diseases related with chronic sinusitis in a summary. Table 3 shows the factors related to the occurrence of chronic sinusitis. Basically, it is associated with environmental factors, or local factors which may change the normal physiology of sinuses and systemic diseases. The proposed underlying mechanisms giving rise to these diseases are similar to the mechanisms causing nasal polyps.

I. Asthma

The linkage between chronic sinusitis and asthma has been suggested from clinical data. Many studies have reported an incidence rate from 40% to 70% of the
radiographic findings of sinus abnormalities, i.e., mucosal thickening, air fluid levels, and total opacification of the paranasal sinuses in patients with asthma.\textsuperscript{132-136} This finding is common both in children and adults. Zimmerman et al.\textsuperscript{137} reported a significant difference in the incidence rate of radiographic sinus abnormalities, 31.2\% in 138 children with asthma, as compared to 0\% for that of controls. They did not find any correlation between sinus abnormality and severity of asthma. In the investigation of sinus involvement in acute asthma, Rossi et al.\textsuperscript{138} reported a high incidence rate of 87\% in radiographic findings of sinus abnormalities in 149 acute asthmatic patients. However, Crater et al.\textsuperscript{139} only reported an incidence rate of 29.2\%. The incidence rate was significantly higher than that of the control group (3.2\%) and had significant correlation with mucosal thickening in the nasal passages, ostiomeatal complexes, ethmoidal and sphenoidal sinuses but not maxillary mucosal thickening.

Both medical and surgical treatments of chronic sinusitis are found to be helpful in the improvement of asthma symptoms or reducing the use of medication.\textsuperscript{140-144} Crater et al.\textsuperscript{139} reported that 11 out of 13 asthmatic patients showed improvement of the CT score of the sinus without any special treatment of the sinus, suggesting that controlling asthma is also helpful in improving the condition of the sinus. Sinusitis usually precedes asthma.\textsuperscript{8} It has been proposed that sinusitis may contribute to asthma by means of three mechanisms: bacteria entering the pharynx from infected sinuses; increased hypersensitivity of the bronchial tree due to an enhanced $\beta$-adrenergic blockade; and reflex bronchospasm through the parasympathetic nervous system.\textsuperscript{8}
Recent studies have also suggested that the decreased level of nitric oxide in the upper airway may increase bronchial hypersensitivity.\textsuperscript{145}

**Table 3. Etiologic factors of chronic sinusitis.**\textsuperscript{146}

<table>
<thead>
<tr>
<th><strong>Infectious</strong></th>
<th>Viral, bacterial, fungal</th>
</tr>
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</table>
| **Local factors** | Craniofacial anomalies:  
\textit{choanal atresia, cleft palate, velopharyngeal insufficiency}  
Nasal obstruction  
\textit{Allergic/nonallergic rhinitis, polyps, foreign bodies, nasogastric tubes, adenoid infection, tumors, rhinitis medicamentosa}  
Trauma  
\textit{barotrauma}  
Local infections  
\textit{Dental infection}  
Prior surgery  
Anatomic variations/aberrations  
\textit{Septal deviation, concha bullosa, Haller’s cells, Paradoxic middle turbinate, atelectatic maxillary sinus, prominent ethmoid bulla}  
Ciliary dyskinesias  
\textit{Kartagener’s syndrome} |
| **Systemic factors** | Asthma, cystic fibrosis, allergic fungal sinusitis |
| **Immune deficiencies** | Congenital  
\textit{Selective antibody deficiency (IgA/IgG subclass deficiency), common variable immune deficiency, vaccine hyporesponsiveness, C4 deficiency, X-linked agammaglobulinemia, Ataxia-telangiectasia, Hyper-IgM syndrome, Hyper-IgE}  
Acquired  
\textit{HIV/AIDS, organ transplant/cancer’s chemotherapy} |
| **Environmental factors** | Air pollution (cigarette smoke, exhaust fumes), Swimming |

II. Non-allergic and allergic rhinitis

Chronic sinusitis commonly coexists with rhinitis. A high incidence rate of an abnormal sinus scan in patients with rhinitis has been reported in many studies.\textsuperscript{147} Rhinitis has been considered as one of the predispositions for chronic sinusitis but opinion remains divided, especially concerning the contribution of allergic rhinitis. It is widely accepted that infection of the nose contributes to the initiation of infectious sinusitis. This kind of rhinitis causes narrowing or closure of the ostium and blocks normal ventilation.\textsuperscript{148-150} Sometimes the purulent infection can persist and turn chronic, especially in those patients with immunodeficiency or ciliary dyskinesia. Allergic rhinitis can also cause narrowing of the ostium. However, the contribution of allergy has not been proven to contribute to the onset of sinusitis. The increased incidence rate of purulent sinusitis of seasonal rhinitis is not higher than that of perennial rhinitis.\textsuperscript{151} Sinusitis is more prone to be related with perennial rhinitis, rather than seasonal rhinitis, calling to question the role of allergy in chronic sinusitis.

III. Cystic fibrosis (CF)

Like nasal polyps, chronic sinusitis is also commonly found in CF patients with a reported incidence rate ranging from 11\% to\textsuperscript{100,152} 100\%.\textsuperscript{100,152} Although the ciliary beat frequency is normal in CF patients, ultrastructure abnormalities and mucociliary transport impairment are common in these patients. Thus, the risk of infection is increased.\textsuperscript{153} Compared to controls, chronic sinusitis patients with CF have a widespread inflammation in the paranasal sinuses, requiring more extensive surgery.
and running a higher risk of a cerebrospinal fluid leak or bleeding.\textsuperscript{152}

\textbf{IV. Primary ciliary dyskinesia (Kartagener’s Syndrome)}

Primary ciliary dyskinesia is closely associated with chronic sinusitis. Noone et al.\textsuperscript{111} reported that 100\% of 78 patients with primary ciliary dyskinesia had chronic sinusitis/rhinitis. Defective structure of the cilia, low concentration of nasal nitric oxide (100\%) and nasal recurrent otitis media (95\%) were found in these patients. These factors may contribute to the onset and prolonged inflammation of sinuses.

\textbf{V. Churg-Strauss Syndrome (CSS)}

Ma et al.\textsuperscript{154} in 1994 reported eight cases of Churg-Strauss Syndrome, whereas 88\% of these cases had sinusitis. Wechsler et al.\textsuperscript{119} reported a similar finding with an incidence rate of 75\%. Although the contribution of eosinophil disorder has been suggested,\textsuperscript{119} the mechanism is not clear yet.

\textbf{VI. Young’s Syndrome}

Chronic sinusitis is commonly found in Young’s syndrome. Studies have reported that, compared to Caucasians, Young’s syndrome is rare in Asia, involving less severe sinopulmonary problems.\textsuperscript{123,125}

\textbf{VII. Immunodeficiency}

Dysfunction of the immune system leads to recurrent infection of the sinus, lungs and
the gastrointestinal tract. Chronic and recurrent sinusitis is frequently found in inherited immunodeficiency, such as common variable immunodeficiency, IgG subclass deficiency, IgA deficiency, X-linked agammaglobulinemia, Ataxia telangiectasia, hyper-IgM immunodeficiency and TAP2 deficiency. \(^{127}\) In the acquired immunodeficiency syndrome (AIDS), the incidence rate of chronic sinusitis is quite high and sometimes coexists with nasal polyps. \(^{155,156}\)

1.4 Diagnosis of Nasal Polyps and Chronic Sinusitis

The diagnosis of nasal polyps and chronic sinusitis should be based not only on the history of the disease and the symptoms, but also on a physical examination, such as endoscopy, CT, MRI etc. In many cases, these examinations are critical for diagnosis. Also, one should exercise caution in explaining results of the physical examination. For example, it has been reported that the incidence rate of abnormality of one or more paranasal sinuses, in the absence of any suspicion of sinus disease, was up to 42.5%, according to cranial computed tomography including MRI. \(^{157}\) Mucosal thickening was the most frequently identified abnormality. System factors should be taken into consideration in the diagnosis as well.

1.4.1 Diagnosis of Nasal Polyps

The diagnosis of nasal polyps is mainly based on an endoscopic examination or computed tomography (CT) because many nasal polyp patients have only minor symptoms. However, symptoms are also helpful in the diagnosis, especially in those
patients with systemic disease.

1.4.1.1 Symptoms

Various symptoms are associated with nasal polyps. There may exist diverse complaints depending on the size of the polyps and the coexistence of other diseases. The main symptom in nasal polyp patients is persistent nasal blockage. In patients with small nasal polyps it may not be obvious. Many of them have a hyponasal voice. Discharge is also common in nasal polyp patients. Other symptoms are complaints such as hyposmia, anosmia, rhinorrhea and sneezing. Anosmia is suggested to be the typical symptom of nasal polyp patients which is not found in patients with sinusitis alone.\(^\text{151}\) In the presence of chronic sinusitis, patients may feel facial pain and headache. Patients may also suffer sleep disturbance and irritability. The quality of life of the patients may be affected accordingly. The evaluation of the quality of life in nasal polyp patients may provide unique information for the illness and treatment.\(^\text{158}\)

Because of the high incidence of nasal polyp coexisting with other diseases, such as asthma, aspirin intolerance and cystic fibrosis, a brief questionnaire or physical examination is strongly suggested.

1.4.1.2 Physical Examination

I. Endoscopic examination

In the diagnosis of nasal polyps, endoscopy plays a very important role and has been taken as the gold standard. In this examination shown in Figure 3, pale,
semitranslucent, watery masses are found to protrude into the nasal cavity. It can be unilateral or bilateral. Both nasal cavities have to be examined.

Figure 3. Endoscopic views of healthy nasal cavity (A) and nasal polyps (B). A. Endoscopic view of a healthy left ethmoid cavity. MT, middle turbinate; IT, inferior turbinate; S, Septum. B. Endoscopic view of nasal polyp. It is semi translucent, round pale outgrowth of nasal mucosa. Normal tissue around it looks more pink and firm. (From http://www.aafp.org/afp/980901ap/slack.html)

Staging systems have been suggested for use in the diagnosis of nasal polyps. Absence of nasal polyps under endoscopy is given 0; polyps that do not prolapse beyond the middle turbinate and may require an endoscopic examination for visualization is given 1; 2 is for polyps extending beyond the middle turbinate and being visible by nasal speculum; grade 3 is for massive polyps which occlude the nasal cavity.160,161

II. Computed tomography (CT)

Prior to sinus surgery, it is necessary to provide information on anatomy, since structures in the population are quite different. Computed tomography (CT) with coronary is helpful to determine the condition in paranasal sinuses. Figure 4 shows a
coronal CT scan of a normal ostiomeatal complex and another one with nasal polyps.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{coronal_CT_scans.png}
\end{figure}

\section*{III. Magnetic Resonance Imaging (MRI)}

When there is suspicion of intracranial extension or involvement of fungus, MRI should be performed.

\section*{IV. Other examinations}

Other tests, such as smell test, rhinometry, serum test, nasal secretion analysis, skin prick test and histology test may be performed. They may provide important information on the treatment of nasal polyps.

\subsection*{1.4.1.3 Differential Diagnosis}

Nasal obstruction can be caused by chronic sinusitis as well as turbinate hypertrophy. They can be easily differentiated by an endoscopic examination. Other diseases, including benign tumors like inverting papillomas, and malignant tumors like...
squamous cell or adenocarcinoma have to be carefully excluded. In children with
nasal polyps, a physical examination for cystic fibrosis has to be done.

1.4.2 Diagnosis of Chronic Sinusitis

The diagnosis of chronic sinusitis is more complicated than that of nasal polyps. First,
evaluation of the duration has to be made. Second, symptoms in chronic sinusitis may
vary. In addition, there may be coexistence of other systematic diseases. Previous
medical treatment may also affect the diagnosis. In general, in the diagnosis of
chronic sinusitis, both the history and the physical examination should be carefully
evaluated.

1.4.2.1 Classification of Sinusitis

Based on the history of the disease, sinusitis is divided into acute, recurrent, subacute
and chronic sinusitis. Acute sinusitis is characterized by disease duration, including
symptoms and sinus inflammation, of less than 8 weeks in adults and 12 weeks in
children. Subacute sinusitis is characterized by a duration that is longer than 8 weeks
but less than 3 months with persisting mild to moderate symptoms and sinus
inflammation. Recurrent sinusitis is the repeated occurrence of acute sinusitis over
four times per year. When the disease duration persists for longer than 8 to 12 weeks,
it is classified as chronic sinusitis. Because of the involvement of treatment in the
course of the disease, patients often do not show any symptoms for the duration of
two or three months. Thus, it has been suggested that episodes lasting less than 10
days and occurring over four times per year should also be diagnosed as chronic sinusitis.\textsuperscript{31,160}

<table>
<thead>
<tr>
<th>Table 4. Classification of sinusitis.\textsuperscript{31,160}</th>
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<tbody>
<tr>
<td><strong>Acute Sinusitis</strong></td>
</tr>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>Children</td>
</tr>
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1.4.2.2 Symptoms

The symptoms of acute and chronic sinusitis are quite similar. They comprise mainly nasal congestion, rhinorrhea and/or drainage. Other symptoms include facial pain, headache, fever, and a decreased sense of smell. Nearby organs can be affected. Patients may have dental pain, cough and otologic symptoms.

