Nasal Polyposis
Having been asked to write a foreword for a book entitled “Nasal Polyposis” the first question that comes up is: Is it really necessary to have a new book on nasal polyposis? The answer is of equal spontaneity: Yes.

More than 30 years ago, Rhinologists became for the first time happier treating nasal polyposis as the topical steroids made the conservative treatment easier, and the new Hopkins rod lens system, with its great visualization facilities, aided new consolidated findings in regard to early diagnosis. In addition, when compared to the classic, radical procedures, which are more than 100 years old, surgical treatment could include many more functional considerations thus avoiding mutilating side effects and late complications, such as mucoceles. Our generation did not like the classic procedures as we knew that most of these patients will come back. Due to the improved clinical diagnostics in particular, a tremendous progress in imaging the indication for surgery was made, aiding a clear diagnosis.

Due to these factors the therapeutic results improved dramatically and Rhinology became a rising star in Otorhinolaryngology.

On the other hand, the only achievement of our therapy is a symptomatic improvement in the patient with polyposis disease as the therapy shrinks polyps and improves the drainage of the sinuses, opening a better way for medicinal treatment. So far an effective causal therapy for nasal polyposis has not been established.

The knowledge about epidemiology, etiology, pathogenesis, and pathophysiology of nasal polyposis has increased in many aspects but a comprehensive summary of the present status has been missing.

We have to thank both the editors for having put together a harmonic team of authors who are basically scientists, experienced clinicians, and surgeons, and the list of these authors reads like a who is who in Rhinology. Globalization and international cooperation have facilitated the sharing of basic research and comparing of therapeutic results across the globe and this has increased the chances of finding the deficits of the treatment and reducing them.

Everything about why polyps develop and how to treat them can be found in this book. Another great advantage of this book is that controversial issues such as fungal-induced inflammation and Staphylococcus aureus-derived Superantigens in nasal polyp disease or functional endoscopic sinus surgery and nasalization are also discussed.

Of specific importance is the last chapter dealing with the evaluation of surgical treatments leading us further to solid evidence-based judgment of what we are doing.
Foreword

I am sure this great compilation of knowledge will be welcomed and appreciated by the interested reader and will work as a basis of future progress in this fascinating field of Otorhinolaryngology.

Hannover, March 2010

Wolfgang Draf
We are pleased to present the First edition of *Nasal Polyposis* compiled of contributions from world renowned international experts on a myriad of etiologic and therapeutic aspects of this complex disorder. While nasal polyposis (NP) represents the most apparent manifestation of CRS and it is standard to categorize CRS regarding presence or absence of NP, NP is a diverse disorder with multiple causes and triggers.

We have organized this book in the first section to reflect the history, epidemiology, and inflammatory characteristics, followed by tools for diagnosis – pathology and radiology. While some purposed CRS causes such as biofilms, fungi, and superantigens are not confined to NP, they nevertheless may contribute to inflammation in NP and these and other etiologic topics are addressed by experts in the field in the following section. Fungal cause of CRS inflammation is controversial and we present two chapters on this reflecting two points of view.

Other disorders are known for their association with NP and include association with asthma and lower airway disorders, systemic vasculitis syndromes, and cystic fibrosis. A chapter is also devoted to the differential diagnosis of NP in children and preceeds special aspects of NP evaluation including olfaction and nitric oxide assessment.

The second half of this book is devoted to therapeutic approaches to NP. The medical therapies of steroids, antibiotics, antifungals, and aspirin desensitization are each addressed in their own chapter. The treatment of NP has been referred to as sandwich therapy by my friend and a contributor, Wytske Fokkens MD, PhD. This reflects the need for medical therapy before and after the surgical therapy which is sandwiched between.

From the first chapter of this book we know that surgical therapy for NP dates back at least to the fifth century BCE, and Hippocrates. The last section of this book returns to surgical methods, including endoscopic sinus surgery, nasalization, aggressive sinus marsupialization, and the modified Lothrop procedure.

Despite medical interventions and the most brilliant surgery, every rhinologist and every expert has patients with recalcitrant or rapidly recurrent disease. There is still much to understand in the management of this complex and diverse disorder. We hope this book will allow you to be the best practioner possible in the care of your patient with NP.

This book would not have been possible without our outstanding contributors. Our two associate editors Harshita Pant MD, PhD now in Adelaide, Australia and Brad Otto, now at Ohio State University, USA were tireless in editing and smoothing
translations across these many chapters. This book would not have been possible without them and we thank them wholeheartedly.

Around the globe we pursue a common goal – better care and understanding of our patients’ nasal polyposis. We may have different opinions on cause and management, but that is true in any field in which causes and best management are still not known. I hope you find the multiple viewpoints a stimulant to questioning and continuing research as well as a guide and help in investigation, categorization, and treatment of nasal polyposis.

21 June 2010

T. Metin Önerci

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History of Nasal Polyposis
Janaki Emani and Fuad M. Baroody

1.1 Introduction

Nasal polyps were first recorded approximately 4,000 years ago. Over the years, there have been significant advances in the understanding of the incidence, epidemiology, and pathophysiology of polyps. The means of diagnosis and medical and surgical treatments have also undergone a major revolution. This chapter reviews the chronological history of nasal polyps, their diagnosis and pathophysiological associations, and the historical milestones that shaped the management of polyps as it is practiced today.

1.2 The History of Rhinology and Nasal Polyps

The earliest record of nasal polyps is found in Egyptian literature of approximately 2,000 years BCE [23]. Rhinologic procedures dating to 700 BCE are depicted in the ancient Hindu and Egyptian medical texts. One of the great Hindu surgeons, Susruta, who practiced in the fifth century, was the founder of modern day rhinoplasty and nasal reconstructive flaps. In 1500 BCE, the ancient Egyptians were known for their familiarity of and dexterity in the nasal cavity as they routinely removed the cranial contents through the nose to prevent facial disfigurement during the mummification process. Though Susruta undertook advanced nasal surgical procedures, Hippocrates (460–370 BCE) is better known as the father of rhinology and medicine, due to his influence during the apex of Greek civilization, in approximately the fifth century BCE. In addition to establishing the Hippocratic oath, Hippocrates also observed and documented medical afflictions related to otolaryngology, including coryza, pharyngitis, intubation, uvulotomy, tonsillectomy, nasal fractures, epistaxis, sinusitis, and nasal polyps [16].

Hippocrates referred to the “nasal growths” as “polypus” due to their resemblance to the sea-polyp, and this name has persisted to this day [23]. Hippocrates and other renowned physicians including Claudius Galen, Paulus Aegineta, and Fabricius Hildanus were known to have treated nasal polyps in their time.

