Topical Review

Nasal biopsy: indications, techniques and complications

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Introduction

The nose is the most accessible part of the respiratory tract and is therefore an invaluable source of respiratory tissue. Biopsy of intra-nasal tissue can help in the investigation and diagnosis of local nasal disease or systemic conditions affecting the nose. The procedure was well-established by the late 19th century when the role of histology in the diagnosis of a variety of nasal conditions had been described (1).

Nasal biopsy is either performed in a fully-equipped operating theatre under local or general anaesthetic or performed in an outpatient clinic. The choice depends on a number of factors including the reason for performing the biopsy, the size of the biopsy required, the opinion of the surgeon, and the general health and preference of the patient.

A nasal biopsy may either be performed for research or to aid clinical diagnosis. For research purposes, the biopsy must have a very low complication rate and be as painless and atraumatic as possible. Subjects must be prepared to return for a subsequent biopsy in longitudinal studies. For diagnosis however, a small biopsy provides only a small volume of tissue for interpretation. Some conditions affecting the nose, such as the granulomatous disorders, have sparse histological features and in a small biopsy these may not be seen. In these circumstances and for effective diagnosis and grading of malignancy, a large biopsy is preferable. Large biopsies should be harvested with turbinate scissors as a formal procedure in a fully-equipped operating theatre, followed by adequate nasal packing for 24–48 h (2).

This paper reviews the clinical and research indications for nasal biopsy. During recent research studies of nasal pathophysiology, 250 nasal biopsies have been performed in 160 subjects at St Bartholomew’s Hospital, London. The technique that has been developed for performing nasal biopsy under local anaesthetic will be described. The complications of the procedure have been monitored during this time and will be discussed.

Indications for Nasal Biopsy

The spectrum of indications for nasal biopsy is illustrated in Fig. 1, and the aim of this review is to illustrate the role of nasal biopsy in the diagnosis or study of conditions affecting the nose.

Clinical Indications

Sarcoidosis

Nasal sarcoidosis was first described by Boeck in 1899 (3) and confirmed by biopsy by Kistner and Robertson (4). It is a chronic disease of unknown aetiology characterized by the presence of widespread, non-caseating granulomata (5). Histologically non-specific, the same appearances may be seen in other granulomatous disorders. It has been suggested that sarcoidosis could be a special form of tuberculosis or caused by an agent such as beryllium, Mycobacterium leprae, a protozoan, fungus or virus (6). Random nasal biopsies have a low yield of granulomatous material and the diagnosis is often one of exclusion (7).

The non-healing granulomata

Wegener’s granulomatosis. Wegener’s classic paper on rhinogenic granulomatosis in 1939 (8) discussed a condition first described by Klinger (9) which is still of unknown aetiology. Patients are systemically-unwell with a variety of clinical features attributed to the development of necrotising granulomatous inflammation of the respiratory tract, focal necrotising glomerulonephritis and a systemic vasculitis. A
biopsy is usually required for a definite diagnosis (10). A nasal biopsy may not show the characteristic features (10–12), but is easier and safer than lung or renal biopsy. A biopsy larger than 5 mm is recommended (10) and the technique which will be described may not provide enough tissue to be useful in this condition.

Lethal midline granuloma. The lethal midline (midfacial) granuloma first described by McBride in 1897 (13) is now considered to be a localized, nasal T-cell lymphoma (14) which causes progressive ulceration of the nose and destruction of adjacent structures. The diagnosis is usually made after immunofluorescence histochemistry. Examination and biopsy may need to be high in the nose and should be performed under operating conditions.

Specific infections

Bacteria

Nasal syphilis. Nasal involvement can occur in all stages of syphilis. Tertiary syphilis is encountered most commonly and the pathological lesion is the gumma (15). The nose may develop septal and palatal perforation, collapse of the dorsum, scarring and stenosis of the nasal passages and an atrophic mucosa (16). The clinical features and serology are usually diagnostic but if in doubt, a biopsy should be performed to help differentiate syphilis from other conditions such as yaws, lupus vulgaris, sarcoidosis, atrophic rhinitis, leprosy, scleroma, leishmaniasis and some tumours (16).