It has been suggested that criteria for the diagnosis of sinusitis should be set up by combining major and minor criteria.\textsuperscript{164} Major criteria are purulent nasal discharge, purulent pharyngeal discharge and cough. Minor criteria include periorbital edema, headache, facial pain, toothache, earache, sore throat, foul breath, increased wheeze and fever. Acute sinusitis is defined when two major or one of the major plus two or
more minor criteria last for more than 7 days. When symptoms persist no longer than 6 to 8 weeks or consist of less than four episodes per year without significant mucosal damage, it should be taken as acute or recurrent sinusitis. Each episode should last less than 10 days. Chronic sinusitis is more difficult to diagnose than acute sinusitis. Nasal obstruction, postnasal drainage, chronic cough, hyposmia may be some signs of chronic sinusitis.

1.4.2.3 Physical Examination

I. **Rhinoscopy and endoscopy**


Using rhinoscopy and endoscopy to evaluate the conditions of the middle meatus, turbinates, sinuses and the ostiomeatal complex for the diagnosis of sinusitis is straightforward and easy. Evidence for sinusitis, such as swelling, color and consistency of the mucous membrane or purulent secretion may be detected. *Figure 5*
is an example of an endoscopic view of chronic sinusitis.

II. **Computed tomography (CT)**

Symptoms in sinusitis are not specific. A CT scan with coronal views has been widely accepted as a diagnostic measure. It provides important information about the extent of the disease, structural abnormalities, and other coexisting or underlying diseases. The information obtained from the CT is necessary especially before sinus surgery, in view of the variation of the anatomy of the sinuses in the population. However, one must bear in mind that no strict correlation exists between symptoms and CT findings. Hwang et al.\textsuperscript{165} reported that in the 115 patients who met the criteria of the Task Force on Rhinosinusitis (TFR), only 70 had a positive CT scanning result. On the other hand, 9 out of 10 patients who did not meet these criteria had a positive CT scan.

Stages of sinusitis depending on the CT image have been suggested. Lund et al.\textsuperscript{160} in 1995 proposed a system based on CT assessment. A sinus group was assigned three possible grades from 0 to 2. 0 was for no abnormality; 1 for partial opacification and 2 for total opacification. Altogether a score based on the endoscopic appearance was compiled. No polyp seen is 0, polyp or polyps confined to the middle meatus is 1, and polyps beyond the middle meatus is 2. Bhattacharyya et al.\textsuperscript{166} evaluated the Lund score in 130 patients and reported that it exhibited reliable sensitivity and above-average specificity for the diagnosis of CRS, especially when it was considered together with the patient’s history and physical findings. Figure 6 shows a CT scan of
chronic sinusitis.


**III. Magnetic Resonance Imaging (MRI)**

MRI is meaningful in the diagnosis of fungal sinusitis.

**IV. Other examinations**

Skin prick tests are often employed in the diagnosis of sinusitis mainly for airborne allergens. In vitro tests such as RAST can be used to determine the level of specific IgE. In a case of persistent purulent discharge with treatment of antibiotics, a microbiological analysis should be carried out for deciding on an effective treatment. A biopsy is necessary for histology when there is suspicion of malignant or fungal growth. Bachert et al.³¹ also suggested a leukocyte count and differential count, especially in a case of the acute type; a cytology and nasal mediator evaluation in case of eosinophilic and neutrophilic rhinitis; a saccharin test and electro microscopy for a ciliary function test, and antineutrophilic cytoplasmic antibody when Wegener’s
disease is suspected.

1.5 Histopathology of Nasal Polyps and Chronic Sinusitis

The normal ultrastructure of nasal mucosa was discussed in chapter 1.1. In general, normal nasal mucosa consists in a pseudostratified columnar ciliated mucus membrane. The submucosa has blood vessels, glands and various cell types. In normal individuals, cells in the nasal mucosa are mainly macrophages, fibroblasts, lymphocytes and plasma cells. However, in pathological conditions, cell patterns will change, suggesting an underlying pathogenesis. In this section, we will discuss the histopathology changes in nasal polyp tissue and inflamed sinus mucosa of chronic sinusitis patients which will help us to understand the underlying mechanism. We will further discuss cell patterns of sinusitis and nasal polyps in chapter 1.6. A histology examination is suggested in the diagnosis of nasal polyps and chronic sinusitis to exclude other diseases, such as granulomatosis and malignant growth.

1.5.1 Histology of Nasal Polyps

Nasal polyps are characterized by chronic inflammation. Histologically, it has several characteristics which are different from the normal nasal mucosa. Kaliner et al.\textsuperscript{29} suggested the three following characteristics of histological changes in nasal polyps: first, there is differentiation of epithelium, including hyperplasia of basal cells and goblet cells, and metaplasia of squamous; second, there is high infiltration of inflammatory cells, such as eosinophils; third, glands are cystically dilated and
inspissated which makes them different from seromucinous glands in normal nasal mucosa. Nasal polyps can be classified into four types according to histology.167

I. Edematous, eosinophilic nasal polyp

As suggested by the name, this kind of nasal polyp is characterized by severe edema and high infiltration of eosinophils. In addition, goblet cell hyperplasia is common. Basement membrane is often thickened. Besides the high infiltration of eosinophil, there is also a remarkable increase of mast cells. Fibroblast cells are rare. This kind of nasal polyp is the most common type which accounts for 85-90% of nasal polyp. It is often bilateral.

II. Chronic inflammatory polyps

In contrast to the edematous nasal polyps, edema and hyperplasia of goblet cells are absent in this type. Instead, squamous metaplasia are common in the epithelium. Lymphocytes are the major infiltrating cells. This type accounts for about 10% of nasal polyps.

III. Polyps with hyperplasia of seromucinous glands

This type often has an edematous feature as type I. The difference is that numerous seromucinous glands can be found. There is no atypia and glands are distributed separately. It accounts for about 5% of the sinonasal polyps.

IV. Polyps with atypical stroma

In this type of nasal polyps, atypical stromal cells are limited to a certain area. It seldom happens for the whole tissue to show atypical stromal cells. They are bizarre fibroblast-like cells which represent reactive fibroblast and there is lack of mitoses.
Only less than 1% of the nasal polyps belong to this type.

Bachert et al. \cite{31} summarized the epidemiology of nasal polyps together with histology. In general, eosinophilic nasal polyps account for 65% to 90% of the cases, whereas neutrophilic nasal polyps account for 15% to 20% by histology. Nasal polyps with aspirin-intolerance, intrinsic asthma, allergy and Churg-Strauss syndrome are classified into the eosinophilic type. Polyps with cystic fibrosis, Kartagener’s syndrome and Young’s syndrome are characterized by neutrophilia.

### 1.5.2 Histology of Chronic Sinusitis

The histology change in chronic sinusitis is similar to that of nasal polyps. Common features of chronic sinusitis include differentiation of the epithelium such as goblet cell hyperplasia, basement membrane thickening; and changes in lamina propria, such as atypical gland formation, mononuclear inflammatory cell infiltration and subepithelial edema.\cite{168} However, there are no clear histology patterns of chronic sinusitis. Although some studies gave evidence of eosinophilia in chronic sinusitis,\cite{169,170} it was suggested that eosinophilia was mainly found in chronic sinusitis with nasal polyps but not chronic sinusitis alone.\cite{151} Neutrophils are predominant over eosinophils, mast cells and basophils in chronic sinusitis.\cite{151} Malekzadeh et al.\cite{171} in 2003 suggested two histological subtypes of chronic rhinosinusitis: the first type mainly has eosinophilia and polyposis formation; the second type is characterized by glandular hyperplasia and hypertrophy. It has also
been reported that inflammatory cells in chronic sinusitis were mainly lymphocytes and plasma cells.¹⁶⁸

1.6 Pathogenesis of Nasal Polyps and Chronic Sinusitis

Darke-Lee et al.⁶³ pointed out that the study of pathogenesis of nasal polyps had three stages, including: the evaluation of any underlying condition; understanding any factors in the pathogenesis of the tissue edema; and understanding the symptoms caused by these reactions. As we reviewed in chapter 1.3, both nasal polyps and chronic sinusitis are multifactorial diseases that correlate with many pathologic conditions. It is suggested that nasal polyps and chronic sinusitis are more likely the end point of many diseases. Many mechanisms have been suggested as causes of their formation, the two most important theories consider allergy and infection. However, reports remain controversial. In this section, we will review the pathophysiology suggested in research of nasal polyps and chronic sinusitis with their proposed roles. The overall pathogenesis will be introduced followed by the roles of inflammatory cells and chemical mediators. A summary of the pathogenesis of nasal polyps is shown in Table 5.

We will review mechanisms suggested to contribute to the pathogenesis of nasal polyps and chronic sinusitis in this section. Mechanisms with underlying diseases are discussed in chapter 1.3.
1.6.1 Pathogenesis of Nasal Polyps and Chronic Sinusitis

Table 5. Pathogenesis of nasal polyps.\textsuperscript{63}

<table>
<thead>
<tr>
<th>Genetic predisposition</th>
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<tbody>
<tr>
<td>Mucosal reactions</td>
</tr>
<tr>
<td><em>Allergic inflammation</em></td>
</tr>
<tr>
<td><em>Infection</em></td>
</tr>
<tr>
<td><em>Nonallergic infection</em></td>
</tr>
<tr>
<td><em>Trigger cell: mast cell, eosinophil, lymphocyte, macrophage</em></td>
</tr>
<tr>
<td><em>Inflammatory mediators</em></td>
</tr>
<tr>
<td><em>Mucous glands</em></td>
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<tr>
<td><em>Alteration in the connective tissue</em></td>
</tr>
<tr>
<td>Anatomical abnormality</td>
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<tr>
<td><em>General anatomy of the ethmoid labyrinth</em></td>
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<tr>
<td><em>Junction of the ethmoid sinuses and the nasal cavity</em></td>
</tr>
<tr>
<td><em>Bernoulli phenomenon</em></td>
</tr>
<tr>
<td>Neurovascular changes</td>
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<tr>
<td><em>Relative paucity of the sinus vascularity</em></td>
</tr>
<tr>
<td><em>Loss of autonomic control</em></td>
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</tbody>
</table>


1.6.1.1 Allergy

I. Nasal polyps

Nasal polyps were taken as a manifestation of allergy in the 1930s,\textsuperscript{172} mainly because eosinophilia is the major common phenomenon in nasal polyp tissue. In addition, asthma, which can be an atopic disease, is closely related with nasal polyps. Symptoms of nasal polyps are similar to those of allergic rhinitis, and increased local
IgE is common in polyp fluid.\textsuperscript{151} 

In the 1970s, a few epidemiology studies reported that nasal polyps were more common in nonatopic patients than atopic patients. Caplin et al.\textsuperscript{44} reported an incidence rate of nasal polyps in 3000 atopic patients of only 0.5%. In another study by Settipane et al.,\textsuperscript{12} the incidence rates of nasal polyps in allergic and nonallergic asthma were 5% and 13%, respectively. In allergic and nonallergic rhinitis, the incidence was 1.5% vs. 5%. A recent study in Greece by Grigoreas et al.\textsuperscript{40} reported that nasal polyps were more common in patients with nonallergic respiratory diseases (rhinitis or asthma) than those with allergic respiratory disease (10.8% for the former and 2.1% for the latter). In addition, patients with perennial respiratory allergy (rhinitis, asthma) had a higher incidence of nasal polyps than those with seasonal respiratory allergy (4.8% as compared with 0.4%). Similar findings were reported in Japan which mentioned that the incidence rate of atopy in patients with eosinophilic nasal polyps was only 29.7%.\textsuperscript{173} There is no evidence from these studies that atopic patients are more prone to develop nasal polyps than nonatopic patients. However, there are controversial reports. A study in 1999 in Thailand by Pumhirun et al.\textsuperscript{174} reported that in nasal polyp patients, the incidence rate of positive skin prick test was 40% (24/40) whereas that of the control group was 20% (6/30). Asero et al.\textsuperscript{175} reported an incidence rate of 70% of positive skin prick test to airborne allergens in nasal polyp patients which was significantly higher than the incidence rate of 60% in patients with general allergic respiratory diseases. A remarkably high incidence rate of
positive allergy tests in nasal polyp patients of 96.5% was reported by Bunnag et al.\textsuperscript{7}

Whether the difference is because of the populations studied, environmental factors or sensitivity of the tests is not clear yet.

Although elevated serum IgE is not a common feature in nasal polyp patients, many studies have shown a local IgE production. Some studies reported that there was no correlation between local IgE elevation and positive skin prick test. It was suggested that the local IgE increase was not determined by atopy.\textsuperscript{176} Small et al.\textsuperscript{177} reported in 24 patients that underwent nasal polypectomy, 75% had higher local total IgE in nasal fluid than serum total IgE. 79% of the patients had elevated local specific IgE but only 47% of them had positive skin prick test. However, there are other controversial reports suggesting a correlation between local and systemic IgE production. Perkins et al.\textsuperscript{172} reported that elevated local IgE was only found in those who had positive skin prick test or RAST. Similar results from Bunnag et al.\textsuperscript{7} reported that 96.5% of the 57 nasal polyp patients in their study were reactive to at least one allergy test.

Besides the contribution of common inhalant allergens, Bachert et al.\textsuperscript{51} suggested the role of bacterial superantigen, because specific IgE to Staphylococcal enterotoxins was identified in nasal polyp tissue. Furthermore, elevated local total and specific IgE were correlated with tissue eosinophilia in their study. However, systematic IgE does not seem to correlate with tissue eosinophilia. In many studies, a comparison was made of increased mast cell and eosinophil numbers in nasal polyp patients with and
without allergy. No difference was observed, suggesting that infiltration of the two inflammatory cells may not come under IgE-mediated control.\textsuperscript{178-184} The role of inflammatory cells in the pathogenesis of nasal polyps and chronic sinusitis will be further discussed in chapter 1.6.2.