1.3 Etiology and Pathophysiology

Polyps were initially thought to be due to a state of thickened or viscous bodily humors. In the early first century AD, Celsus and others noted that nasal polyps...
were affected by moist weather and warm seasons [16]. The theory that these nasal masses were a manifestation of systemic disease prevailed until the early seventeenth century, when local trauma was hypothesized to contribute to the condition. Boerhaave, in 1744, was among the first to surmise that these growths resulted from elongation of the linings of the sinus membranes [23]. About the same time, Manne and Heister suggested that polyps occurred secondary to obstruction of the ducts of mucous glands.

The nineteenth century was also fraught with controversies regarding the etiology of nasal polyps. Virchow [20] and his pupils thought that these masses were primary tumors including myxomas and fibromas. Eggston and Wolff [9] viewed them as passive edema of mucosa, while others believed in an infectious etiology including sinusitis or osteitis [22]. In 1843, Frerichs and Billroth proposed that polyps were truly a hypertrophy of normal sinonasal mucosa, as the epithelium covering the polyp was similar to the mucosa of the originating sinus [23].

A systematic investigation of etiological associations began in the early twentieth century. In 1933, Kern and Shenck proposed a relationship between allergy and nasal polyps [13]. They found that the incidence of nasal polyps was 25.9% in patients with allergic rhinitis compared with 3.9% in a nonallergic population. They also noted that the ethmoid air cell system was the most common target for the inflammatory response and that polyps frequently originated from this site. Eggston’s [9] concept of the etiology of polyps is that they arise due to basic vascular changes in the nasal mucosa induced by repeated attacks of sinusitis, periphlebitis, and obstruction of return flow of interstitial tissue fluid leading to passive congestion and edema. Advances in immunohistochemistry and immunobiology in the 1940s led to the first description of the predominance of eosinophil and lymphocyte populations in polyps. Anderson and Bing have shown the polyp stroma to be proteinaceous exudate, while Weisskopf and Burn [21] considered that it has acid mucopolysaccharides. Berdal [3] states that accumulation of reagins and ample edema in polyps is due to allergic inflammation. On the other hand, Tandon et al. [17] observed no difference in the histological appearance of allergic and infectious polyps.

Kern and Schenck’s initial report of the strong relationship between allergies and nasal polyps has been questioned by more recent investigations. Capllin et al. examined 3,000 patients with evidence of atopy and found that only 0.5% had nasal polyps [7]. Following their findings, Bunnag et al., reported an incidence of 4.5% of nasal polyps when 300 patients with allergic rhinitis were examined [5]. These, and other, studies have led most allergists and rhinologists to the conclusion that allergic rhinitis may not be a primary causative factor in nasal polyps. Furthermore, Bonfils and colleagues have shown that the presence of allergy does not modify symptoms of nasal polyps or their response to medical treatment [4]. Several other theories about the etiology of nasal polyps are under investigation today: bacterial infections, mucosal inflammation from bacterial superantigens, fungal inflammation, genetic factors (cystic fibrosis, primary ciliary dyskinesia), and aspirin hypersensitivity [5, 6, 8]. The association between cystic fibrosis and polyps was first noted in 1959 by Lurie, and soon thereafter, Schwamann described its relationship with sinusitis [10].

The medicinal properties of acetylsalicylic acid (ASA) have been known for over 3,500 years. Ancient Chinese, Indian, and Egyptian healers prescribed ASA, as extracts from tree bark and leaves, for a variety of symptoms including fever, pain, and labor. In 1880, Felix Hoffman, an employee of a dye manufacturing company owned by Friedrich Bayer, used waste components of the factory to synthesize a stable form of salicylic acid powder. Over the course of 1 year, Hoffmann purified the substance until he produced a pure form of ASA. Soon after its introduction in 1899, aspirin sensitivity was reported by Hirshberg, a German physician. As early as 1929, reports of bronchospasm were noted in aspirin-sensitive patients undergoing polypectomy. Samter and Beer in 1969 reported the triad of aspirin sensitivity, nasal polyps, and asthma [24].

### 1.4 Diagnosis of Nasal Polyps

Contrary to one’s expectation, historical description of polyp diagnosis was not limited to those that protruded through the nares or those that caused physical nasal deformity. In Egyptian literature, Samuel noted that “a polyp shows itself by a bad smell of the nose.” Hippocrates describes polyps as “sacs of phlegm that cause nasal obstruction and derange the sense of smell.” Celsus likened polyps to “the nipples of a woman’s breast” and wrote in his case reports that “large polyps dangled into the pharynx” and “on cold and damp days strangulate a man,” depicting large polyps that obstructed the choanae and oropharynx [23].
Visualization of the anterior nasal cavity was enhanced with the development of the nasal speculum. While cauterizing patients for epistaxis, Hippocrates used a crude tubular speculum. A similar prototype of tubular speculum was also used by Hindu Ayurvedic doctors in 500 BCE [16] and by Haly Abbas (940–980), a prominent figure in Islamic medicine. These early speculums were modifications of instruments used for gynecological and rectal examinations. Fabricius Hildanus (1560–1634) constructed an aural speculum, which closely resembles the modern day nasal speculum. This instrument was molded to its current specifications in the eighteenth century by Peret and Kramer [22].

Sir Morell Mackenzie, who was responsible for establishing Otolaryngology as a unique subspecialty, wrote that Levert, a French obstetrician, used a speculum of polished metal that reflected sunlight to view polyps and tumors of the ears, throat, and nostrils [2]. Until the sixteenth century, candlelight was primarily used to examine the anterior nares. In the 1570s, Aranzii used a glass flask filled with water and candles to intensify the light directed into the patient’s nose. In 1829, a young physician named Benjamin Guy Babington presented a series of flat and angled handheld mirrors at the Hunterian Medical Society and demonstrated the ability to reflect sunlight to the back of the pharynx. He also used a tongue retractor to obtain an unobstructed view. Although Babington did not publish the success of his instrument in viewing the structures of the larynx, other authors over the mid-1800s did mention this device and his techniques [22].

Alfred Kirstein (1863–1922) was responsible for the introduction of artificial light to the field [15]. The instrument consisted of a flat spatula illuminated by a urologic hand lamp. Subsequently, Kirstein developed the first headlight that remarkably resembles those that are in use today (Fig. 1.1). Perhaps of greatest significance was the advent of both flexible and rigid fiberoptic endoscopes in the late 1900s, which have revolutionized the examination of the upper aerodigestive tract in otolaryngology.

The development of X-ray techniques in the nineteenth century also influenced the diagnostic algorithm of polyps. The Caldwell, Waters’, and submentovertex views became essential in identifying the opacification of the sinuses and bony abnormalities. Computerized axial tomography (CAT) that was developed by Hounsfield in 1970 surpassed conventional radiographs and provided superior imaging of the sinuses. Although CT scans are not essential for the diagnosis of most nasal polyps, they are important in determining the extent of sinonasal disease and planning surgical treatment.

1.5 Treatment of Nasal polyps

The recurrent nature of nasal polyps was known since the Hippocratic era. Hippocrates wrote about patients who required multiple treatments and recognized that even after performing a directed excision, additional
therapy was needed to prevent redevelopment of polyps. Thus throughout, till today, polyps are treated both medically and surgically.