Rhinoscleroma. Rhinoscleroma starts in the nose but progresses through the respiratory tract to the bronchi (17). It is a granulomatosis caused by Klebsiella rhinoscleromatis and diagnosed by a biopsy in which Mickulicz cells and Russell bodies are characteristic findings (17,18). Treatment is continued until two consecutive cultures from biopsy material are negative (18).

Tuberculosis. A rare condition predominantly affecting the nasal septum, nasal tuberculosis (TB) has been reported as a primary infection (19), but is normally secondary to lung disease. If bacteriological examination of nasal mucus does not show tubercle bacilli, a biopsy may demonstrate the typical appearances of TB.

Lupus vulgaris is an indolent chronic TB infection of nasal and facial skin which usually involves the mucocutaneous junction of the nasal septum. A biopsy will show the characteristic appearance of the tuberculous granuloma within the reddish firm 'apple-jelly' nodule, which typically stands out in greater contrast when the surrounding skin is blanched by pressure from a glass slide.

Leprosy. Leprosy is classified as lepromatous, tuberculoid or borderline (20), and is caused by Mycobacterium leprae, an acid-fast bacilli similar to M. tuberculosis. In 97% of patients with lepromatous leprosy, the nasal mucosa is involved and the discharge is infectious even when there are minimal systemic signs (21). Thus the nasal discharge is the principal route of transmission of the disease (21). Particularly in lepromatous leprosy, the mucosa and cartilage of the septum can be extensively destroyed, and biopsy of turbinate mucosa shows characteristic features (22).

Pathogenic fungae and yeast. The taxonomic classification of these conditions is complex and well-described by Emmons et al. (23). They are of greater clinical importance in tropical countries rather than European countries, but they are also associated with immune-deficiency disorders and so are assuming increased relevance in the advanced world.

The phycomycoses. Orbital and central nervous system mucormycosis (rhinocerebral phycomycosis) is an aggressive, fulminating, often fatal disease of the nose and paranasal sinuses (24) caused principally by Mucor circinelloides, Absidea corymbitera and Mucor javanicus (order Mucorales). Because Basidiobolus (order Entomophtharales) has been implicated, the term phycomycosis was recommended (25). Rhinocerebral phycomycosis (mucormycosis) is usually associated with immune-deficiency or serious pre-existing illness, and characteristically presents as a black, necrotic turbinate resembling a mass of clotted blood. The necrosis spreads directly and intravascularly to the paranasal sinuses, orbit, cribriform plate, meninges and brain. The disease is confirmed by biopsy, and rapid diagnosis and treatment is needed to prevent irreversible damage or death.

Entomophtharamycosis conidiobolae (rhino-phycomycosis) is the other phycomycosis of rhinological interest. Usually a tropical disease, it is caused by Conidobolus coronatus (order Entomophtharales) and presents with nasal granulomata and polyps. Lesions usually start at the inferior turbinate and spread to the sinuses and face. Histologic examination of a biopsy specimen shows characteristic features.
Rhinosporidiosis. Rhinosporidiosis is a chronic infection of the nose caused by the fungus *Rhinosporidium seeberi*. It can present with epistaxis due to a bleeding polyp on the nasal mucosa (26). Microscopic examination of nasal mucus may reveal spores, and biopsy shows a characteristic histologic appearance. Bleeding after biopsy may be excessive and biopsy should not be performed on an outpatient.

Aspergillosis. Aspergillosis causes nasal obstruction and a mouldy-smelling nasal discharge. The fungus grows as a grey (*Aspergillus fumigatus*) or black (*A. niger*) false membrane which has characteristic histologic features. The disease can be fatal (27), especially in immunocompromised patients when it can resemble rhinocerebral phycomycosis.

Histoplasmosis. Histoplasmosis is a diffuse disease of the reticuloendothelial system caused by *Histoplasma capsulatum*. Nasal involvement is rare but can be demonstrated by examination of a biopsy specimen.

Protozoa. Nasopharyngeal leishmaniasis is caused by the protozoan *Leishmania braziliensis*, and is transmitted by the sandfly (*Phlebotomus*). It is characterized by the presence of Leishman-Donovan bodies in the granulomatous tissue which may develop in the nose.