\textbf{II. Chronic Sinusitis}

The role of allergy in the pathogenesis of chronic sinusitis remains unclear. There are two studies by Slavin who reported a cause-and-effect relationship between allergen exposure and changes in paranasal sinuses.\textsuperscript{185} SPECT (single photon emission computed tomography) was used to detect metabolic activity and dynamic physiology in sinuses. The studies proved that in the ragweed season, allergic rhinitis patients with a positive ragweed skin test not only had inflamed nasal mucosa, but also showed significant hyperemia of the sinuses. Although sinus X-ray was normal, the bone uptake increased around the sinuses. After the ragweed season, the bone uptake returned to normal. In another study, ragweed pollen was insufflated into the nostril of a patient allergic to ragweed and a control. The patient showed increased metabolic activity near the sinuses whereas the control had pollen only near the turbinate but not near the sinuses. Pollen may enter the sinus cavity indirectly. In another study by Pelikan et al.,\textsuperscript{186} an immediate reaction and a late-phase reaction with compatible X-ray changes in sinuses and symptoms were reported after a nasal provocation challenge test in chronic sinusitis patients. The above studies demonstrated the physiology change of the sinuses after allergen challenge which may not be observed
in X-rays, suggesting a possible role of allergen exposure in the pathogenesis of chronic sinusitis.

Although sinus change after allergen challenge has been demonstrated, the role of allergy in chronic sinusitis remains controversial. For example, the relation between sinusitis and allergic rhinitis is attributed mainly to the narrowing of the ostium. Sinusitis correlates more closely with perennial rather than seasonal rhinitis. Allergic fungal sinusitis only accounts for 2% to 10% of chronic sinusitis patients needing surgery. Although Ponikau et al. reported that 93% of chronic sinusitis patients were diagnosed as allergic fungal sinusitis, the evidence of IgE-mediated allergy was lacking. Only 29% of the patients showed a positive reaction to the skin prick test (SPT) and 5% showed delayed type hypersensitivity. An elevated level of total IgE and specific IgE was identified in 33% and 28% of the patients, respectively, which did not differ significantly from that in controls. In a recent study by Gutman et al., the incidence rate of positive SPT in patients with chronic sinusitis was 62.5±7%. However, perennial allergens were more frequent than seasonal allergens. In addition, noninfectious inflammation characterized by eosinophilia is commonly seen only in chronic hyperplasia sinusitis with nasal polyps (CNS/NP). Georgitis et al. reported that in the sinus lavage fluid of chronic sinusitis patients, neutrophils were the major cell type with a low percentage of mast cells, basophils or eosinophils. Bachert et al. also suggested that in patients having chronic sinusitis without nasal polyps, the hallmark is neutrophilia but not eosinophilia. In general, the role of allergy
in the pathogenesis of chronic sinusitis remains controversial.

1.6.1.2 Infection

I. Nasal polyps

Chronic infection of the nose and sinuses is commonly found in nasal polyp patients. Commonly found pathogens are β-hemolytic streptococci, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. Virus infection has also been suggested as a probable cause of nasal polyps, such as the Epstein-Barr virus and the human papilloma virus. There is also a case report of Cytomegalo virus in an AIDS patient with chronic sinusitis and nasal polyps. However, the etiology of viruses in nasal polyps is not clear and some studies did not support the existence of viruses in polyp tissue.

II. Chronic Sinusitis

The role of infection in chronic sinusitis remains controversial. It is well accepted that acute sinusitis is closely correlated with infection. However, although microorganisms have been identified in chronic sinusitis, it was suggested that bacteria were not the primary cause of chronic sinusitis. Thus, the question arose as to whether the bacterial infection initiated the pathogenesis of chronic sinusitis or was only secondary to the conditions favoring bacteria growth in sinus cavities. Various factors may contribute to the infection of the sinuses, including narrowing of the OMC (ostiomeatal complex) by multiple causes and decreased ability of clearance.
OMC obstruction will block normal drainage and induce a pathological environment favoring bacterial overgrowth. In addition, obstruction will cause the formation of negative intra sinus pressure because of reabsorption of the air in the nasal cavity. Thus, microorganisms in the nasal cavity may go into the sinuses when the patient sneezes. An abnormal structure of the sinus can also cause sinus ostial narrowing. However, it was suggested that the incidence rate of abnormality of the sinuses was not higher in patients with sinusitis than controls. Havas et al.\textsuperscript{157} reported an incidence rate of 42.7\% in 666 patients for whom there was no suspicion of sinus diseases. Bolger et al.\textsuperscript{195} reported an incidence rate of 83.2\% of bony abnormality both in patients with sinus complaint and in controls. Other factors, such as nonallergic and allergic rhinitis, can also cause narrowing or closure of the ostium and block normal ventilation.\textsuperscript{148-150} Sinusitis with underlying diseases, including cilia dysfunction, for example, primary ciliary dyskinesia and Churg-Strauss Syndrome, and disturbances in mucociliary transport such as cystic fibrosis and immunodeficiency can increase the risk of sinus infection. This increased risk results mainly from the impaired ability to clear microorganisms caused by decreased ciliary functions and hypersecretion of mucus.

In acute sinusitis, the most commonly reported pathogens are *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Moraxella catarrhalis*.\textsuperscript{64} In chronic sinusitis, besides those mentioned above, there are also *Staphylococcus aureus*, coagulase negative *Staphylococcus* and anaerobic bacteria are also reported. According to the
reports, a positive bacteria culture of multiple species was common in chronic sinusitis patients. The most commonly found anaerobes were *Peptostreptococcus*, *Propionibacterium*, and *Prevotella* species; the most common aerobes were *Staphylococcus* and *Streptococcus* species. In addition to bacteria, Lusk et al. pointed out that fungus infection may play an important role in the development of sinusitis in patients with immunodeficiency. It was also suggested that fungus infection may be commonly related with chronic sinusitis, not only in patients with immunocompromised diseases. In addition, the contribution of allergy to a more severe infection of sinusitis has been shown in animal models.

### 1.6.1.3 Genetic Predisposition

Genetic factors are thought to play an important role in the pathogenesis of nasal polyps and chronic sinusitis. It has been reported that family history and system disorder under genetic control are commonly found in the patients. However, large-scale family studies are lacking. Although genetic studies have been done in related diseases, such as CF, Young’s syndrome and primary ciliary dyskinesia, the genetic contribution to nasal polyps and chronic sinusitis is far from known. Further studies in family members may provide unambiguous information.

#### 1. Nasal polyps

Genetic factors have been suggested in the pathogenesis of nasal polyps. Dark-Lee et al. reported nasal polyps in identical twins in 1992. In the study by Greisner et
al., 199 14% (7/50) of nasal polyp patients had a family history. Rugina et al. 23 reported that among the 224 nasal polyp patients in his study, a family history was found in 52.66% of them, which was higher than that of asthma (43.58%).

Most of the genetic studies were performed in nasal polyp patients with CF which was discussed in chapter 1.3. Voynow et al. 200 analyzed the mucin mRNA expression in epithelial cells and reported that nasal polyps expressed more MUC5 mRNA than MUC1 or MUC2 mRNA. Prados et al. 201 reported that the MZ phenotype of alpha 1-antitrypsin was more frequently observed in nasal polyp patients with intrinsic asthma or ASA-Triad compared to controls.

HLA (human leukocyte antigen) patterns have been studied in nasal polyp patients. HLA-A, HLA-B and HLA-C are class I MHC (major histocompatibility complex) which present peptides to and recognized by CD8+ T cells. HLA-DR, HLA-DQ and HLA-DP are class II MHC which present peptides to CD4+ T cells. Moloney et al. 202 reported that an increased HLA-A1/B8 haplotype was found in nasal polyps with asthma and/or aspirin intolerance but not in nasal polyps alone. However, in the study of Luxenberger et al., 203 no such correlation was found compared to controls. Instead, a significant association was found between HLA-A74 and nasal polyps. Molnar-Gabor et al. 204 reported that HLA-DR7-DQA1*0201, and -DQB1*0202 haplotype had two to three times higher odds ratios (ORs) in nasal polyp patients compared to controls. Donato et al. 205 reported two siblings with pansinusitis, nasal
polyps, and bronchiectasis had HLA class I antigen deficiency and dysfunction of natural killer cells because of mutation in the TAP2 gene.

In a recent study Fritz et al.\textsuperscript{206} reported that mammaglobin mRNA which is associated with breast neoplasia was expressed 64 fold higher in nasal polyp patients with allergic rhinitis than those without. The followed immunostaining confirmed mammaglobin protein expression specific on goblet cells of nasal polyps, suggesting that deregulated cell growth was involved.

Although family history has been mentioned in some studies, evidence is still lacking in the literature. In addition, the involvement of multiple diseases in patients with nasal polyps makes a genetic study more complicated.

II. Chronic Sinusitis

Genetic studies of chronic sinusitis are mostly carried out in those with underlying diseases, as discussed in chapter 1.3. In a study in 1999 of 82 Japanese patients with intractable chronic sinusitis Takeuchi et al.\textsuperscript{207} reported a strong association with HLA B54 antigen (class I) compared with controls.

1.6.1.4 Defects in Sodium and Ion Influx

The studies of electrophysiology of nasal polyps were first carried out on patients with cystic fibrosis. As introduced in chapter 1.3, CF is associated with defects of the
gene encoding CFTR which regulates the chloride transport in epithelial cells. Thus, the position of CFTR is affected. It is interesting that CFTR mutation as well as abnormal distribution has been identified in patients with chronic sinusitis or nasal polyps but no CF.\textsuperscript{104,208} It has been suggested that a severe mutation of CFTR gene may lead to CF whereas a mild mutation is related to sinusitis and asthma.\textsuperscript{209} In addition, studies indicate that epithelium damage will lead to a low expression of CFTR in patients with or without CF.\textsuperscript{210,211} A poor expression of CFTR has been proven in the epithelium of nasal polyp patients who often show epithelial damage.\textsuperscript{210,211} In summary, both CFTR gene mutation and airway remodeling will affect CFTR expression. In addition, although luminal chloride channel defect in CF has not been identified in nasal polyp epithelial cells, increased sodium absorption under the control of inflammatory mediators has been demonstrated.\textsuperscript{106}

1.6.1.5 Nitric Oxide

Nitric oxide (NO) is a small gaseous molecule produced in the nervous system, the cardiovascular system, and the upper and lower airways. The generation of NO is under the control of nitric oxide synthases (NOS). One NOS isotype, inducible NOS (iNOS) was suggested to be present in epithelial cells and can be activated by cytokines or bacteria products.\textsuperscript{212} NO plays an important role in non-specific immunoreactions and inflammation. An animal model in iNOS knockout mice proved that NO is an important factor against inflammation.\textsuperscript{213} NO also fulfils important functions in vasoregulation, hemostasis, neurotransmission, immune defense, and
However, according to another study, NO is a kind of inflammatory mediator.\textsuperscript{215} In the airway, NO can upregulate ciliary function and is the first-line of the host defense against microorganisms.\textsuperscript{214} It is also an aerocrine messenger between the upper and lower airways. There are high concentrations of NO in the nasal cavity and paranasal sinuses.\textsuperscript{216,217} NO is mainly produced by epithelial cells in the paranasal sinuses.\textsuperscript{216} Other cells in the airway, such as endothelial cells, neutrophils and macrophages can also produce NO.\textsuperscript{218}

Altered nasal NO concentrations have been reported in pathological conditions such as allergic rhinitis,\textsuperscript{219,220} sinusitis,\textsuperscript{221,222} nasal polyps,\textsuperscript{212,215,223} cystic fibrosis\textsuperscript{224} and primary ciliary dyskinesia.\textsuperscript{111,112} A decreased level of nasal NO concentration in patients with chronic sinusitis compared to controls has been reported.\textsuperscript{225,226} A linkage between NO concentration and functional and morphological changes of the mucociliary system has been proposed. The NO level in nasal polyp patients has been found to be significantly lower than that in patients of allergic rhinitis. That level has been correlated with the extent of nasal polyps.\textsuperscript{223} A successful treatment will increase the NO level. In some studies, although inflammation can activate iNOS in the epithelium, nevertheless the blockage of the ostiomeatal complex caused by nasal polyp and inflammation will ultimately prevent the NO generated in the sinuses from reaching the nasal cavity. In other studies, there was a significantly higher NO content in nasal polyp patients with atopy than patients without atopy.\textsuperscript{227} The interesting role of NO in various diseases remains to be further explored.
1.6.1.6 Nervous System and Neuropeptides

The presence of neuropeptide-containing sensory, parasympathetic and sympathetic nerves in human nasal mucosa is well established. Type C nociceptive nerve releases neuropeptides, including substance P (SP) and calcitonin gene related peptides (CGRP). They are able to increase plasma extravasation and glandular secretion which play an important role in the immediate-acting mucosal defense. SP is also thought to mediate neurogenic inflammation. Dysfunction of the autonomic nervous system was thought to play a role in nasal polyp formation. Neuropeptide release induced by capsaicin in nasal polyps was decreased compared to that of the control group. Further studies demonstrated the existence of multi neuropeptides in nasal polyp tissue, such as SP, vasoactive intestinal peptide (VIP) and neuropeptide Y (NPY). Studies in the animal model of sinusitis showed an increased level of SP and CGRP in sinus mucosa. In nasal polyps, equal levels of SP, VIP and bombesin-flanking peptide (BFP) was identified, compared to normal mucosa from controls. The exact role of neuropeptides needs to be further clarified.