### 1.5.1 Medical Treatment

Hippocrates used nasal packs and tampons coated with honey and copper salts in an attempt to curtail the recurrence of polyps; however, the effects of this treatment are unknown. A Roman physician, Claudius Galen, treated polyps primarily medically with oily applications, goose fat, calf tallow, and irritating medications like turpentine [23]. No further significant descriptions of the medical management of polyps were found until the twentieth century [19].

Kern and Schenk’s description of the relationship between allergies and polyps paralleled the discovery that histamine caused allergic reactions. Italian pharmacologist Daniel Bovet synthesized antihistamines during much of the 1930s, and in 1944, the first nontoxic antihistamine became available to the public. Thus, antihistamines were used as a primary and postsurgical treatment for polyps. Evidence for a helpful role of antihistamines in nasal polyposis is lacking and they are now primarily used to treat concomitant allergic rhinitis, if present. The current mainstay of medical therapy is corticosteroids.

The discovery of steroids represented a new era of treatment. Anabolic steroids were first isolated and chemically characterized during the 1930s and topical and systemic steroids were used for the management of nasal polyps since the 1970s [14, 18]. Van Camp was one of the first to describe the use of preoperative oral steroids to shrink the polypoid tissue and facilitate removal [18]. Intranasal steroids are very frequently used in the treatment of nasal polyposis and have been shown to reduce the size of polyps, delay recurrences, and decrease the need for repeat surgery [1].

### 1.5.2 Surgical Treatment

The history of the surgical treatment of polyps is most intriguing and gruesome. In the Treatises, Hippocrates delineated several methods he used to remove polyps. One method involved using a soft sponge, large enough to fill the nasal cavity that was fastened to several pieces of string. Then a forked flexible metal probe was passed through the nostrils and into the pharynx with the strings tied to the forked end of the probe. The sponge was then pulled through the oral cavity, pushing the polyps out [23]. The sponge method was used to remove polyps until the 1880s. For larger polyps, Hippocrates used a crude snare by fashioning a loop of sinew around the base of the polyps and passing one end through the pharynx, which effectively avulsed the polyps (Fig. 1.2). He also used a hot iron passed through the nostrils to cauterize polyps. After these treatments, Hippocrates placed stents smeared with oil, honey, and copper powder in the nasal cavities [23].

Roman medicine was dominated by Aulus Cornelius Celsus, also known as the Roman Hippocrates, who wrote the book series “De Medicina.” Celsus frequently treated polyps with caustic agents, but also used a sharp spatula-like instrument to separate the polyp from the bone and removed it with a hook-like instrument from the nose [16]. The “knotted-string method” was utilized in the sixth and seventh centuries by Paulus Aegineta, who wrote: “taking a thread of moderate thickness, like a cord, and having tied knots upon it at a distance of two or three finger breadths, we introduce it into the nose via a double headed speculum upward to the ethmoid openings, then drawing it with both hands, we saw away … at the fleshy bodies.” In the pre-Renaissance period (1000–1200s), Rolando, a famed Italian physician, also used the knotted string and the spatula methods to remove polyps [16].

Not much changed in the surgical methods until the 1600 and 1700s, when snares and forceps were developed. Though Fallopius (1523–1562) was credited for developing the snare, medical specialists from Japan and India were using snares even prior to that. Fallopius wrote, “I take a silver tube which is neither too narrow nor too broad and … brass wire, sufficiently thick, preferably the wire with which harpsichords are made. This doubled I place in the tube so that from this wire a loop is made at one end of the tube, by which, used in the nares, I remove the polyp. When the polyp is engaged in the loop, I push the tube to the root of the polyp, and then pull on the metal threads and thus I constrict the roots of the polyp and extract it …” [23]. The forceps, introduced first by Fabricius in the mid-1600s, were actually scissors curved at the end. John Van Horne (1621–1770) added teeth at the point of the instrument to provide a better grip on the polyps. Benjamin Bell,
the eighteenth century prominent Scottish surgeon, published in a System of Surgery (1791) a range of snares and forceps to remove polyps [16, 23]. Many modifications of the forceps ensued over the following years (Fig. 1.3). For larger polyps, surgeons described splitting the nasal alae and sometimes even the soft palate. The advocates of these procedures maintained that these open approaches offered better visualization, and thus, more complete excisions of the polyps [16, 22].

Throughout the eighteenth and nineteenth centuries, the struggle in treating primary and recurrent nasal polyposis continued. Until the use of endoscopy became popular, more extensive intranasal procedures such as Caldwell-Luc radical antrostomy, intranasal ethmoidectomy, and external frontoethmoidectomy were also utilized. These procedures stripped mucosa and altered the nasal and paranasal sinus landmarks [11]. Even with such extensive intervention and medical therapy, polyp recurrence was still a problem.

Significant changes in sinonasal surgery were brought about with the development of endoscopic

The general design and function of modern day snares closely resemble those illustrated here. The McKenzie (top) and Krause (bottom) snares were developed in the late 1700s. (Adapted from Lack)
sinus surgery (ESS). Although the term “endoscopy” was coined by a French urologist Antonin Jean Desormeaux (1815–1894), it was a German physician, Phillip Bozzini, who developed the first endoscope, known as the “Lichtleiter,” in 1805 [2]. The instrument consisted of an eyepiece and a container for a candlelight that was reflected by a mirror through a tube. Bozzini used his rudimentary endoscope to examine the bladder, rectum, and pharynx. Another German urologist, Max Nitze, modified the “Lichtleiter” by creating a metal tube with a series of lenses within. Several water-cooled platinum wires were threaded through the tubes and used as the light source. In 1950, Storz introduced the first fiberoptic endoscope that bears resemblance to those used today [2]. Hirshmann, in 1901, first applied endoscopy to sinonasal disease. He modified a cystoscope and used it to view the maxillary sinus and middle meatus through an enlarged dental alveolus. Despite the technological advancements, it was not until the1960s that the endoscope gained popularity in the diagnosis and surgical treatment of sinonasal diseases. This newfound interest was due in part to the increasing popularity of minimally invasive intervention in all surgical specialties and in part to the works of Walter Messerklinger of Graz, Austria. His work involved the anatomical and physiological study of the nose and paranasal sinuses and their mucosal blanket. Most importantly, he noted the patterns of mucus clearance of different areas of the nose and sinuses through various ostia and into the infundibulum and that disruption of the mucocilliary transport or obstruction of normal flow led to disease. With Messerklinger’s discoveries, functional endoscopic sinus surgery (FESS) was introduced in the late 1960s in Germany, and David Kennedy is credited for introducing FESS in the United States in 1985 [12].