Tumours

The large variety of tumours that affect the nasal cavity will not be discussed further because in most cases, a detailed intranasal examination and large representative biopsy is prudent for optimum diagnosis and treatment. This should be performed in an operating theatre.

Berylliosis

Berylliosis is usually suspected from occupational exposure (5). To aid diagnosis, a large biopsy of the inferior turbinate or anterior septum can be taken, and so the technique which will be described is not suitable.

Research Applications

The research applications of nasal biopsy are only limited by the facilities available, and the development of research techniques. Research can be categorized into studies using freshly-biopsied nasal tissue or alternatively, studies can be performed on nasal epithelial cell cultures (Fig. 1).

FRESH TISSUE

Studies on fresh tissue may focus on nasal tissue morphology (28,29), inflammatory cellular infiltrates of lymphocytes, eosinophils and mast cells (28,29), ciliary activity (30), or goblet cell activity (31). The study design may compare normal controls with patients who suffer nasal disease (28,29), compare individuals in and out of pollen season (28,29), or compare individuals before and after treatments or drugs (32).

CELL CULTURES

Studies on cell cultures are particularly useful research tools. Nasal epithelial cells can be grown from nasal biopsies as purified cultures which are free of other cells such as fibroblasts, eosinophils and lymphocytes. The environment of the cell culture can be strictly controlled in a way that is impossible in the nose of a patient. Aspects studied include the release of cytokines (33,34), ciliary activity (35), and epithelial cell permeability (36). The effect of pollutants and irritants (33,34), or allergen presentation can be studied. The effect of drugs on epithelial culture (33,34) before or after challenge with irritant or allergen is another research avenue.

In vitro studies of cilia beat frequency (CBF) are often based on cytological samples obtained by brush sampling, but a biopsy or cell culture may show ciliary activity better. However, local anaesthetics can affect CBF as discussed later and this must be considered.

The Technique of Nasal Biopsy

During recent research studies of nasal pathophysiology, biopsy of nasal tissue under local
Anaesthetic was performed on 160 subjects. The first 90 subjects had two individual biopsies performed on each occasion, making a total of 250 biopsies. A detailed report of a safe and well-tolerated technique that has been developed during the course of these biopsies is described, and the complications of the biopsy procedure are presented.

Environment

For diagnosis, a large biopsy may provide better histologic representation of the disease process in some conditions. Biopsies larger than 3–4 mm are best performed in an otolaryngology-equipped operating theatre, so that rapid and effective nasal packing can be performed if excessive haemorrhage occurs.

For research, smaller biopsies are acceptable. The technique which will be described was developed to obtain tissue for research, and is conducted in the sitting position as an outpatient. It is safe for one or two biopsies of 2–3 mm diameter.

Nasal biopsy of the inferior turbinate has a risk of haemorrhage, so the operator must be familiar with the anatomy of the nasal fossae and must have adequate equipment both to illuminate the interior of the nose, and take the biopsy. It must be possible to deal with any complications immediately. Essentially, the biopsy must be taken by an otolaryngologist in a properly equipped area. A third party is invaluable to take the used biopsy forceps and ensure that the biopsy is suitable, whilst the operator concentrates fully on the subject. More importantly, the third party will be available to help with an eventuality such as the subject fainting.

Anaesthesia

After careful application of anaesthetic, the biopsy was generally painless. The nose was thoroughly examined. A small pledget of cotton wool soaked with 0.5–0.75 ml of 10% cocaine solution was placed, using crocodile forceps, between the inferior turbinate and the septum, resting on the floor of the nose (Plate 1). Care was taken to avoid causing epithelial trauma with the forceps. The subject rested under observation for 10–15 min to allow anaesthesia and vasoconstriction to take effect. Cocaine, particularly when swallowed, may cause systemic autonomic effects and observation is prudent. The subject did not always sense the effect of the anaesthetic in the nose, but often the incisor teeth felt numb because of the block to the nasopalatine nerve which traverses and supplies the nasal septum and passes through the incisive canal to supply the gum of the incisor teeth (37). More widespread intra-nasal anaesthesia, such as is delivered from sprays, was unnecessary as was the traditional technique of performing a nerve block of the branches of the pterygopalatine ganglion at the sphenopalatine foramen.