1.6.1.7 Other Mechanisms Proposed

Aerodynamic factors have been proposed for the development of nasal polyps. It has also been suggested the origin of nasal polyps may be related to a significant alteration of aerodynamic flow, i.e., the lateral wall of the nose. Energy metabolism has been suggested to play a role in the pathogenesis of sinusitis and nasal polyps.
1.6.2 Inflammatory Cell and Chemical Mediators in Nasal Polyps and Chronic Sinusitis

The development of cellular and molecular biology has brought the studies of pathogenesis in nasal polyps and chronic sinusitis into a new decade. Chemical mediators can include peptides, proteins, amines or lipids. These are formed by one cell and have the ability to affect changes in other responding cells. In the upper and lower airways, mast cells, basophils, eosinophils, macrophages and neutrophils are traditionally taken as sources of chemical mediators. Epithelial cells, endothelial cells and fibroblasts considered previously to be mainly structural tissue, have also been proved to release many types of chemical mediators. Although the pathogenesis underlying nasal polyps and chronic sinusitis is unclear, the infiltration of inflammatory cells and upregulation of chemical mediators have been widely studied. However, their exact roles still remain unclear. The cross talk between chemical mediators is important for inflammatory cell regulation. In this section, we will review the proposed role of inflammatory cells and chemical mediators in the pathogenesis of nasal polyps and chronic sinusitis.

1.6.2.1 Th1 and Th2 Cytokines

There are two subsets of activated T lymphocytes, the T helper cell (CD4+ subset) and the cytotoxic/suppressive T cell (CD8+ subset). T helper cells are further subdivided into Th1 and Th2 cells, according to their cytokine profile. INF-γ, TNF-α and IL-2 are released by Th1 cells after stimulation by bacteria, virus and
mycobacteria. IL-4, IL-5, IL-10 and IL-13 are released by Th2 cells following stimulation by helminthic and environmental allergens. Both Th1 and Th2 cells can produce IL-3 and GM-CSF. Thus, Th1 cytokines are taken as the manifestation of infection which will cause migration and activation of neutrophils, whereas Th2 cytokines are related with allergy and mainly regulate the functions of eosinophils, mast cells and macrophages. Th1 cytokines will lead to delayed-type hypersensitivity, whereas Th2 cytokines favour IgE synthesis. The two pathways are considered to inhibit each other. Synthesis of Th1 and Th2 cytokines is also affected by other cytokines. Major Th1 and Th2 cytokines with their sources and functions are introduced in detail.

I. INF-γ (Th1)

The principle cell sources of INF-γ are Th1 cell, CD8+ T cell and natural killer (NK) cells. INF-γ plays roles in the activation of macrophages and endothelial cells. It can also increase the expression of class I and II MHC molecules in various cells as well as antigen processing and presentation to T cells.

II. Tumor necrosis factor α (TNFα)

The major sources of TNF are activated mononuclear phagocytes, as well as activated T cells, NK cells and mast cells. The principle function of TNF is recruitment and activation of neutrophils and monocytes. It can also activate endothelial cells and mediate the apoptosis of many cells.

III. IL-1 (Th1)

The major cell sources and principal function of IL-1 are similar to those of TNF.
Activated mononuclear cells, macrophages, neutrophils, epithelial and endothelial cells can all synthesize IL-1. Its main function is mediating host immunity against infection. There are two forms of IL-1, i.e., IL-1α and IL-1β. IL-1β is the major form found in circulation.

IV. **IL-2 (Th1)**

Both CD4+ T cells and NK cells can release IL-2. It has multiple functions on lymphocytes. With regards to T cells, IL-2 promotes their proliferation and cytokine production as well as maturation of CD8+ T cells. With regards to B cells, IL-2 stimulates their proliferation and antibody synthesis. IL-2 also stimulates proliferation and activation of NK cells and differentiation of macrophages.

V. **IL-4 (Th2)**

IL-4 is a cytokine derived from T helper lymphocytes, cytotoxic T cells (CD8+ T cells), mast cells and basophils. It first became known as a B cell growth factor. Later, it was shown to be the major inducer of the differentiation of CD4+ T cells to the Th2 subset. It is also essential for IgE production. Other functions of IL-4 include stimulation of CD8+ T cell differentiation, inhibition of NK cell proliferation and mast cell activation by endotoxin, increasing ion transport by the epithelium, increasing fibroblast proliferation and increasing VCAM adhesion molecule expression in the endothelium.

VI. **IL-5 (Th2)**

IL-5 is synthesized primarily by T cells (Th2 and CD8+ T cell), mast cells, eosinophils and NK cells. In nasal polyps, eosinophils, but not lymphocytes have been
suggested to be the major cell source of IL-5. It was reported that 80.1% of eosinophils expressed IL-5, and 90.9% of the IL-5+ cells were eosinophils. \(^2\) A controversial report suggested that T lymphocytes were the major source of IL-5 in nasal polyp tissue. \(^4\) IL-5 is identified as a T-cell reactive cytokine. In addition, it has been proven to have multiple functions on eosinophils, such as proliferation, chemoattraction, adhesion, activation, enhanced survival and degranulation. IL-5 can also stimulate the differentiation of B cells, which leads to the production of immunoglobulins. It is also a stimulating factor for T cells, especially cytotoxic T cells. One other major function of IL-5 is stimulation of basophils which will release histamine and leukotriene.

**VII. IL-10 (Th2)**

The main sources of IL-10 are macrophages and T lymphocytes. It has the function of inhibiting activated macrophages. It can also inhibit IL-1, IL-6, IL-8, IL-12 and TNFα production by mononuclear phagocytes. Because of the inhibition of costimulators and class II MHC molecules on macrophages, T cell activation is also inhibited. Cytokines production by T lymphocytes, including INF-γ and IL-2 by Th1 lymphocytes, IL-4 and IL-5 by Th2 lymphocytes is also inhibited. On the other hand, IL-10 stimulates proliferation and immunoglobulin secretion of B cells.

**VIII. IL-13 (Th2)**

IL-13 is structurally similar to IL-4. They have about 30% homology and share many biological functions. IL-13 is mainly released by CD4+ T cells. Its major role is to inhibit macrophage activation. It inhibits monocyte-mediated ADCC and reduces...
cytokine and chemokine production by monocytes. It also induces the IgE isotype switch. Although IL-13 can not induce the differentiation of Th2-lymphocytes as IL-4, it is suggested that in clinical allergic diseases, IL-13 may have more important proinflammatory influences than IL-4.

**IX. GM-CSF (Th1 and Th2)**

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is produced by T lymphocytes and many other cell types, such as macrophages, structural cells as well as eosinophils. It was first recognized that GM-CSF has the ability to induce stem cell differentiation to granulocytes and macrophages/monocytes. Later, its role in the modulation of the biological activities of mature hemopoietic cells was identified. In addition, it can activate eosinophils and prolong their survival.

**X. IL-3 (Th1 and Th2)**

IL-3 is multilineage colony-stimulating factor (multi-CSF) which can promote the expansion of cells. In mice, IL-3 can promote growth and development of mast cells. In humans, its function is unclear.

Other cytokines involved in nasal polyp development and sinusitis include: TNF-β, which is mainly synthesized by Th1 cells. It inhibits macrophages as well as the proliferation of T cells and B cells. TNF-β is also termed as lymphotoxin which has tumor cytotoxic effects and enhances phagocytosis by macrophages and neutrophils; Interleukin-6, which is synthesized by Th2 cells, macrophages and many other cells, induces B cell differentiation and antibody production as well as stimulation of
fibroblast proliferation and collagen synthesis; and other subsets, such as the transforming growth factor-β (TGF-β) which may be involved in inducing mucosal induced tolerance. Depending on the nature of allergens as well as genetic and environmental factors, T cell will produce Th1/Th2 cytokines which may be skewed to one extreme or another. Although in animal models there is a clear cut component of Th1 or Th2 by induced immunization or infection, this is not the case in the human being. The network of cytokine interactions is complex as many of them have overlapping functions. Many cells are able to synthesize multiple types of cytokines. However, each cytokine has its unique character in addition to common functions shared by other chemical mediators.

**Table 6. Principle cell sources and main functions of major Th1 and Th2 cytokines.**


<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Principle cell sources</th>
<th>Primary targets</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF-γ (interferon γ)</td>
<td>Th1 cell, CD8+ T cell and natural killer cells</td>
<td>Macrophages</td>
<td>Differentiation, activation to express MHC class I and II, nitric oxide synthase, IL-1 and TNF</td>
</tr>
<tr>
<td>TNFα (Tumor necrosis factor α)</td>
<td>Monocyte/macrophages</td>
<td>Tumor cells and almost all cells in the body</td>
<td>Enhanced apoptosis; enhanced cytokine, MHC class I and II, and adhesion molecule expression; cytotoxicity</td>
</tr>
<tr>
<td>IL-4</td>
<td>CD4+ and CD8+ T cells</td>
<td>B cells</td>
<td>Growth and activation; production of MHC class II, IL-6, TNF, CD23, CD72; switch factor for IgE and IgG1; inhibits IgM, IgG2 and IgG3; increase TLR-4 on B cells Th1 cells Inhibition differentiation Th2 cells Differentiation CD8+ cells Differentiation and IL-5 production NK cells Inhibits proliferation</td>
</tr>
<tr>
<td>Cytokine</td>
<td>Principle cell sources</td>
<td>Primary targets</td>
<td>Effects</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------</td>
<td>-----------------</td>
<td>---------</td>
</tr>
<tr>
<td>IL-1</td>
<td>Monocytes/macrophages</td>
<td>Th2 cells</td>
<td>Cytokine production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CD8+ T cells</td>
<td>Cellular cytotoxicity, cytokine production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B cells</td>
<td>Differentiation, proliferation and immunoglobulin production</td>
</tr>
<tr>
<td>IL-2</td>
<td>CD4+ lymphocytes</td>
<td>T lymphocytes</td>
<td>Clonal expansion of Ag-specific cells; differentiation and cytokine expression; maturation of CD8+ T cells</td>
</tr>
<tr>
<td>IL-5</td>
<td>CD4+ and CD8+ T cells</td>
<td>Eosinophils</td>
<td>Proliferation, chemoattraction, adhesion, activation, enhanced survival, and degranulation, increase NGF expression</td>
</tr>
<tr>
<td>IL-10</td>
<td>Murine CD4+ Th2; human CD4+ Th0, Th1, Th2 and CD8+ lymphocytes</td>
<td>Monocytes Macrophages</td>
<td>Differentiation to macrophages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibits expression of MHC class II and many adhesion molecules; inhibits INF-γ and TNF production, resulting in switch of T cell differentiation from Th1 to Th2</td>
</tr>
<tr>
<td>IL-13</td>
<td>CD4+ and CD8+ T cells</td>
<td>B cells</td>
<td>Similar to IL-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monocytes</td>
<td>Enhanced MHC class II integrins; reduced production of IL-1 and TNF</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Activated macrophages and T cells</td>
<td>Eosinophils, neutrophils and macrophages</td>
<td>Proliferation, differentiation, survival and enhanced cytokine production</td>
</tr>
<tr>
<td>(Granulocyte-macrophage colony-stimulating factor)</td>
<td></td>
<td>Megakaryocytes</td>
<td>Eosinophil degranulation, platelet production</td>
</tr>
<tr>
<td>IL-3</td>
<td>T lymphocytes</td>
<td>Hematopoietic stem cells</td>
<td>Proliferation of differentiation</td>
</tr>
<tr>
<td>IL-6</td>
<td>Monocyte/macrophages</td>
<td>B cells</td>
<td>Differentiation into plasma cells; switch factor for IgG1 and IgA</td>
</tr>
<tr>
<td></td>
<td>Monocytes/macrophages</td>
<td></td>
<td>Inhibits LPS stimulates IL-1 and TNFα production</td>
</tr>
</tbody>
</table>
1.6.2.2 Microenvironment of Nasal Polyps and Chronic Sinusitis

I. Nasal Polyps

The cytokine profile found in polyp tissue is a mixture of types of Th1 and Th2. The reported cytokines in nasal polyps with elevated concentration or mRNA expression include Th1 cytokines such as IL-1, INF-γ, IL-12, TNF-α, Th2 cytokines such as IL-4, IL-5, IL-6, IL-13, GM-CSF, IL-3, and TGF-β which are synthesized by both Th1 and Th2 cells; and finally TGF-β which is a potent inducer of myofibroblasts. Enhanced expression of receptors for IL-2 and IL-5 have also been reported. Other cytokines elevated in nasal polyps include: adhesion molecules such as ICAM-1 (intercellular adhesion molecule-1), VCAM-1 (vascular adhesion molecular-1), growth factors such as vascular permeability/vascular endothelial growth factor (VPF/VEGF) which is a major inducer of angiogenesis and capillary permeability, keratinocyte growth factor (KGF) which is a fibroblast growth factor, stem cell factor (SCF) which is a mast cell growth and survival factor; and profibrotic cytokines related to deposition of collagen, such as IL-11 and IL-17 which have been reported in CHS/NP (chronic hyperplasia sinusitis/nasal polyps).