1.6 Conclusions

Nasal polyps have been recognized for a long time. Although many theories about their cause have evolved over the years, we are still left with controversy and uncertainty about the etiology. The diagnosis and treatment strategies have undergone a colorful evolution. Today, we have overcome most of the difficulties in the diagnosis and significantly improved the technical aspects of surgical treatment. Nevertheless, we still face recurrent disease and the need for repeat surgical procedures. Thus, to this day, the quest for the cure of nasal polyps remains an important goal.

References

2.1 Introduction

Mounting evidence suggests that nasal polyposis (NP) is a clinical manifestation of multiple possibly coexisting immunologic pathways, and because this entity likely reflects an array of disease states, the epidemiology is difficult to characterize. Phenotypically, chronic rhinosinusitis (CRS) can be classified as either CRS without NP or CRS with NP. CRS without NP, in general, reflects TH1-mediated inflammation [45]. Idiopathic CRSwNP comprises the vast majority of cases of NP, and this term typically implies a clinical picture of diffuse sinonasal polyposis dominated by TH2-mediated (eosinophilic) responses, at least in western patients. In rare cases, a distinct genetic, immunologic, or metabolic defect has been associated with the development of diffuse NP, and these cases will be discussed below. Furthermore, CRS with NP must be differentiated from antrochoanal polyps, which account for only 5% of polyp cases [24]. Antrochoanal polyps are usually unilateral and solitary and most often arise from the maxillary sinus. This is a distinct disease process that often presents at a younger age compared to CRSwNP. In contrast to CRSwNP, antrochoanal polyps reveal lesser degrees

Allergic fungal rhinosinusitis is a known underlying pathophysiologic etiology in a subset of CRS patients and is strongly associated with NP.

Ethnic and geographic variation has emerged as a potential modifier in NP pathophysiology.
of eosinophilia with a more normal appearing mucosal surface and basement membrane [31].

The prevalence of NP in the population has been grossly estimated as 1–4%, though supporting evidence for this finding is scarce [24]. Older reports have suggested a prevalence ranging from 0.2 [12] to 2.2% [16], and autopsy studies have reported an incidence of bilateral NP at 1.5 [43] to 2% [25]. Various comorbidities such as allergic rhinitis (AR), generalized atopic status, and asthma have all been proposed as factors in the genesis of NP. Yet the data for these associations have been the subject of on-going investigations and conflicting reports can be identified. Variations in prevalence have also been reported as a function of demographic factors, including age and gender. In addition, hereditary factors and ethnic variations exist and must be considered. The present chapter is dedicated to elucidating the epidemiology of CRS with NP in general, as well as in the context of comorbid disease states and known underlying pathophysiologic processes.

2.2 Allergy and Asthma

Classic teaching has implied that NP formation is a product of an allergic response (atopy) to inhalant allergens. Although this relationship seems intuitive, current data suggest that this association is weak. NP prevalence in patients with AR is estimated to be between 1.5 [40] and 1.7% [14], and this incidence approaches that of the general population as previously described.

Large cohort studies have revealed a strong association between asthma and NP while consistently challenging the relationship between atopy and NP. In one investigation of over 2,000 patients, Settipane reported that NP were more common in nonallergic asthmatics vs. allergic asthmatics (13 vs. 5%, \( p < 0.01 \)) [39]. These data were corroborated by Grigoeras et al. who analyzed 3,817 Greek patients with chronic rhinitis and asthma. Overall, the incidence of NP in this population was 4.2% and NP prevalence was the greatest in nonallergic asthmatics vs. allergic asthmatics (13 vs. 2.4%). There was an association between NP and perennial allergy as opposed to seasonal [14].

Other studies have examined as to how factors such as NP and atopy may correlate with CRS severity, as measured by CT scan. In a group of 193 CRS patients treated at a tertiary care center, statistical analysis revealed that atopy was significantly more prevalent in the CRS without NP subgroup (32.3%) compared to those with CRS with NP (27.5%). Although the mean Lund–Mackay score was slightly greater in atopics vs. nonatopics (14.2 vs. 12.3, \( p = 0.05 \)), significance was lost when the cohort was separated into those with and without NP. In contrast, increased radiologic severity was observed in the CRS with NP group. Overall, these data suggest that the presence of NP is unrelated to atopy and is a better predictor of advancing radiologic disease [35].

A similar study examined 106 patients from a tertiary care center of which 49% were atopic by skin endpoint titration. Overall, atopics and nonatopics exhibited no difference in the prevalence of NP (38 vs. 37%). Presence of asthma, however, was an independent predictor for the existence of NP, which was observed in 57.6% of asthmatics vs. 25% of nonasthmatics \( (p=0.0015) \). As with previous reports, Lund–Mackay score was the greatest in nonatopic asthmatics, followed by atopic asthmatics, and then nonasthmatics. As expected, the Lund–Mackay score was the greatest in the polyp group, but it is important to note that this association was found to be independent of atopic status. In summary, these data indicated that asthmatic patients are more likely to have polyps than nonasthmatics [32]. Furthermore, the presence of asthma and polyps were each significant predictors of disease severity as measured by Lund–Mackay score. In contrast, atopy appears unrelated (or perhaps weakly related) to either polyp growth or advancing severity of radiologic disease.

The pathophysiology of CRS with NP and asthma may reflect a similar chronic inflammatory response in the upper and lower airways, at least in a subset of patients. An abundance of eosinophils is typically seen in the polyp tissue of patients with CRS with NP, while this is not consistently observed in patients with CRS without NP [17]. The inflammatory cellular infiltrate in asthmatics is also composed of eosinophils, mast cells, and CD4+ T lymphocytes [42]. Bachert et al. has theorized that the relationship between severe CRS and asthma may be due to the production of inflammatory cytokines in airways which induce the upregulation of eosinophils, mast cells, and basophils by the bone marrow upregulation. These inflammatory cells then migrate to the airway mucosa resulting in a reactive inflammatory response leading to NP formation [6].
2.3 Gender and Age

It has been suggested that the incidence of NP increases with age [14, 39]. Settipane reported that NP frequency reaches a peak in patients who are 50 years and over [39]. Furthermore, he reports that asthmatics over 40 years of age are four times more likely to have NP than those under 40 (12.4 vs. 3.1%, p < 0.01) [39]. Larsen et al. reported similar results in a uniform population of Danish patients. Of 252 patients, they observed NP most commonly in patients who were 40–60 years old. Additionally, patients over 80 years of age were unlikely to have NP. The mean age of diagnosis of NP was 51 in males and 49 in females. In sharp contrast, unilateral antrochoanal polyps were diagnosed at a much younger age: males 27 years, females 22 years [24].

The discovery of NP in children is extremely rare. The estimated incidence of NP in patients less than 16 years of age is 0.1 [39] to 0.216% [24]. In a study of 1,051 pediatric allergic patients, only one had NP [40]. If NP are found in a child, a workup for cystic fibrosis (CF) should be conducted.