Immediately before taking the biopsy, the pledget was removed and any mucus or crusts gently wiped away with a piece of cotton wool carried on a Jobson Horne probe (Downs Surgical, Sheffield, U.K.).

Lignocaine and cocaine both have an adverse effect on ciliary beat frequency (38) and this must be considered in studies of ciliary beat frequency in fresh tissue. Brush biopsy is an effective method of obtaining ciliated cells without the need for local anaesthetic. In studies using epithelial cell cultures, the biopsy can be performed using cocaine as the anaesthetic, without any subsequent effects on ciliary activity.

Site of Biopsy

The biopsies were taken from the lower fringe of the inferior turbinate, 1–2 cm from the anterior curved edge (Plate 2). This area has good accessibility and its shape suits the jaws of most biopsy forceps. It is also exposed to the influence of inspired air with its noxious or allergic substances. The tissue has sufficient depth of lamina propria and the epithelium is usually ciliated and columnar; although more anteriorly, squamous epithelium may be found (39).

Instrumentation

The biopsy specimen must be large enough to provide evaluative histologic information. It is important to provide tissue which has not been crushed.

Large biopsies can be taken with scissors or a knife, but this is not safe in the outpatient setting. For the research biopsies, small oval punch forceps
were used. They provide specimens with smooth edges and the sharp jaws slice a core of tissue through the oval receptacle. Tangential pressure and tissue crushing, such as would be caused by cupped forceps, is avoided. The forceps must be robust and easy to use.

Gerritsma forceps (Viru Instruments, Oegstgeest, The Netherlands) provide an excellent core of tissue in an atraumatic way (Plates 3 and 4). The biopsy size is about 2.5 mm diameter and the forceps were designed specifically for nasal mucosal biopsies (40). However, the authors found them prone to failure.

IMMEDIATE POST BIOPSY CARE

Immediately after the biopsy, a pledget of dry cotton wool was placed against the biopsy site. The subject was observed for 15 min before the cotton wool was removed under direct vision. Initially, a torpedo-shaped cotton wool pack was placed in the nose with the end sticking out slightly. The subject was instructed to remove the cotton wool after a few hours and once home. This was performed for the first 60 subjects, all of whom had two biopsies performed on each occasion. Some subjects reported that removing the cotton wool was not pleasant and
was frequently accompanied by a brief epistaxis. Due to this, a decision was made to stop placing a torpedo in the nose routinely, and subjects were simply observed for a further 10 min. Packing was only placed in the nose if there was still active bleeding. When brisk haemorrhage followed removal of the first post-biopsy pledget, another pledget was placed in the nose and left for a further 10 min. Should bleeding still occur, a torpedo was placed as formerly described. All subjects were advised to rest as much as possible for the rest of the day, and warned that the nose may ooze blood during this time.

CARE OF THE BIOPSY

The exact care of the tissue depends on the intended analysis. It is always important that the biopsy is handled carefully to avoid crushing it. Generally, tissue should not be left for more than 15 min without some form of preservation. Tissue may be immediately fixed in formal saline (10% v/v formaldehyde in isotonic saline) or paraformaldehyde. Alternatively, it may be snap-frozen in liquid nitrogen or carried in phosphate-buffered saline to be either fixed as above or frozen in OCT (Merck, Poole, U.K.). Formaldehyde-fixation is usually followed by embedding in paraffin wax. Paraformaldehyde-fixed tissue can be embedded in wax or soaked in sucrose and then frozen in OCT. For morphological studies of cellular architecture, tissues are usually sectioned in wax. Wax sections are durable and have good longevity.

In studies where cellular antigens will be examined using monoclonal antibodies, cryostat sections provide better antigen preservation than wax sections (41). Some monoclonal antibodies can be used with formaldehyde-fixed tissue but some are unsuitable. For monoclonal immunohistochemistry, tissue can be placed in OCT and frozen in liquid nitrogen for sectioning in a cryostat. If freezing within 15 min is not possible, fixation in paraformaldehyde can preserve tissue for monoclonal antibody work.