The cytokine pattern in nasal polyps remains controversial. Although the reported cytokine pattern in nasal polyps varies from study to study, IL-5 and INF-γ are almost the universal components. Bachert et al. investigated cytokines concentrations of IL-1β, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, TNFα, GM-CSF, and IL-1RA. Only the
IL-5 concentration was significantly higher in polyp tissue than controls. On the contrary, normal nasal mucosa had significantly higher levels of IL-1β and IL-1RA than nasal polyps. Rudack et al.\textsuperscript{264} reported similar findings indicating a major role for IL-5 in nasal polyp formation. Many other studies reported a mix of IL-5 and INF-γ in nasal polyp tissue.\textsuperscript{249}

Whether the cytokine profile is decided by the condition of allergy has been discussed by many studies. It has been suggested that atopy does not determine the cytokine pattern in nasal polyps.\textsuperscript{253,265-267} However, there are also reports of a difference found between allergic and nonallergic nasal polyps. In the studies of patients with nasal polyps or CHS/NP by Hamilos et al.,\textsuperscript{52,244,252} allergic patients were characterized by higher levels of IL-4, IL-5 and IL-13, while nonallergic patients had higher levels of INF-γ, GM-CSF and TNF-α. A significant correlation was also reported between the IL-5 concentration and tissue IgE in atopic nasal polyp patients.\textsuperscript{254}

Chemokines (chemoattractant cytokines) are a family of cytokines ranging from 8 kD to 12 kD. They have a homologous structure and mainly play a role as leukocyte chemoattractants to an inflammatory site. CC chemokine signals through the CC chemokine receptors (CCR)-2 and -3 and has effects on monocytes, eosinophils, and basophils, inducing allergic and nonallergic inflammation.\textsuperscript{268} Their major sources are structural cells such as endothelial cells, epithelial cells and fibroblasts.\textsuperscript{269-273} Inflammatory cells such as eosinophils are also an important source.\textsuperscript{274,275} Synthesis
of chemical mediators is induced by infectious stimuli.\textsuperscript{269,270} Th1 cytokines, for example TNF and IL-1, can also initiate chemokine production.\textsuperscript{271-273,276} In nasal polyps, it has been reported that not only Th1 but also Th2 cytokines can regulate the production of chemokines.\textsuperscript{277} Various chemokines, such as IL-8,\textsuperscript{275} RANTES\textsuperscript{274} and eotaxin\textsuperscript{51,278}, are considered to play an important role in nasal polyp formation. IL-8 is synthesized by macrophages, lymphocytes, neutrophils and structural cells. IL-8 is a chemoattractant for neutrophils and T lymphocytes. It can also inhibit IgE production and histamine release. It has been suggested that nasal neutrophilia correlates with IL-8 level.\textsuperscript{279} An in vitro study demonstrated that IL-8 prolonged eosinophil survival.\textsuperscript{280} RANTES is one of the histamine-releasing factors and a potent chemoattractant for eosinophils, monocytes, T lymphocytes and basophils. It also has chemotactic activity on eosinophils. Eotaxin binds selectively to the chemokine receptor CCR3 and attracts eosinophils, basophils and T lymphocytes.\textsuperscript{281} Both nonallergic and allergic nasal polyps are reported to have significantly higher levels of eotaxin\textsuperscript{282,283} and RANTES\textsuperscript{274,282-284} than controls. They are proposed to play an important role in the regulation of eosinophil migration and activation. Controversial reports argued that there was no difference between the RANTES level in nasal polyps and tissue from controls.\textsuperscript{283} It has been suggested that nasal eosinophilia and eosinophil cationic protein (ECP) level were significantly correlated with levels of eotaxin but not with RANTES. Activation of the epithelium nuclear factor-kappa B (NF-kappa B) caused by stimuli was proposed to be responsible for chemokine release and thus regulate local inflammation such as eosinophilia.\textsuperscript{285}
In recent years, cysteinylation leukotrienes (cys-LTs), i.e. LTC4, LTD4 and LTE4, have been suggested to contribute to the local inflammation in nasal polyps and other respiratory diseases such as asthma and allergic rhinitis. There are two pathways for arachidonic acid (AA) metabolite synthesis. One is converted into prostaglandins (PGs) and thromboxanes (Txs) by cyclooxygenase, and the other is converted into hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs) by lypooxygenase. Aspirin can inhibit the cyclooxygenase pathway and stimulate the lypooxygenase pathway. Corticosteroids, however, will inhibit the release of AA from membrane phospholipids, thus causing a decreased production of both pathways. A disturbance of AA metabolism has been suggested to contribute to the pathogenesis of nasal polyps. AA metabolism of nasal polyps is significantly lower than that of normal nasal mucosa.\(^{286}\) In addition, allergic nasal polyp patients are more prone to producing CO (carbon oxide) products than nonallergic patients. Nasal polyp patients with high recurrence rates exhibits higher LTC4 levels.\(^{287}\) Other studies have reported that the predominant metabolite of AA in nasal polyps is 15-HETE.\(^{288}\) Higher LTC4/D4/E4 levels in polyp tissue compared to controls have also been reported.\(^{51,289}\) In addition, a significant correlation between LTC4/D4/E4 concentrations with local total IgE has been evidenced.\(^{51}\) A controversial report has suggested no difference in LTC4/D4/E4 concentrations between nasal polyps and controls.\(^{278}\) Although the role of leukotrienes in the inflammation of nasal polyps remains controversial, use of an antagonist of leukotrienes has been shown to improve the symptoms of nasal polyp patients.\(^{290,291}\)
Although increased levels of many chemical mediators have been identified, results remain controversial. Their complicated interaction still remains unclarified. In addition, many studies have been done in vitro. Whether these conditions can be applied in vivo is still being questioned. Chemical mediators related to specific cells, such as histamine released from mast cells and basophils, major basic protein (MBP) and eosinophil cationic protein (ECP) released from eosinophils, will be discussed in chapter 1.6.2.3.

II. Chronic Sinusitis

Although it is widely accepted that IL-8, IL-1β and TNF-α contribute to the pathogenesis of acute sinusitis, the cytokine profile in chronic sinusitis is not well characterized. Chronic sinusitis is characterized by elevated levels of multi chemical mediators, including cytokines such as IL-1β, TNF-α, INF-γ, IL-4, IL-5, IL-10, IL-13, IL-6, GM-CSF, and IL-3; chemokines such as IL-8; RANTES and eotaxin; other chemical mediators such as IL-11 and IL-17, epidermal growth factor (EGF) and transforming growth factor-α (TGF-α), sICAM-1(soluble intercellular adhesion molecule-1), VCAM-1, LTC4/D4/E4 as well as prostaglandin D2. It has also been suggested that the serum level of IL-12 which is an antioxidant, is significantly lower in patients with chronic sinusitis compared to controls. Although elevated levels of both Th1 and Th2 profiles have been reported, Th2 cytokines are thought to play a more important role in the pathogenesis chronic sinusitis. Treatment of chronic sinusitis will lead to a shift
from Th2 profile to Th1 profile; for example, the Th1 profile would include a decreased expression of IL-4 with an increased expression of INF-γ.\textsuperscript{303,304} However, studies of chemical mediators in chronic sinusitis remain controversial. Lennard et al.\textsuperscript{293} reported that the cytokine profile in chronic sinusitis was Th1 as shown by IL-1β and TNF-α secretion rather than the Th2 pattern. Rudack et al.\textsuperscript{264} reported that there was no elevation of Th1 or Th2 cytokines in chronic sinusitis patients compared to controls, including IL-1β, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, GM-CSF and INF-γ. IL-3, which can be synthesized by both Th1 and Th2, was suggested to be the predominant cytokine in chronic sinusitis.\textsuperscript{297}

Many studies have suggested that there are distinct cytokine profiles in allergic as opposed to nonallergic chronic sinusitis patients. Ghamdi et al.\textsuperscript{295} reported that in allergic chronic sinusitis, both the IL-4 and IL-13 mRNA expressions were elevated. However, in nonallergic chronic sinusitis, only IL-13 but not IL-4 was higher compared to controls. Hamilos et al.\textsuperscript{52} reported that IL-3, GM-CSF were at higher levels in both allergic and nonallergic CHS/NP patients. In addition, the allergic group had higher IL-4, IL-13 and IL-5 levels whereas the nonallergic group had higher INF-γ and TNF-α levels.\textsuperscript{52,252} It has been proposed that although IL-5 and GM-CSF were elevated in both allergic and nonallergic patients with chronic sinusitis, there may be distinct cytokine pathways since the atopic patients had more alpha IL-5 receptor mRNA-positive cells, whereas nonatopic patients had more alpha GM-CSF receptor positive cells.\textsuperscript{305} Ghaffar et al.\textsuperscript{306} reported that although IL-6 messenger RNA
was more highly expressed in the epithelial and subepithelial cells of allergic and nonallergic chronic sinusitis patients compared to controls, atopic patients had a significantly higher coexpression of a mast cell marker, suggesting that a different mechanism was involved. The chemical mediators contributing to the development of chronic inflammation in sinusitis and their interactions need to be further clarified.

1.6.2.3 The Cross-talk between Inflammatory Cells and Chemical Mediators in Nasal Polyps and Chronic Sinusitis

Multiple inflammatory cells have been identified in nasal polyps and chronic sinusitis. The inflammatory cell patterns in nasal polyps and chronic sinusitis are similar, with contributions from eosinophils, lymphocytes, mast cells, neutrophils, and structural cells. However, the mechanism underlying their infiltration remains an enigma. These cells, besides their traditional roles, may have far more complicated functions. Understanding the function and cross-talk between inflammatory cells and chemical mediators is essential for looking into the pathogenesis of nasal polyps and chronic sinusitis.

I. Nasal Polyps

Eosinophils are the major inflammatory cells identified in nasal polyps. Other cells, such as lymphocytes, neutrophils and mast cells are also important cells in the pathogenesis. Structural cells in nasal polyps not only act as physical protection but also contribute to the development of nasal polyps. These inflammatory cells are regulated by multiple chemical mediators. On the other hand, they serve as important
sources for these mediators.

*Eosinophils*

Eosinophilia is the major inflammatory event in the pathogenesis of nasal polyps. As we discussed in the histology of nasal polyps, 85-90% of the nasal polyps are classified as eosinophilic nasal polyps. Studies have also demonstrated that the activated eosinophil (EG2+ as activation marker) in nasal polyps is significantly higher than that of controls.

Eosinophils become mature in bone marrow under the influence of several cytokines, including IL-2, IL-3, IL-5 and GM-CSF. When activated, tissue eosinophils will degranulate and release chemical mediators such as eosinophil major basic protein (MBP) and eosinophil cationic protein (ECP). In nasal polyps, eosinophils synthesize a series of chemical mediators, including TNF-α, IL-6, IL-13, IL-4, IL-5, GM-CSF, RANTES, eotaxin and TGF-β. Other chemical mediators such as leukotrienes, prostaglandins and platelet-activating factor (PAF), platelet-derived growth factor (PDGF), matrix metalloproteinase (MMP)-9 and membrane type (MT)4-MMP can also be released by the activated eosinophil. Studies have shown MBP and ECP deposition in nasal polyp tissue and nasal lavage fluid. The correlation between MBP and epithelium damage has been confirmed. MBP is toxic to mammalian cells, parasites, and bacteria in vitro. It has the function to activate platelets, to activate mast cells and basophils which will release histamine; to stimulate neutrophil superoxide production, degranulation, and IL-8.
production.\textsuperscript{324} ECP has the function of stimulating mucus secretion, whereas MBP plays the opposite role of inhibiting secretion.\textsuperscript{106} Another major role of MBP is to significantly increase sodium flux into the interior of the epithelial cell.\textsuperscript{106}

The role of chemical mediators in eosinophil attraction, adhesion, activation and prolonged survival has been well studied. In the nasal polyp endothelium, intercellular adhesion molecule 1 (ICAM-1), E-selectin, P-selectin and VCAM-1 were reported as the major eosinophil adhesion receptors.\textsuperscript{325,326} P-selection was suggested as an important factor contributing to eosinophil adhesion.\textsuperscript{326} IL-1β, TNF-α, IL-4 and IL-13 were suggested to play a critical role in VCAM-1 upregulation, and to promote eosinophil adhesion.\textsuperscript{106,327} Galectin-9 expression in endothelial cells induced by INF-γ was also suggested to contribute to eosinophil adhesion.\textsuperscript{328}

As reviewed in chapter 1.6.2.2, GM-CSF,\textsuperscript{329} IL-5,\textsuperscript{265} TGF-β\textsubscript{1},\textsuperscript{265} eotaxin\textsuperscript{265} and RANTES\textsuperscript{330} are the major chemical mediators of eosinophil regulation in nasal polyps. They may act as potent eosinophil attractants and activate eosinophils or prolong their survival. For example, GM-CSF and IL-5 were suggested to play important role in eosinophil attractant, activation as well as prolonged survival.\textsuperscript{280,311,329,331,332} INF-γ inhibits eosinophil activation in the short term but stimulates it in the long term. In addition, chemical mediators may exert their roles through interactions with each other. For example, IL-4, IL-13 and INF-γ have the potential to induce the expression of eotaxin-2/CCL24 which regulates eosinophils.\textsuperscript{277} TNF-α induced upregualtion of
MMP from eosinophils is directly involved in eosinophil migration and tissue remodeling by the degradation of extracellular matrix components and modulation of activity of other proteins.\textsuperscript{315}

Others factors contributing to tissue eosinophilia are IgE and IgG,\textsuperscript{333} IL-8,\textsuperscript{280} IL-3,\textsuperscript{331} protein kinase C (PKC),\textsuperscript{334} Bcl-xl,\textsuperscript{335} CD18-\beta2, CD11a-c, CD29-\beta1, CD49d-\alpha4,\textsuperscript{336} cytokine growth-related oncogene-\alpha (GRO-\alpha),\textsuperscript{337} 15-HETE\textsuperscript{338} and platelet-activating factor (PAF).\textsuperscript{339} It has also been suggested that eosinophilia in nasal polyps may be established by the various mechanisms triggered by the type of stimulation. Park et al.\textsuperscript{280} demonstrated that challenge of atopic nasal polyp tissue in vitro will cause upregulation of GM-CSF and IL-8, which will prolong eosinophil survival. This can be blocked by antibodies to GM-CSF or IL-8. However, challenge with PHA will cause prolonged eosinophil survival which can not be blocked by the antibodies, suggesting that different mechanisms are involved.