As with age, the literature varies in relation to the impact of gender on the development of NP. In Settipane’s review of 211 NP patients, there was an equal distribution of males and females, 50.2 vs. 49.8% respectively [40]. Data published more recently using the Danish National Health Care insurance system to identify patients treated for NP differ with this prior observation. In fact, this cohort exhibited an increased incidence of NP in males over 20 years as compared to age-matched females. The male:female ratio of patients with NP was 2.9 in ages 40–50 and maximal at 6.0 for patients between 80–89 years of age [24]. The incidence was the greatest in both males and females in the age range of 40–69 years. In this group, NP was present in 1.68 male and 0.82 female patients per thousand annually. It is important to note that data from this Danish initiated study represent a homogeneous population of 252 NP patients culled from 5 years of retrospective data.

2.4 Genetics

Genetic inheritance has been proposed as a possible etiology of NP. Studies have suggested that up to 14% of patients with NP have a family history of NP [13]. Attempts to delineate a hereditary pathway using monozygotic twin studies have yielded mixed results. In a report of twins with steroid-dependent asthma, only one had bronchospastic aspirin intolerance and NP while the other did not manifest these phenotypic traits [38]. Further attempts have been made to show an association of NP in families. In a cohort of 174 NP patients, 25% had a first degree relative with polyps (parent, sibling, or child) [10]. Forty-four patients manifested Samter’s triad (aspirin intolerance, asthma, and NP) and 36% of these patients had a first degree relative with NP. Furthermore, 32% (57) of the polyp patients had both NP and asthma of which 30% had a first degree relative with polyps. Though a genetic predisposition to form NP is likely a significant factor, there is no clear Mendelian inheritance pattern in the vast majority of NP cases, and a gene–environment interaction is likely at work.

There are various disorders that are genetically inherited in which the formation of NP is a disease characteristic. CF is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. The gene product of CFTR is a chloride ion channel primarily in the exocrine glands of the lungs, liver, pancreas, and intestines. Approximately, 20% of patients with CF have NP [39]. A diagnostic work-up for CF should be conducted in any patient under the age of 16 who presents with NP.

Primary ciliary dyskinesia (PCD), also known as Kartagener’s syndrome, is characterized by CRS, bronchiectasis, and situs inversus (reversal of internal organs). Defects in the dynein arms of cilia are primarily responsible for the immotility seen on mucosal biopsy; however, radial spoke defects and microtubular transposition anomalies have been identified [41]. Ultimately, the frequency of ciliary beat is abnormal and uncoordinated. PCD has been seen in both men and women leading investigators to conclude that this is an autosomal recessive disorder. However, recent observations of a nonconsanguineous family with retinitis pigmentosa (RP) and PCD have suggested an X-linked inheritance pattern [29]. It is likely that there may be more than one mode of inheritance pattern for PCD as investigation into left-right axis deviations in vertebrates has shown an autosomal dominant, recessive, and X-linked pattern [9].

When initiating medical treatment for CRS in patients with either CF or PCD, culture-directed
therapy should be considered. CF patients have a high likelihood of *Pseudomonas aeruginosa* infection and antibiotic therapy should be tailored to this pathogen. CF patients are often treated with maintenance antibiotics directed against *P. aeruginosa* consisting of macrolides or fluoroquinolones. Therapy may be aerosolized to increase the concentration delivered to the tissues with a low toxicity profile [44].

Young’s syndrome is another disorder characterized by recurrent sinopulmonary disease, obstructive azoospermia, and NP [15]. This disease differs from CF and PCD in that sweat chloride tests are normal, as is ciliary function demonstrated by normal sperm tails and tracheal biopsies. Spermatogenesis is normal and the azoospermia results from an excess of inspissated secretions in the epididymis [15, 37]. The prevalence of Young’s syndrome remains unclear, but it has been suggested to be responsible for up to 7.4% of male infertility [39].

A systemic vasculitic disorder, Churg–Strauss syndrome (CSS) commonly presents with upper airway symptoms. Originally felt to be comprised of four hallmark characteristics, bronchial asthma, CRS, eosinophilic vasculitis, and granulomas [30], there is likely phenotypic variation to this syndrome. The American College of Rheumatology accepts six primary characteristics of CSS: asthma, eosinophilia >10%, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. To qualify for a diagnosis of CSS, four of the six criteria should be present, yielding a sensitivity of 85% and a specificity of 99.7% [27]. CSS is a systemic vasculitis of small to medium-sized vessels and is associated with AR and/or CRS with or without NP [2, 3]. The exact mechanism of CSS is unknown, but eosinophil activation likely plays a major role [2]. Otolaryngologic manifestations may consist of AR, CRS with or without NP, nasal crusting, otitis media, and rarely, sensorineural hearing loss and unilateral facial palsy [2]. NP is present in up to 60% of patients with CSS and is likely an indicator of early disease [3]. Corticosteroids are highly effective in treating patients with NP associated with CSS [3].

### 2.5 Aspirin Intolerance

NP are frequently observed in patients who are insensitive to aspirin (acetylsalicylic acid) or nonsteroidal antiinflammatory drugs. In this subset of patients, these medications induce an acute asthmatic response within 30–90 min of ingestion [36]. This “triad” of symptoms, (bronchial asthma, CRS with NP, and aspirin insensitivity) is often referred to as Samter’s triad or ASA-triad. In a majority of affected patients, aspirin challenges produce an acute bronchial response with rhinorrhea and nasal obstruction [33]. Aspirin insensitivity that causes urticaria without bronchospasm has not been associated with NP. It has been estimated that up to 50% of aspirin insensitive patients have NP and that 36% of patients with NP may have some form of analgesic insensitivity [39]. However, while considering all the patients undergoing endoscopic sinus surgery (ESS), including CRS with and without NP, approximately 4.6% had ASA-triad [19].

The development of a fully realized ASA-triad likely occurs over time. Initially, patients may present with chronic rhinitis. Within 5–10 years, aspirin-induced asthma will become apparent. Shortly thereafter, NP becomes prominent [34]. Nonallergic rhinitis with eosinophilia syndrome (NARES) has been proposed as a precursor in the pathway leading to ASA-triad [28]. It has been shown that NP epithelial cells from ASA-triad patients have abnormalities in basal and aspirin-induced generation of eicosanoids (products derived from arachidonic acid metabolism including prostaglandins, thromboxanes, and leukotrienes), ultimately leading to aspirin sensitivity [21].

NP of ASA-triad patients likely represent a unique phenotype of severe inflammation, which is more recalcitrant to both medical and surgical intervention. The NP of ASA-triad patients demonstrate increased edema and inflammatory infiltrate compared to the NP of aspirin tolerant patients [7]. Additionally, ASA-triad patients’ response to surgery is universally poor, undergoing approximately ten times as many ESS procedures as that of ASA tolerant patients [19]. Furthermore, ASA-triad patients have a significantly higher rate of symptom recurrence (nasal obstruction, facial pain, postnasal drip, and anosmia), regrowth of NP at 6-month follow up [7, 19], and lack of statistical improvement in FEV1 [7].