FURTHER ADVICE TO THE SUBJECT

Subjects were told to expect some oozing or bleeding on and off for the remainder of the day, and particularly with rhinitic subjects the nasal mucus will be stained with blood. Advice was given to avoid physical exertion until the following morning.

The Complications of Nasal Biopsy

The complications of nasal biopsy in 160 subjects have been recorded. Subjects were provided with a direct telephone number so that staff could be accessed when problems occurred. In an attempt to gain insight into the more minor problems which subjects experienced, a random sample of 50 subjects were telephoned 2–4 weeks after the biopsy and questioned.

Subjects were recruited by advertisement, word of mouth or through outpatient clinics in the Departments of Otolaryngology and Respiratory Medicine and Allergy at St Bartholomew’s Hospital, London. All subjects were either normal controls or individuals who had allergic rhinitis, and the studies had the approval of the Hospital Ethical Committee. Biopsy was performed by an otolaryngologist (AJP) according to the technique described above. The first 90 subjects underwent biopsy using fenestrated forceps (Downs Surgical, Sheffield, U.K.) and each subject had two biopsies of the same inferior turbinate. The latter 70 subjects underwent a single biopsy using Gerritsma forceps (Viru Instruments, Oegstgeest, The Netherlands). General observations about nasal biopsy will be made, rather than a comparison of complications of the two types of forceps.

COMPLICATIONS RELATING TO THE ANAESTHETIC

The anaesthetic was generally complication-free. Six subjects (4%) described the insertion of the cotton wool as significantly unpleasant and a further 30 subjects (19%) found it to be slightly uncomfortable. The vast majority were not concerned about the anaesthetic. In no cases did the cotton wool pledget become misplaced.

Cocaine is a sympathomimetic drug, blocking synaptic re-uptake of noradrenaline. The maximum recommended dose of cocaine varies from 1.5 mg kg⁻¹ (42) to 3.0 mg kg⁻¹ (43,44). Subjects received 0.5 ml–0.75 ml of a 10% solution, not all of which would be absorbed. Toxicity is usually due to a tachydysrhythmia but in some patients, cocaine can cause a bradycardia due to central vagal stimulation. The latter is usually associated with low levels of systemic cocaine (45). A minority of patients who receive cocaine paste for local anaesthesia have a vasovagal-type reaction consisting of bradycardia and hypotension.

The anaesthetic made one subject feel faint 5 min after application. Her pulse was noted to be 56 beats min⁻¹ and after a few minutes she felt well again. The biopsy was conducted with no further complications. No subjects actually fainted before the biopsy.

COMPLICATIONS DUE TO THE PROCEDURE

Anatomical considerations

The nasal fossae are often asymmetrical with one inferior turbinate more suited to biopsy than the
Significant haemorrhage

Primary. A protective sheet was placed over each subject but this was never soiled. Blood ran out of the nose onto the upper lip of two subjects, but bleeding was never more severe than that. A cotton wool pack was placed in the nose within 5 s of biopsy in most patients, and in the first 90 patients who underwent two biopsies on each occasion, no patient haemorrhaged in such a way as to stop the second biopsy being possible.

The first 60 subjects had a torpedo of cotton wool placed in the nose routinely after removal of the post-procedural pledget. Bleeding came through the torpedo about 2 h after the procedure in one subject, who reported back for replacement of the cotton wool following which bleeding ceased. Of the latter 100 subjects, two suffered a primary haemorrhage and though not routine at the time, torpedoes were placed in the nose for safety. In one of these two subjects, the torpedo had to be replaced before bleeding abated to an extent compatible with leaving the department. There were no sequelae. The second patient telephoned after 3 h stating that he had suffered some bleeding but it had spontaneously stopped. He was advised to rest and no further bleeding occurred. Home removal of the torpedo was uneventful in all three subjects.