**Lymphocytes**

Lymphocytes play a central role in adaptive immunity. The precursors of lymphocytes arise from the same pluripotent stem cells in bone marrow. These stems cells give rise to B and T lymphocytes as well as natural killer (NK) cells. Maturation of B cells is completed in bone marrow but maturation of T cell is completed in the thymus. IL-7 is the principle stimulator of proliferation of the progenitors of B and T lymphocytes. Expression of antigen receptor gene is the major event of B and T cell maturation. The
antigen receptors are important in survival, proliferation and maturation of lymphocytes. T cells will differentiate into CD4+ or CD8+ T lymphocytes after maturation. CD4+ cells are also called T helper cells which synthesize cytokines (Th1, Th2, Th3) and molecules in response to antigen stimulation. The antigen stimulation is passed by antigen presenting cells (APCs), such as dendritic cells and macrophages. Secretions from CD4+ T cell will stimulate the activity of B cells and macrophages. CD8+ T cells which are also called cytotoxic T cells are activated by infections and mainly synthesize INF-γ and lymphotoxin which is important in lysing the target cell. In addition, IL-4 and IL-5 can also be released by CD8+ T cell when activated by IL-4, thus stimulating B cell activation and recruiting eosinophils. B cells plays a major role in immune response by synthesizing immunoglobulins (IgM, IgD, IgG, IgE, IgA). B cells are also able to release cytokines by stimulation with some microantigens. IL-4 and IL-13, INF-γ, TGF-β can stimulate IgE, IgG, IgA production, respectively. In the germinal centers, B cells may differentiate into plasma cell or memory B cells.

Although lymphocytes play an important role in adaptive immunity, in studies of nasal polyp they were not regarded as significant as eosinophils. However, Morinaka et al.340 reported a higher expression of lymphocytes than eosinophils in nasal polyps. According to another report, lymphocytes were one of the major inflammatory cells in CF patients with nasal polyps.341

As introduced in the anatomy of the nose, normal nasal mucosa has more T cells than
B cells and more CD4+ T cells than CD8+ T cell in a ratio of 2-3:1. In polyp tissue, T lymphocytes were prominent over B lymphocytes. CD19+ B cells, IgE+ plasma cells and HLA-DR+ cells are all rare. A controversial report mentioned significantly higher levels of HLA-DR+ cells in polyp tissue compared to controls. Significantly higher levels of CD8+ T cells compared with CD4+ T cells in nasal polyps have been reported. CD8+ T cells in nasal polyps were also reported to have significantly higher levels than that in nasal mucosa from healthy controls. On the contrary, the nasal mucosa from healthy controls had a significantly higher level of CD4+ T cells than found in the middle and inferior turbinate of nasal polyp patients. In addition, the middle turbinate of nasal polyp patients had a similar pattern of CD4+ and CD8+ T cells as that of the polyp tissue. There is also a controversial report on the predominance of CD4+ T cells but not CD8+ T cells, which represents only 15-20% of the lymphocyte population in nasal polyp tissue. In that study, it was also mentioned that mast cells were closely related with CD4+ and MHC class II+ T cell. According to another report, a significantly higher level of B cells was present compared to controls, although most studies did not find a high infiltration of B cells.

Stoop et al. evaluated T cell numbers in the middle and inferior turbinates of patients before and after treatment. It showed more CD8+ T cells than CD4+ T cells during endoscopic sinus surgery (ESS). After ESS followed by half a year’s treatment with topical corticosteroids, CD4+ T cell numbers increased significantly. Six months
later, however, CD4+ T cell numbers decreased. In another study Hamilos et al.\textsuperscript{349} reported that CD4+ T cells in nasal polyps decreased after four weeks of topical corticosteroid treatment. Mastruzzo et al.\textsuperscript{350} reported increased CD8+ T cells in nasal polyps after treatment with topical corticosteroids. In summary, it has been demonstrated that nasal polyp is a disease related to T cell dysfunction. Treatment will change T cell subsets.

P and L selectin have been suggested to play an important role of in T cell adhesion in nasal polyps.\textsuperscript{351} Multiple chemical mediators, which are T cell chemoattractant, such as eotaxin,\textsuperscript{281} have been identified in nasal polyps. It was reported that T cells had IL-3 like activity and played a role in basophil/mast cell and eosinophil accumulation in vitro.\textsuperscript{181,352} T cells are important sources of many chemical mediators in nasal polyps, such as IL-5\textsuperscript{244,249} especially in those associated with allergy\textsuperscript{244}, INF-γ\textsuperscript{249} and IL-6\textsuperscript{306}. However, Xu et al.\textsuperscript{243} reported that only 3.7% of lymphocytes and neutrophils were positive for IL-5. T lymphocytes in nasal polyps also express CCR3, which will recruit eosinophils to the allergic inflammation site through production of Th2 cytokines such as IL-4 and IL-5.\textsuperscript{281} Over expression of GRβ on lymphocytes which may be related to topical steroid resistance was also reported.\textsuperscript{353} Lymphocytes were also reported to express MT4-MMP and were correlated with IL-11 in nasal polyps\textsuperscript{262}. Activated T cells can also induce CD137 expression by eosinophils from allergic patients.\textsuperscript{354} The interaction of T cells with nasal epithelial growth and differentiation factors, and blood-borne progenitors was shown to play an important role in the local
accumulation of basophils, mast cells, and eosinophils in nasal polyps. Studies have been carried out on the mechanism of T cell accumulation in nasal polyps. T cells in nasal polyps had a low production of IL-4 but a high production of interferon, together with high IgA levels in polyp tissue. This suggested that nasal polyps did not present a typical type I hypersensitivity response. It was also reported that nasal polyp T cells had a significantly higher expression of IL-2 receptor and ICAM-1 compared to blood T cells. In nonallergic patients, CD8+ T cells had a significantly higher expression of ICAM-1 than allergic subjects, suggesting that a different mechanism may be involved. Mechanisms involving virus infection as well as superantigens have also been considered.

HLA patterns in nasal polyps were discussed in chapter 1.6. CD8+ T cells recognize HLA-A, B and C whereas CD4+ T cells recognize HLA-DP, DQ and DR. Thus, investigating of HLA patterns may help to understand the roles of lymphocyte subsets in the pathogenesis of nasal polyps. Although a significant higher level of HLA-DR+ cells was found in nasal polyps, and the middle turbinate than in the inferior turbinate, a controversial report claimed that there was no difference between HLA-DR+ cells in allergic and nonallergic patients compared to controls. Interestingly, CD8+ T cells were reported to positively correlate with HLA class II antigen. The role of INF-γ in the regulation of HLA class II antigen expression in epithelial cells may be related to this finding.
**Mast cells**

Mast cells are an important component in allergy as well as in innate immunity and infections. Stem cell factor (SCF) and IL-3 are important for mast cell survival and growth.\(^{358}\) In addition, IL-6, prostaglandin E2 (PGE2) and IL-15 contribute to mast cell survival whereas IL-4 and IL-10 inhibit their development.\(^{358}\)

It is well known that mast cell plays a central role in Type I allergy through the IgE-meditated pathway. Activation of mast cell will release histamine, leukotrienes, prostaglandin D2 as well as tryptase. The release of tryptase has been taken as the specific marker for mast cell degranulation. In addition, mast cells are able to produce TNF-\(\alpha\) which is a chemoattractant and activator of neutrophils,\(^{359}\) thus it plays an important role in infection. Mast cells are also considered important in parasite infections, mastocytosis, systemic anaphylaxis, cutaneous allergic reactions, asthma, allergic rhinitis, arthritis and fibrosis.\(^{358}\)

Studies of the role of mast cells in the pathogenesis of nasal polyps suggest an important role. Degranulation of mast cells was not only identified in polyp tissue but also in the paired middle turbinate.\(^{360}\) Highly increased levels of histamine, tryptase or IgE were found in nasal fluid and/or nasal polyp tissue.\(^{176,317,361-363}\) Mast cell numbers in nasal polyp tissue was reported to be remarkably higher than in the sinus mucosa of sinusitis patients and interestingly, the middle turbinate mucosa of allergic rhinitis patients.\(^{364}\) The epithelium rather than subepithelial layer and lamina propria was
reported to be the major location of mast cells.\textsuperscript{364} This finding is similar to that identified in hay fever.\textsuperscript{365} However, mechanisms underlying mast cell infiltration and activation remain unclarified because of controversial reports. First, no difference was found in mast cell infiltration in allergic and nonallergic nasal polyp patients, although mast cells were found to be distributed superficially in atopic patients.\textsuperscript{366} Another major finding was that high levels of histamine, tryptase and IgE in the nasal fluid of polyp patients had poor correlation with clinical hypersensitivity.\textsuperscript{176,317,362,363} Nor did IgE+ mast cells correlate with clinical hypersensitivity.\textsuperscript{367} Studies involving challenge of nasal polyp tissue by anti-human IgE or extracts of house dust mite or mixed grass pollens only demonstrated a partial role of IgE-mediated allergy.\textsuperscript{368} In addition, mast cells were reported to be located in the submucosa but not in the epithelium of nasal polyps.\textsuperscript{369} A study of allergic fungal sinusitis revealed large amounts of neutrophil elastase and MBP, but not the presence of any tryptase in mucin.\textsuperscript{370} Patients with asthma and aspirin sensitivity had lower histamine levels than patients with nasal polyps alone.\textsuperscript{361} It was also reported that mast cells in nasal polyps was similar to that in sinusitis, and controls with scarce IgE but high IgA and IgM.\textsuperscript{371} All of these studies question the role of type I hypersensitivity in mast cell degranulation in nasal polyps.

Besides the traditional role of the mast cell, studies have also revealed its interesting relationship with many chemical mediators in nasal polyps. For example, there was a significant correlation between tryptase and MMP-2, MMP-9 and TGF-\(\beta\)1 in nasal polyps, suggesting their contribution to mast cell migration.\textsuperscript{372} SCF (stem cell factor),
a survival and growth factor for mast cells, was highly expressed in the epithelial and fibroblast cells of nasal polyps and allergic rhinitis. Basic fibroblast growth factor (bFGF), which is a polypeptide that is mitogenic for a wide variety of cell types, was shown to be released by mast cell in nasal polyps. Vascular permeability/vascular endothelial growth factor (VPF/VEGF) which favors vascular permeability, and oestrogen receptors (ER) and progesterone receptors (PR), which are sex hormone receptors, are also secreted by mast cells. In addition, a correlation was suggested between mast cells and neutrophils, and also between mast cell number and CT score. Whether mast cells indicates a role for allergy in the pathogenesis of nasal polyps is far from known.

**Plasma cells**

Plasma cells are lymphocyte-like cells and are derived from B cells. They secrete several kinds of cytokines and immunoglobulin, thereby playing an important role in chronic inflammation. Studies have reported that nasal polyps and the paired middle turbinate had higher levels of plasma cells than the inferior turbinate, especially in those patients with cystic fibrosis or host defense deficiency. In addition, plasma cells have been shown to express cyclooxygenase (COX-2) and IL-6, as well as vascular permeability factor (VPF) or vascular endothelial growth factor (VEGF). However, there was also a report showing poor infiltration of IgE-producing plasma cell.
**Neutrophils**

The neutrophil is traditionally recognized as an important factor in innate immunity against infection and injury. In recent years, the neutrophil has been ascribed far more functions beyond the role of professional phagocytes. It not only expresses Fc receptor, complement components, cationic antimicrobial proteins and NADPH proteins, but also varieties of chemical mediators.\(^{381}\) A neutral serine protease-elastase which is present in the granule of neutrophils with bactericidal properties not only provides protection but also causes tissue damage.\(^{370}\)

Studies of neutrophil infiltration in nasal polyps remain controversial, i.e. high infiltration in polyp tissue\(^{382}\) or mucin\(^{370}\), as opposed to lack of difference between nasal polyps and controls.\(^{307,316}\) There was also a report of similar infiltration between nasal polyps and the paired middle or inferior turbinate.\(^{383}\)

The mechanism of neutrophil infiltration in nasal polyp has been the subject matter of many studies. The correlation between neutrophil infiltration and bacteria count in nasal polyps has been reported.\(^{384}\) A significantly higher neutrophil level was found in patients with a higher frequency of infectious diseases, for example, CF patients and patients with host defense deficiency.\(^{376,378}\) Besides having a role in infection control, neutrophils have been suggested to play a role in the regulation of mucin production.\(^{370}\)
Infiltration by neutrophils in nasal polyp tissue is under the control of multiple chemical mediators. IL-8, a potent chemoattractant and activator of neutrophil has been identified in nasal polyps. It was reported that neutrophil numbers correlated with IL-8 and LPS-receptor CD14 in nasal secretion. Cytokine growth-related oncogene-alpha (GRO-alpha) was reported to be a potent mediator of neutrophil recruitment and proliferation. GM-CSF initiates neutrophil differentiation. In studies of adhesion molecules, ICAM, P-selectin, platelet-activating factor and CD18 (beta2), CD11a-c were reported to contribute to neutrophil recruitment, whereas VCAM-1 and E-selectin do not appear to mediate neutrophil adhesion.