### 2.6 Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a known underlying pathophysiologic etiology in a subset of CRS patients and is strongly associated with NP. Classically, a diagnosis
of AFRS is made when the following five hallmark characteristics are present: a type I hypersensitivity to dematiaceous fungi, NP, paranasal CT scan findings of inspissated mucus with calcification, eosinophilic mucus containing Charcot-Leyden crystals without fungal invasion into the surrounding sinus mucosa, and positive fungal stains from sinus contents [8, 22]. Intraoperatively, the eosinophilic mucus is inspissated, tan colored with a thick sticky consistency. Rarely does a patient with suspected AFRS satisfy all five of these criteria. However, the diagnosis can be made based on clinical suspicion and intraoperative observations of eosinophilic mucus and NP. Staining for fungal elements in intraoperative biopsies has proven to be inconsistent even in patients who are strongly suspected of having AFRS.

The incidence of AFRS has not been well established, but patient characteristics likely influence disease manifestation. Approximately 5–10% of CRS with NP patients have AFRS [8, 11]. This is typically a disease of younger adults, with a mean age of diagnosis between 22 [26] and 28 years of age [46], which is significantly lesser than that observed in non-AFRS patients. Studies have suggested that there is an increased prevalence of AFRS in southern, more humid climates. Recent reports have suggested that lower socioeconomic status may also play a role. In patients treated at a tertiary medical center in South Carolina, a significant proportion of the AFRS patients (24.1%) were uninsured or Medicaid recipients as opposed to 5.2% of the non-AFRS CRS with NP group. Furthermore, a significant portion of the AFRS group was African American (61.1%) who resided in counties with a greater African American population and more advanced poverty status [46]. These data raise the point that although AFRS may be more prevalent in various ethnic groups, socioeconomic status may also be a factor in that African Americans accounted for a significant portion of the un- or underinsured. It may be possible that lower socioeconomic status and thus, lack of access to health care, may have allowed for disease progression in this series.

### 2.7 Ethnicity and Geography

As the exact mechanism of NP formation remains a topic of investigation, ethnic and geographic variation has emerged as a potential modifier in the pathophysiology. In a Caucasian population, NP have been shown to have a strong eosinophilic component, likely due to the upregulation of interleukin (IL)-5 [4]. In addition to increased IL-5, eotaxin and eosinophilic cationic protein (ECP) are significantly elevated in NP homogenates and indicate amplified eosinophilic inflammation [45]. Additionally, transforming growth factor (TGF) \( \beta \)1, a cytokine known to stimulate the extracellular matrix and inhibit IL-5 synthesis [1], is downregulated in NP [45]. Therefore, a cytokine cascade culminating in the overproduction of IL-5, with downregulation of TGF-\( \beta \)1, may potentiate the eosinophilic response and have deleterious effects on the extracellular matrix simultaneously [45]. Of note, these results originate from a population of Caucasian patients from the country of Belgium.

Interestingly, this increase in eosinophils in NP is not consistent across various ethnicities. NP in Asian countries show a neutrophilic pattern rather than the previously discussed eosinophilic [18]. Yet, the clinical manifestation of NP remains similar between Asians and Caucasians. Zhang et al. attempted to further characterize the variations seen in Asian polyps. Polyp tissue samples from 27 Chinese patients from the Guangdong province of China were harvested. As with similarly affected Caucasian patients, most of the Asian patients had been treated with nasal steroids and antibiotics. Some had received Chinese herbal medicines. The samples were compared to a group of matched Caucasian Belgian patients, where Chinese polyps had a significantly lower incidence of eosinophils (\( p < 0.01 \)) [47]. A Korean cohort has shown a similar preponderance of noneosinophilic NP [20]. In this study of 30 NP patients, not only were 66.7% noneosinophilic, but the basement membrane thickness of the polyps was found to be significantly thinner in the noneosinophilic vs. eosinophilic group (8.2±3.5 μm vs. 13.9±4.5 μm) [20].

Though the predominant inflammatory cellular infiltrate differs between Caucasians and Asians, commonalities are also apparent. Zhang et al. [47] reported that ten of the Asian polyps contained IgE against *Staphylococcus aureus* enterotoxins (SAE), which is consistent with the previously reported data that one-third of Caucasians with NP and asthma have IgE to SAE [5]. As in white subjects, tissue IgE and sIL-2R are elevated in Asian polyps. Eosinophilic infiltrate is decreased in Asian polyps as measured by ECP and IL-5/eotaxin levels compared to the tissue from
Caucasians. Total IgE was elevated in allergic NP compared with nonallergics, but ECP was not increased. Thus allergic disease likely has a negligible impact on ECP levels and eosinophil recruitment. Similar findings have been made in Caucasian polyps [5, 32, 35]. TGF-β1 was significantly downregulated in Asian polyps compared with inferior turbinate controls. Furthermore, TGF-β1 was extremely low in the NP groups with IgE to SAE suggesting a modulatory effect of staphylococcal enterotoxins. This finding has previously been observed in Caucasians. Of the Asian group, only two had asthma and nine were allergics. There was no difference between the allergics and nonallergics in relation to eosinophilic infiltrate.

It is clear that variation in the physiology of NP differs amongst Asians and Caucasians, yet there have been only limited investigations into other ethnic and racial backgrounds. A collaboration between three otolaryngology departments from various continents, Eritrea (Africa), China (Asia), and Switzerland (Europe) attempted to better characterize the racial variation of NP [23]. In this report, the African and Chinese participants did not receive preoperative steroids or antibiotics whereas the Caucasians were treated preoperatively with prednisolone 1 mg/kg/day for 5 days as well as trimethoprim/sulfamethoxazole for 10 days. Compared to Chinese and Caucasians, Africans presented with more progressive disease in which NP extended into the nasal cavity and were ulcerated. Eosinophil density was also greater in African polyps ($p<0.001$) compared to Chinese and Caucasian NP. There was no difference in the amount of eosinophils between Chinese and Caucasian NP. Plasmocytes and lymphocytes were abundant in Chinese and Caucasian NP and rare in African NP. No difference was observed in the number of mast cells in any group. Unfortunately, the patients included in these analyses were not standardized in relation to preoperative treatment. The Caucasian cohort had been treated with preoperative steroids which would likely suppress the presence of inflammatory mediators in the polyp biopsies. Both the Chinese and African cohorts received no preoperative treatment. The root cause of these discrepancies is likely due to socioeconomic disparities among the study countries resulting in a significant variation in the patients’ access to health care and likely affected the molecular data. Just as NP of Caucasians and Asians can exhibit significant cellular and molecular differences, it is possible that polyps from African patients also show significant variation in cellular and molecular profile.

**Take Home Pearls**

- NP is a phenotypic manifestation of multiple possible immunologic processes.
- The significant association between NP and asthma suggests similar underlying pathophysiology that is independent of atopy.
- Although some CRS with NP cases are associated with established genetic syndromes, most patients likely have multiple, subtle, and as yet unknown genetic variations that combine with environmental factors resulting in polyp formation.
- Further study is necessary to elucidate the key factors that account for the variability in polyp epidemiology.

**References**

2  Epidemiology of Nasal Polyps

3.1 Introduction

The term polyp refers to the macroscopic appearance of a pedicled tissue arising from a mucosal surface and projecting into a lumen or cavity. The histopathology of polypoid tissue affecting the nose and paranasal sinuses is diverse, ranging from inflammatory nasal polyps to benign and malignant epithelial, mesenchymal, and hematolymphoid neoplasms (Table 3.1). In the context of chronic rhinosinusitis (CRS), “polyp” refers to benign nongranulomatous inflammatory tissue projection with an epithelial lining within the sinonasal cavity. There are several histopathological features that differentiate CRS nasal polyps from other types of polypoid lesions occurring in the nose and paranasal sinuses. Furthermore, nasal polyps may have some unique characteristics that are distinguishable from the surrounding nonpolypoid CRS mucosa.

3.2 Normal Sinonasal Histology

The normal sinonasal histology is characterized by structural components including the epithelium, basement membrane, and submucosal tissue, and nonstructural components including resident and nonresident cells from the lymphoid and myeloid lineage.

3.2.1 Structural Component

Epithelium and basement membrane: The anterior 2 cm of the nasal cavity is lined by skin, composed of an epidermis with keratinizing stratified squamous epithelium, a fibrocollagenous dermis, and adnexal glands. The rest of the nasal cavity is lined by respiratory-type mucosa that is derived from ectoderm, also known as the Schneiderian membrane. Normal sinonasal mucosa is depicted in Fig. 3.1. The respiratory epithelium consists of four major cell types: ciliated columnar or cuboidal cells interspersed with goblet cells, nonciliated columnar cells with microvilli, and basal cells. The ratio of
columnar cells to goblet cells is approximately 5:1 and this ratio may vary depending on the site [21]. The normal respiratory-type epithelium often shows scattered areas of metaplastic squamous or cuboidal epithelium, and this is especially seen in the inferior turbinates [3]. The cells contain tight junctions and rest on a basement membrane composed principally of collagen fibers (types I, III, IV, V, VI, and VII) and other constituents that include heparan sulfate proteoglycan, laminin, and nidogen [1]. The basement membrane is delicate; however, in the inferior turbinate, a thick basement membrane may be seen. Compared with the nasal cavity, the paranasal sinuses have a thinner, less specialized surface epithelium and lamina propria [22]. These differences in the structural and cellular components between the sinus and nasal mucosa may reflect their different embryological origins and functional differences [2, 17].

The superior turbinate, superior nasal septum, roof of the nasal cavity and superior and medial portion of the middle turbinate are lined by olfactory epithelium also known as neuroepithelium [16]. This is also a ciliated pseudostratified columnar epithelium, which consists of a basal cells, bipolar ciliated olfactory cells, microvillar cells, and supporting or “sustentacular” cells. The central axonal process of olfactory cells passes though the cribriform plate to synapse with neurons present in the olfactory bulbs. With increased age, and following injury and infections, olfactory epithelium shows patchy loss and subsequent replacement with respiratory epithelium. The epithelial surface is covered by mucus produced by goblet cells, submucous glands, and ciliated cells. Mucus is actively propelled by the cilia toward the openings of the sinuses, enabling its drainage into the nasal cavity.

<table>
<thead>
<tr>
<th>Differential diagnostic consideration</th>
<th>Distinguishing clinical features and morphology</th>
<th>Immunophenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal angiofibroma</td>
<td>Size, cellular stroma with thick muscular arteries, young adolescent males</td>
<td>Beta-catenin +, androgen receptor +</td>
</tr>
<tr>
<td>Solitary fibrous tumor</td>
<td>Size, cellular with dense “ropey” collagen and “staghorn” pericytomatous vasculature</td>
<td>CD34 +, bcl-2 +, CD99 +</td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumor</td>
<td>Size, cellular myxoid stroma arranged in fasicles with inflammatory background</td>
<td>Smooth muscle actin +, anaplastic lymphoma kinase (ALK) ±</td>
</tr>
<tr>
<td>Neuroglial heterotopia</td>
<td>Fibrillary matrix, ± ganglion cells</td>
<td>Glial fibrillary acidic protein +, synaptophysin +, neurofilament ±</td>
</tr>
</tbody>
</table>

**Fig. 3.1** Normal sinonasal mucosa (H&E, 100×). The surface is lined by ciliated pseudostratified columnar epithelium with goblet cells resting on a delicate basement membrane. The submucosa consists of delicate connective tissue with lobules of mucous glands and sparse lymphocytes representing NALT.
**Submucosa:** Beneath the basement membrane, the submucosa overlying the cartilage and bony sinonasal framework contains loose fibrovascular connective tissue, stromal cells including numerous seromucinous and minor salivary glands, blood vessels, nerves, and myeloid and lymphoid cells. Multiple seromucinous glands are present in superficial and deep layers and are separated by large venous sinusoids. The lobular units of the glands have a peripheral clustering of serous (~10%) and mucous (~90%) acini that secrete mucins, immunoglobulins, and enzymes that drain sequentially into the intercalated, striated, excretory, and ultimately, the main ducts. The main duct communicates with the epithelial surface. Over the age of 60, these mucoserous glands may show oncocytic change, a senescent phenomenon characterized by the abnormal accumulation of mitochondria in the cytoplasm imparting a granular densely eosinophilic appearance by light microscopy. The underlying vasculature consists of subepithelial capillaries, periglandular microvessels, and numerous arterial and venous anastomoses. The capillaries have specialized fenestrations that facilitate transport of fluid and high-molecular weight compounds. These networks communicate with venous erectile vessels that are irregularly shaped with multiple smooth muscle layers and are most prominent in the submucosa of the nasal turbinates (Fig. 3.2). Here, the prominence and irregularity of these veins may simulate an arteriovenous malformation or cavernous hemangioma to those who are unfamiliar with the regional histology. Glands are usually more abundant in the normal middle turbinate, whereas veins are more prominent in normal inferior turbinate [8].

### 3.2.2 Nonstructural Components

The lymphoid compartment in the sinonasal mucosa is comprised of single lymphocytes scattered among the epithelial cells and lamina propria, and the nasal-associated lymphoid tissue (NALT) [13]. The NALT are discrete unencapsulated aggregates of lymphoid cells, akin to that in the mucosa-associated lymphoid tissue in the gut (Peyer’s patches). However, NALT are not as well formed in the sinonasal mucosa, but may become more pronounced in chronic inflammation. The lymphocyte population is composed of T cells, B cells and...
plasma cells, natural killer (NK) cells, and natural killer T (NKT) cells, and the myeloid cells include monocytes, macrophages, dendritic cells, granulocytes (including neutrophils and eosinophils), and mast cells. These cells form an integral component in the adaptive and innate mucosal immune responses.