Besides the correlation with chemical mediators, the relationship between neutrophils and other inflammatory cells in nasal polyps has also been suggested. In vitro studies demonstrated that nasal turbinate and nasal polyps were able to release high molecular weight-neutrophil chemotactic activity following stimulation with calcium ionophore, antigens, anti-IgE or homogenization. Also, a significant correlation was identified between neutrophil elastase+ cells and activated mast cells or eosinophils. Neutrophil elastase may contribute to tissue inflammation and remodeling by inducing the expression of secretory leukocyte protease inhibitor.

**Macrophages**

Macrophages play an important role in both innate and adaptive immunity. In innate immunity, the expression of endotoxin receptors, TLR-2 and TLR-4 by macrophages
can directly initiate a reaction. It is not only a professional antigen presenting cell, but it also releases several kinds of chemical mediators, such as IL-10, leukotrienes, TGF-β, IL-12, IL-18, INF-γ, IL-1 and GM-CSF.

It has been suggested that the macrophage is one of the most important cell clusters in nasal polyps. Its interaction with T cells may play an important role in the pathogenesis of nasal polyps. A significantly more highly activated macrophage (CD68+) has been identified in nasal polyps, as compared to the inferior turbinate. In another study, the number of CD68+ macrophages in polyp tissue was reportedly equal to that of eosinophils. However, the infiltration of CD68+ macrophages in CHS/NP was not significantly higher than that in controls.

Although macrophage infiltration has been identified in nasal polyps, its contribution is not well understood. Macrophages are important antigen presenting cells. The finding that HLA+ macrophages were mainly found in the subepithelial area of nasal polyps may be related to this role. However, its infiltration mechanism and function may be more complicated. Firstly, macrophage infiltration and differentiation may vary under the control of chemical mediators such as GM-CSF. Second, the role of macrophages goes much further beyond antigen presentation. IL-6 secretion by macrophages has been identified in both allergic and nonallergic chronic sinusitis patients with nasal polyps. A recent study of DC-SIGN (dendritic cell-specific ICAM-grabbing non-integrin) which is a C-type lectin, has identified its expression
on macrophages.\textsuperscript{398} DC-SIGN can bind adhesion molecules on surfaces of naive T cells and the endothelium. It is highly expressed on the surface of immature dendritic cells (DCs) which mediate efficient activation of T cells. These unsolved questions regarding the roles of macrophages suggest that its contribution to the pathogenesis of nasal polyps remains unclear.

\textit{Structural Cells: epithelial cells, endothelial cells, fibroblasts}

Structural cells in nasal mucosa have usually been considered to be a physical barrier against infection. In recent years, their ability to produce many kinds of chemical mediators has been recognized. Thus, they not only form the basic structure of nasal mucosa. In nasal inflammation, these cells do not just have histological changes, but they also contribute to the development of the inflammatory process.

Increased epithelial cell proliferation is commonly found in nasal polyps.\textsuperscript{399} The epithelial cell in nasal polyps has been shown to express cytokines such as GM-CSF,\textsuperscript{178} IL-6,\textsuperscript{178} IL-1\textbeta,\textsuperscript{400} and TNF-\textalpha\textsuperscript{400}; chemokines such as IL-8,\textsuperscript{178} eotaxin,\textsuperscript{332} and RANTES\textsuperscript{332}; growth factors such as vascular endothelial growth factor (VEGF),\textsuperscript{313} and basic fibroblast growth factor (bFGF)\textsuperscript{373}; other chemical mediators such as ICAM-1,\textsuperscript{257} and prostaglandin.\textsuperscript{401} Epithelial cells in nasal polyps also express HLA-DR, which suggests the involvement of antigen processing.\textsuperscript{257} The mucin gene mRNA which is related to mucin hypersecretion\textsuperscript{402} and glucocorticoid receptor beta\textsuperscript{403} are also expressed by epithelial cells. Fibroblasts in nasal polyps can release
GM-CSF, TGF-β, IL-6, ICAM-1, CCL, IL-8, RANTES, eotaxin, as well as inducible cyclooxygenase (COX-2). Endothelium in nasal polyp mainly releases adhesion molecules, such as ICAM-1, P-selectin, L-selectin, and VCAM-1. They also secrete RANTES, vascular endothelial growth factor (VEGF), galectin-9, and nuclear factor. The expression of multiple chemical mediators and other factors not only contributes to morphological change but also regulates infiltration and activity of inflammatory cells in nasal polyps.

*Atopy and cell pattern*

It has been suggested that atopy does not affect the inflammatory cell pattern in nasal polyps. Park et al. investigated mast cell, eosinophil, neutrophil and pan T cell staining in both atopic and nonatopic nasal polyp patients, and found no significant difference between the two groups. In another study carried out by the same group in patients with Samter’s syndrome, and nasal polyp patients with or without allergy, the only significant difference found was a higher level of eosinophils in allergic patients than in patients with Samter’s syndrome. Pawliczak et al. reported that both eosinophils and mast cells were abundant in atopic and nonatopic nasal polyp patients. Mast cells in atopic patients were prone to distribute themselves in superficial nasal mucosa, showing a significant correlation with eosinophilia. Hamilos et al. reported that eosinophilia was the major characteristic of both allergic and nonallergic CHS/NP.
**Inflammatory cells in Different Populations**

Although the inflammatory cell pattern in nasal polyps has been well studied in Caucasians, data of its etiology and pathophysiology in Asians are still lacking. Studies conducted in Japanese patients reported that neutrophilic nasal polyps accounted for 40% of nasal polyps which is a much higher incidence rate than in Caucasians. In contrast to this, the incidence rate of eosinophilic nasal polyps was 41.7% to 65.2% which was much lower than that reported from western countries, i.e., 93.6% in Finland and 93.3% in Germany. Another study in Thailand also reported a lower incidence rate of 55.8% of eosinophilic nasal polyps. In addition, large numbers of lymphocytes were found in the submucosa of polyp tissue in the Japanese study. The incidence rate of defined atopy in eosinophilic nasal polyps in Japanese was 29.7%, which was similar to the Caucasian incidence. Lacroix et al. examined the histology of nasal mucosa and nasal polyps in black Africans, Chinese and Caucasians. The Africans had a significantly higher eosinophil level, and more rarely lymphocytes and plasmocytes than the Asians and Caucasians. In general, no major difference was found among the three groups. The author suggested that nasal polyp is the same inflammatory disease in all ethnic groups.

**II. Chronic Sinusitis**

The inflammatory cell pattern of chronic sinusitis mainly includes neutrophils, eosinophils and Th2 lymphocytes. Other cells, such as basophils and mast cells, have also been reported. The inflammatory cell patterns in adults and children were similar
but there was a significantly higher level of eosinophilia, neutrophilia and tissue remodeling in adults. In acute sinusitis, neutrophils and mononuclear cells are the major inflammatory cells. In allergic fungal sinusitis, mast cell and eosinophil degranulation were the main phenomena. Patients with underlying diseases may have a more unique infiltration. For example, neutrophilia rather than eosinophilia was the common feature of chronic sinusitis patients with host defense deficiencies or CF. Microenvironmental effects related with tissue inflammation in chronic sinusitis are similar to those in nasal polyps, including chemical mediators related with the attraction, adhesion, activation and prolonged survival of inflammatory cells. On the other hand, there are secretions of multiple cytokines and chemokines by the inflammatory and structural cells. The related chemical mediators will not be further discussed in this section.

**Eosinophils**

A significantly higher level of eosinophils in sinus mucosa of chronic sinusitis patients than in controls is one of the major characteristics of chronic sinusitis, both in adults and children, allergic and nonallergic patients. A strong, significant correlation was identified between tissue eosinophilia and disease severity determined by CT scanning. Hamilos et al. reported that in CHS/NP, it was the eosinophil level that was significantly higher in the sinus mucosa than controls, but not the levels of neutrophils, lymphocytes or macrophages. Eosinophilia in chronic sinusitis was reported to be not comparable to that in nasal polyps. In another report,
tissue eosinophilia was similar in chronic sinusitis patients with or without nasal polyps.\textsuperscript{169} Compared with neighboring tissues, a significantly higher eosinophilia level was found in the ethmoid sinus mucosa than in the paired maxillary sinus mucosa and the inferior turbinate.\textsuperscript{419}

It was reported that there is a trend of a higher peripheral eosinophil level associated with the severity of nasal disease, such as coexistence of asthma, polyps and AFS; recurrent infection and reversion of ESS; usage of antifungal treatment as well as multi courses of antibiotics.\textsuperscript{169,420,421} However, it was suggested that in childhood chronic sinusitis, the severity of the disease and coexistence of asthma had no correlation with total and specific IgE in serum.\textsuperscript{422}

\textit{Lymphocytes}

T cell infiltration is another hallmark of chronic sinusitis, especially in patients with asthma and allergic rhinitis or atopy.\textsuperscript{302,318,416} It was suggested that in chronic sinusitis patients with nasal polyps or eosinophilia, levels of both T and B lymphocytes were significantly higher than in patients who had sinusitis alone and controls.\textsuperscript{318,347} In the study of nonallergic chronic sinusitis patients, Grevers et al.\textsuperscript{423} reported elevated lymphocytes, including CD3+, CD4+ and CD8+ T cells as well as B lymphocytes, but neither eosinophils nor macrophages in the inferior turbinate. This finding suggests a diffuse involvement of inflammation and the importance of lymphocytes rather than eosinophils in patients without allergy. However, Hamilos et al.\textsuperscript{307} reported that
lymphocytes in CHS/NP were not significantly higher than controls.

The important role of T cells in cytokine production has been well studied. For example, in CHS/NP, T lymphocytes were the major source of IL-5. Chronic sinusitis has a high elevation of Th2 cytokines which may be closely related with CD4+ T cells. The CD4+ T cell was considered to play a more important role than CD8+ T cell in chronic sinusitis in many studies. Kamil et al. revealed a significantly increased ratio of helper T cell /suppressor T cell in the ethmoid sinus mucosa, as compared with that of the paired maxillary sinus mucosa and the inferior turbinate, suggesting the contribution of CD4+ T cells. According to that report, the concentrations of soluble CD4 receptor (sCD4) was significant higher in the maxillary sinus of both allergic and nonallergic chronic sinusitis than controls. However, there was no significant difference in sCD8. Surgical treatment will decrease both sCD4 and sCD8. Besides these studies emphasizing the importance of CD4+ T cells, there are controversial reports of a more important role of the CD8+ T cell. Nishimoto et al. reported that CD8+ T cells, but neither CD4+ T cells nor CD20+ B cells, were the main lymphocyte subset in chronic sinusitis, especially in patients with fibrous histology. Interestingly, HLA-DR+ cells were commonly found in their study. Another study from Liu et al. reported similar findings of infiltrated CD8+ T cells in allergic and nonallergic chronic sinusitis patients. However, in that study, both HLA-DR+ cells and IgE+ plasma cells were rare. It was also reported that nonallergic chronic sinusitis patients had more CD8+ T cells in the sinus mucosa than patients with
allergy as well as controls.\textsuperscript{295} In this study, CD8\(^+\) T cells in allergic chronic sinusitis patients increased after treatment with steroid therapy. Studies in sinusitis patients with immunodeficiency reported a decreased number of CD4\(^+\) T cells and CD3\(^+\) pan T cells.\textsuperscript{427} The change of the CD4/CD8 ratio in HIV patients had an obvious effect on serum IgE production, suggesting an independent polyclonal activation of B cells.\textsuperscript{428}

The mechanism underlying lymphocyte infiltration in chronic sinusitis remains an enigma. Although lymphocyte infiltration is more predominant in allergic patients,\textsuperscript{52,416} studies have demonstrated their involvement in infection as well. Ramadan et al.\textsuperscript{429} reported that in the process of virus induced sinusitis in a mouse model, the B cell rather than T cells or macrophages was the major cell influx in the early reaction. However, it was suggested that different animal lines may have a different tendency toward a Th1 or Th2 lymphocyte response.\textsuperscript{430} Another study of induced acute sinusitis by \textit{Streptococcus pneumoniae} bacteria in rabbits revealed elevated neutrophils, eosinophils, lymphocytes, plasma cells as well as mucosal infiltration and epithelial degeneration.\textsuperscript{431} Whether these findings of induced acute sinusitis can be applied to humans is not clear. In human studies, both T and B cell elevation in acute sinusitis were identified.\textsuperscript{415} T cells were distributed diffusely but B cells were more prone to cluster near blood vessels or under the epithelium. This may help us to understand the development of chronic sinusitis. An important report from van de Plassche-Boers et al.\textsuperscript{432} suggested defects in T cell reactivity may be commonly related with chronic sinusitis. The defects include defective delayed-type
hypersensitivity (DTH) towards microbial antigens, such as *Haemophilus influenzae*, *Streptococci* and *Candida albicans*. This study group also suggested the contribution of abnormal monocyte chemotaxis to this defective T cell-mediated immunity. Another study of fungal sinusitis related with *Aspergillus* reported a significant reduction in the proliferative response to both T- and B-cell mitogens in peripheral blood, suggesting a defect in recalling antigen. In these patients, total lymphocyte counts and immunoglobulin levels were normal. However, leukocyte subset analyses showed significantly decreased CD11+ cells (macrophages, monocytes and NK cells) but increased CD25+ cells (interleukin 2-receptor-bearing cells). Study from Bernstein et al. in recurrent chronic sinusitis in childhood revealed the inability of adenoidal T cells to switch B cell differentiation into immunoglobulin-secreting plasma cells. They suggested that this phenomenon was controlled by cytokines which may cause defective IL-2 production. The exact role of lymphocytes, especially T cells in infection to microorganisms is unknown.