3.3 Nasal Polyp Histopathology

3.3.1 Chronic Rhinosinusitis with Nasal Polyps

Approximately 20% of CRS patients have nasal polyps [9]. Presence of polyps may signify a distinct type of CRS with recalcitrant disease. Clinical conditions often associated with nasal polyps include asthma, asthma and aspirin sensitivity (Samter’s triad), eosinophilic mucus chronic rhinosinusitis (EMCRS, including allergic fungal sinusitis), cystic fibrosis, Churg–Strauss disease, Kartagener’s syndrome, and Young’s syndrome. Histologically, polyps have been classified into several groups, based on the proposed etiology, predominant inflammatory cell infiltrate, and stromal appearance. This classification is purely descriptive and not specific to an underlying associated disorder or pathology.

3.3.1.1 Macroscopic Pathology

Macroscopically, most polyps have an edematous, smooth and shiny appearance with a soft consistency compared with the surrounding nonpolypoid mucosa. The cut surface is usually pale, edematous with a translucent appearance (Fig. 3.3). Biopsies from long-standing disease may be firm and solid white suggesting extensive fibrosis. Polyps are generally mobile and often attached via a stalk to the underlying mucosa. The surrounding CRS mucosa and middle turbinate is generally more erythematous and is firm to palpation. The CRS mucosa, depending on the degree of edema, may appear polypoid, but does not have a discrete stalk. Polyps commonly arise from the middle meatus and the sphenoethmoidal recess and are often bilateral. However, unilateral polyps are not uncommon. Polyps vary in size, and in severe cases, may completely fill the nasal cavity. In long-standing polyps, the sinonasal bones may remodel and cause broadening of the nasal dorsum.

The mucosa of the middle turbinate, inferior turbinate, uncinate process, and septum may also have broad-based polyps. A large polyp originating from the inferior turbinate is unusual [4]. Polypoid mucosa in the posterior portion of the inferior turbinate is not uncommon, referred to as a “mulberry” turbinate [10], and is usually not associated with CRS. Contrary
to the middle and superior turbinates, the anterior portion of the inferior turbinate is rarely polypoid and this may be due to the presence of squamous epithelium and the aerodynamics in the region. A polyp arising from the maxillary sinus and into the nasal cavity is characteristic of antrochoanal polyp and is generally unilateral [25]. Nasal polyps associated with CRS do not usually have macroscopic surface ulceration, and the presence of such may indicate other pathologies. A more lobulated or “bunch of grapes” may signify other pathologies such as a sinonasal papilloma; however, based on the appearance alone, the underlying pathology is not always possible to determine. Therefore, all polyps, especially unilateral ones, need a histopathological examination at some point.

A proportion of CRS with nasal polyps also has characteristic thick, dark, and tenacious mucus, termed eosinophilic mucus. This mucus is typically seen in allergic fungal sinusitis but is also present in patients with severe and recalcitrant polyposal CRS including cystic fibrosis and Sampter’s triad and in the lungs of allergic bronchopulmonary aspergillosis. In many cases, the pathology of allergic fungal sinusitis may have been missed because the mucus was not examined for fungal elements.

3.3.1.2 Microscopic Pathology

The major histological characteristics of nasal polyps and CRS mucosa compared with normal mucosa include (1) structural changes involving the epithelium, submucosa, and sometimes underlying bone; and (2) the nature and degree of inflammatory cell infiltrate. Nasal polyps are typically lined by respiratory epithelium and have a basement membrane with variable thickness and an underlying stroma with a range of structural changes and inflammatory cells. Polyps have historically been classified based on their histological structural appearance and the nature of predominant inflammatory cell population into (1) edematous, eosinophilic, or “allergic” polyps, (2) chronic inflammatory polyps, and (3) seromucinous, glandular polyps. The description eosinophilic vs. noneosinophilic polyps is often used in the literature. But this classification is not specific to any associated or underlying pathology.

Edematous and eosinophilic polyps are the most common type and are also known as “allergic” nasal polyps. However, only a small proportion of CRS with NP have coexisting allergy and the controversy involving an allergic etiology is discussed elsewhere. These polyps are lined with respiratory epithelium with a range of mucosal alterations that include ulceration, granulation tissue, acute mucositis, epithelial and goblet cell hyperplasia, and squamous metaplasia. The basement membrane is often thickened, and there is abundant submucosal edema (Fig. 3.4). Mucus retention cysts are common and varying amounts of mixed inflammatory cell infiltrates contain mostly eosinophils, plasma cells, and scattered lymphocytes. The mucoserous glands are often incorporated within the edematous polyps. The edematous and eosinophilic polyps are seen in the whole spectrum of associated disorders including, EMCRS, allergic fungal sinusitis, Sampter’s triad, cystic fibrosis, and Churg–Strauss syndrome. Classically, nasal polyps associated with cystic fibrosis have delicate rather than thickened basement membranes and less stromal eosinophilia, and more neutrophils, hence termed neutrophilic polyps. Also characteristic is the presence of dense, deeply eosinophilic inspissated mucus secretions.

Chronic inflammatory polyp, also known as fibroinflammatory polyp, is less common, forming less than 10% of inflammatory nasal polyps [14]. These may represent a spectrum of edematous polyps, where occasionally, when a polyp is traumatized, the stroma may undergo secondary inflammatory change resulting in a myofibroblastic proliferation that may mimic a soft tissue neoplasm. The main histological features are the presence of submucosal fibrosis and an often prominent mixed inflammatory infiltrate with a lymphoid predominance often with germinal centers. Similar to other sinonasal polyps, mucoserous glands are still present within the polyp, unlike true mesenchymal lesions that tend to displace mucoserous glands. The surface epithelium is likely to show squamous metaplasia as a marker of chronicity (Fig. 3.5). Polyps with hyperplasia of seromucinous glands are less common. Lesions in this category are relatively new and somewhat controversial as to their relationship with true epithelial neoplasms, and include respiratory epithelial adenomatoid hamartoma and seromucinous hamartoma [23, 24].
**Fig. 3.4** Edematous polyp (H&E, 20x). This polyp shows slightly thickened basement membranes (arrows) and marked submucosal edema resulting in extensive clear space between submucosal connective tissue fibers. Inset (H&E, 400x) – scattered throughout are mixed inflammatory infiltrates including eosinophils and plasma cells.

**Fig. 3.5** Chronic inflammatory changes in polyps.  
(a) (H&E, 20x). This polyp shows an exuberant lymphoid hyperplasia with reactive germinal centers.  
(b) (H&E, 100x). This polyp shows mucosal ulceration (right) and squamous metaplasia (left)