**Neutrophils**

Neutrophilia is taken as the major inflammatory cell in acute sinusitis and this has been shown in animal models. In chronic sinusitis, the role of the neutrophil remains controversial although many chemical mediators in favor of neutrophil chemoattractant, adhesion and activation have been identified. Although some studies reported that neutrophil numbers were not increased in chronic sinusitis and that there was no correlation between neutrophil elastase and epithelium
damage, other studies demonstrated that neutrophil was one of the major inflammatory cells with a diffuse involvement in chronic sinusitis, especially nonallergic chronic sinusitis and chronic sinusitis without nasal polyps. Large amounts of neutrophil elastase were found in the sinus fluid of these patients. In patients refractory to treatment, neutrophils were recognized as the most important inflammatory cell type. In this case, LTC4/D4/E4 and PGD2 in sinus fluid were comparable to that in allergic rhinitis. Neutrophilia was reported to be severe in adult chronic sinusitis as compared to children. Neutrophil is located in both intraepithelial and subepithelial areas rather than the lamina propria. In patients with underlying diseases, such as cystic fibrosis and primary ciliary dyskinesia, neutrophilia is the main characteristic.

Besides the debate on neutrophilia in chronic sinusitis, the underlying mechanisms are also uncertain, and especially the correlation of neutrophilia with allergic inflammation. In allergic chronic sinusitis, the neutrophil was not considered to play as important a role as in nonallergic patients. However, other studies suggested that neutrophils not only correlate with infection, but also with allergic inflammation. Kowalski et al. reported that neutrophil chemotactic activity (NCA) in nasal lavage was present in chronic sinusitis, allergic rhinitis as well as controls. Among the three groups, allergic rhinitis patients had the highest NCA. Another study of Lee et al. reported that although eosinophil and neutrophil presence was found in the nasal secretion of chronic sinusitis (CS), allergic rhinitis (AR) and normal controls, the
mechanism may be different. In AR, eosinophilia was correlated with mast cell infiltration, whereas eosinophil numbers correlated with neutrophils in CS patients. In addition, the eosinophil/neutrophil ratio was higher than 0.1 in AR but lower than 0.1 in CS and controls. In the study of allergic fungal sinusitis patients, neutrophil elastase was present in both tissue and mucin. It was suggested that the contribution of neutrophils may be equal to that of the eosinophil in AFS. The role of neutrophils in infection as well as allergic inflammation in the upper airway disease needs further study.

Mast Cells and Basophils

Whether the mast cell contributes to the development of chronic sinusitis and its correlation with allergy in the disease is still controversial. Some studies suggested that the presence of mast cells was rare in chronic sinusitis, especially in those related with infection. According to a report, no difference could be observed in mast cell number in nasal polyps, sinusitis and controls. In this study, IgE was scarce but IgA and IgM had high levels. Also, the absence of tryptase in nasal fluid was evidenced. Controversial reports suggested that mast cell degranulation was seen both in atopic and nonatopic chronic sinusitis patients, especially in those with aspirin sensitivity, atopy and childhood chronic sinusitis. Ethmoid sinus and paired inferior turbinate were reported to have a significantly higher mast cell level than the paired maxillary sinus. Mast cells in chronic sinusitis were similar to that in the middle turbinate from allergic rhinitis but lower than in nasal polyps.
mast cells were present in both atopic and nonatopic patients, especially in those with nasal polyps and asthma.\textsuperscript{367} Although in AFS there was no tryptase in the mucin, in the respiratory area tryptase was present in high levels.\textsuperscript{370} The mechanism underlying mast cell infiltration in chronic sinusitis and its contribution are far from known.

**Macrophages**

In animal model of virus-induced acute sinusitis, a moderate influx of macrophages was identified.\textsuperscript{429} In the study of chronic sinusitis, it was reported that macrophage numbers increased especially in patients with allergy.\textsuperscript{416} In chronic sinusitis patients with CF, a significant correlation between macrophages and recurrence was identified.\textsuperscript{378} However, a study of *Aspergillus* chronic sinusitis reported that CD11+ cells (macrophages, monocytes and natural killer-cells) decreased compared to controls.\textsuperscript{447} There was a report of equal infiltration of macrophages in CHS/NP and controls.\textsuperscript{307} The role of antigen presenting and innate immunity of macrophage in chronic sinusitis is not clarified yet.

**Structural Cells**

As regards the contribution to the chronic inflammation of nasal polyps, epithelial cells,\textsuperscript{448} endothelial cells\textsuperscript{449} and fibroblasts\textsuperscript{450} also play important roles in chronic sinusitis.
Atopy and Cell Pattern

The correlation of inflammatory cell infiltration with atopy in chronic sinusitis remains controversial. Studies have reported similar inflammatory cell infiltration in atopic and nonatopic patients, including eosinophils, mast cells, macrophages as well as CD3+ and CD4+ T cells. Reports from other studies suggested that allergic sinusitis could be differentiated from chronic suppurative sinusitis with a significant proportion of activated eosinophils. Demoly et al. observed higher infiltration of lymphocytes and mast cells in chronic sinusitis patients with allergic rhinitis than those without allergy, but there was no difference of eosinophil and macrophage elevation. There are also other reports of differences in T cell subsets, i.e., a significantly higher level of CD3+ T cells in allergic CHS/NP patients and a significantly higher level of CD8+ T cells in nonallergic chronic sinusitis patients. Hamilos et al. also reported that allergic CHS/NP patients had more IL-5+ mast cells and IL-5+/CD3+ T cells, whereas the nonallergic patients had more IL-5+ eosinophils. Although the correlation of eosinophil, mast cell and lymphocyte infiltration with allergy is undetermined, it was reported that the prevalence of sinusitis is significantly higher in patients with allergic disease (asthma, allergic rhinitis, atopic dermatitis). However, there may be no correlation between the severity of sinusitis with total or specific serum IgE.

1.7 Treatment of Nasal Polyps and Chronic Sinusitis

Nasal polyps and chronic sinusitis are both chronic inflammatory diseases with high
recurrence. The recurrence rate of nasal polyps is 15% to 100%, and it is especially higher in cases with underlying diseases, such as CF, aspirin intolerance, eczema and asthma. The treatment of nasal polyps and chronic sinusitis involves medical treatment and surgical treatment. Usually, a combination of medical and surgical treatment is applied because of the insufficient effect of using one method alone. In addition, the diagnosis and treatment of the underlying etiology factors is critical.

1.7.1 Treatment of Nasal Polyps

1.7.1.1 Medical Treatment

The medical treatment of nasal polyps, as suggested by Mygind et al., is aimed at eliminating nasal polyps or reducing their size considerably, so as to re-establish an open nasal airway and nasal breathing, to relieve rhinitis symptoms, to re-establish the normal sense of smell and to prevent recurrence. Meanwhile, the above author suggested that it was not necessary to eliminate sinus pathology.

Medical treatment based on topical and/or oral corticosteroid is the first line of treatment of nasal polyps. Corticosteroids have been shown to reduce the size and improve symptoms of nasal polyps effectively. It also facilitates prevention of relapse after surgical treatment. Studies have shown the effect of steroids in reducing inflammatory cell infiltration in polyp tissue, including eosinophilia and eosinophil activation, CD4+ T lymphocytes, antigen presenting cells and mast
An in vitro study also demonstrated that corticosteroids can induce apoptosis of inflammatory cells in nasal polyps. According to many other studies, steroids increase the expression of TNF-α and reduces the expression of proinflammatory chemical mediators such as P-selectin, IL-4 and IL-13, GM-CSF, IL-5, IL-6 and IL-8, and eotaxin. Over expression of the glucocorticoid receptor splice variant GRbeta in inflammatory cells may contribute to steroid insensitivity in nasal polyps.

Other medical treatments in nasal polyps have also been suggested, including antibiotics, such as macrolides which are not only effective in decreasing the virulence of bacteria, but also in decreasing the polyp size and the IL-8 level in nasal lavage; anti-leukotrienes, which may be effective in patients with aspirin intolerance; furosemide which is an inhibitor of the sodium chloride cotransporter channel at the basolateral surface of the respiratory epithelial cell; capsaicin which is usually effective in reducing symptoms of vasomotor rhinitis; mizolastine which is a potent and selective H1-receptor antagonist; antimycotic agent amphotericin B (AmphoB) which was cytotoxic for nasal polyp epithelial cells; anti-histamine and anti INF-α etc. However, further large scale, placebo-controlled clinical trials are needed to fully assess the effectiveness of these medical treatments.

Although steroids can improve symptoms of nasal polyp patients, they are not
efficient in eradicating nasal polyp tissue. As reported by Tuncer et al., only 12% of the patients in the study had fully cleared polyp tissue after steroid treatment. In 88% of the patients, ablation of polyp tissue could not be achieved while 12% did not respond to medical treatment at all. In addition, long term use of systemic steroids may cause side effects. Thus, surgical intervention is needed.

1.7.1.2 Surgical Treatment

Surgery is reserved for medical failures or for patients with a contraindication for drug therapy. Surgical treatment is aimed to remove polyp tissue in nasal cavity and sinuses while preserving the anatomic structures and normal mucosa. Functional endoscopic sinus surgery (FESS) is the standard surgical treatment of nasal polyps nowadays. Other techniques include polypectomy, Caldwell-Luc and intranasal ethmoidectomy. FESS has been proven to improve the quality of life of the patients satisfactorily, and is found to be more effective in improving symptoms compared to other techniques. In general, 78% to 88% of the patients have improved symptom scores after FESS, whereas the improvement rate was 43% to 84% in those treated with other techniques. Overall complications in FESS and conventional techniques amounted to 1.4% and 0.8%, respectively.

Long-term use of steroids and follow-up are suggested after surgical treatment because of the high recurrence of nasal polyps. The recurrence rates treated by various techniques was 8% for FESS, 14% for Caldwell-Luc, 28% for endoscopic
ethmoidectomy and 35% for polypectomy. However, the duration of the follow-up procedure may affect the recurrence rate considerably. In the 20-year follow-up study by Vento et al. of 41 nasal polyp patients, the recurrence rate was 85%. In those patients with aspirin intolerance, the recurrence was especially high, followed by those with allergy and proposed intrinsic allergy.

1.7.2 Treatment of Chronic Sinusitis

In the treatment of sinusitis, the aim is to eradicate infection, provide reversal of sinus obstruction and return effective mucociliary clearance. Because the etiology of sinusitis is not clear yet, whether sinusitis is a medical or surgical disease is under discussion. Physicians hold different ideas on the diagnosis and treatment of the disease. The treatment of allergic fungal sinusitis which is a unique type of sinusitis, involves aggressive sinus surgery followed by medical management such as allergen immunotherapy, topical and systemic corticosteroids, antihistamines and antileukotrienes. In patients refractory to treatments, underlying conditions including allergy, immune deficiency, cystic fibrosis, gastroesophageal reflux, and structural abnormalities, CHS/NP, AFS and aspirin intolerance, have to be taken into consideration and diagnosed carefully.

1.7.2.1 Medical Treatment

Medical treatment methods of sinusitis are listed in Table 6. Different medical treatments are applied according to the classification of sinusitis. In the treatment of
chronic sinusitis, steroids, as that in nasal polyps, is the first line choice, although whether a steroid spray can enter the sinuses is uncertain. Antibiotics are widely used in the treatment of chronic sinusitis. Besides the role of anti infection, antibiotics, such as macrolides, have also been proven to inhibit inflammatory cell chemotaxis, cytokine synthesis, adhesion molecule expression, reactive oxygen species production, and airway mucus hypersecretion.  

Table 7. Medical treatment of sinusitis.  

<table>
<thead>
<tr>
<th>Classification</th>
<th>General treatment measures</th>
<th>Antibiotics</th>
<th>Antihistamines</th>
<th>Steroid nasal spray</th>
<th>Ipratropium bromide nasal spray</th>
<th>System steroids</th>
<th>Immuno-therapy</th>
</tr>
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<tbody>
<tr>
<td>Acute</td>
<td>+</td>
<td>+</td>
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<td>Subacute</td>
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<td>Recurrent</td>
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<td>Chronic</td>
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<tr>
<td>Acute exacerbation of CRS*</td>
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<td>+</td>
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<td>+</td>
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</tr>
</tbody>
</table>

*) CRS: chronic rhinosinusitis. +, beneficial; -, not beneficial; ±, beneficial in some cases.

Medical treatment in chronic sinusitis has been proven to improve symptoms of patients effectively together with radiographic improvement. However, those patients with nasal polyps and/or previous sinus surgery are more often frequently refractory to medical treatment.

1.7.2.2 Surgical Treatment

Surgical intervention is applied when medical treatment fails in the treatment of chronic sinusitis. FESS is the essential method used to open the OMC and remove the sinus disease with minimal manipulation of the surrounding normal tissue. Other
techniques include aspiration and Caldwell–Luc. Although most of the patients have improved symptoms after surgical treatment, 5% to 25% of the patients still have persisting symptoms. Long term use of medical treatment and follow-up is suggested.

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