Reactionary. One subject needed to be admitted due to haemorrhage. A two-biopsy procedure had been performed uneventfully, and the subject had removed the torpedo with ease, 4 h after the procedure. A spontaneous epistaxis which necessitated admission and nasal packing occurred while the subject was resting at home, 7 h after the procedure. No further sequelae arose.

Non-significant haemorrhage. As Fig. 2 illustrates, haemorrhage which was not severe enough to warrant the subject seeking medical help, is classified into either that occurring during the day of the biopsy, the day after the biopsy, or at any other time.

Of the 50 subjects questioned, 23 subjects had no problems whatsoever. Brief epistaxis after removal of the torpedo occurred in three patients. Oozing of blood or brief episodes of minor bleeding during the day of the biopsy occurred in 22 subjects. Bleeding during the day after the biopsy was very rare, occurring in only two subjects. No subject reported bleeding at any other time.

Failure to obtain an adequate biopsy

The technique described yielded an adequate biopsy on nearly all occasions. In total, 250 biopsies

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<th>Significant</th>
<th>Reactionary haemorrhage</th>
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<td>Primary</td>
<td>Occurring during the day of biopsy</td>
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<tr>
<td>Non-significant</td>
<td>Occurring the day after biopsy</td>
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<td>Occurring at any other time</td>
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Fig. 2 A classification of haemorrhage following nasal biopsy.

other. The side of the biopsy was pre-determined in most studies, but turbinate anatomy never prevented biopsy. When severe septal deflection would have prevented a biopsy of either side, biopsy was not performed on the basis that the nasal cycle must be significantly affected and the abnormal physiology would render studies erroneous. In such circumstances, it was recommended that subjects visit an otolaryngologist because corrective surgery may improve their nasal problems.

Painful biopsy

Generally cutting the biopsy was totally painless. A tearing sensation which could either be felt or heard was reported in 45 subjects (28%). The biopsy was only described as painful in four subjects (2.5%), but all commented that the pain was only momentary. None of these subjects had found application of the anaesthetic unpleasant. One subject suffered an abrasion to the septum from the jaw of the crocodile forceps when placing the immediate post-procedural pledget of cotton wool. The subject did not suffer any significant haemorrhage.

Vasovagal attack

One subject fainted shortly after taking the biopsy. Fortunately, the haemostatic post-procedural pledget of wool had just been inserted and no haemorrhage occurred. The operator and assistant attended to the subject until recovery occurred.

Haemorrhage

Haemorrhage may occur synchronously with the biopsy (primary) or it occurs at some point afterwards, following a spell of haemostasis (reactionary). For the purposes of this study, haemorrhage has been further classified as significant, in which medical help was needed and non-significant, in which medical help was not required (Fig. 2).
were taken from 160 subjects. The biopsy forceps had to be reintroduced into the nose because of an inadequate yield on six occasions (98% success rate). The operator felt that there was a learning curve to the procedure, in that four of these failures occurred in the first 22 subjects (44 biopsies). It was not possible to attribute relative success rates to any specific type of forceps.

Conclusion

Nasal biopsy is, in essence, no different from a biopsy at any other site: a supposedly representative sample of tissue is removed, as an aid to diagnosis, from an area suspected of being affected by a disease process.

Nasal biopsy has been performed for many years on both inpatients and outpatients, yet very little has been written on the subject. The authors are unaware of any previous studies which provide a systematic description of the technique, or which quantify its complications in detail.

A nasal biopsy can help to diagnose a wide variety of local or systemic disease processes. This paper has highlighted some of the more common or important conditions. However, it is not always necessary to perform a biopsy in the conditions discussed. The paper has not discussed every possible condition in which a nasal biopsy can help make the diagnosis. The technique described may have a low diagnostic yield in some conditions, because of their sparse histologic features. Some conditions demand an examination of the nose and postnasal space under anaesthetic.

The results of this study have implications for conditions in which a large biopsy is usually harvested. Although diagnostic success rates after large biopsies are greater, so are the complications. It may be appropriate to perform a small biopsy initially, as this is generally painless and complication- and inconvenience-free. Those biopsies which do support a diagnosis will reduce the number of patients who have to endure a large biopsy in an operating theatre, usually under general anaesthetic, followed by an inpatient stay with the nose packed to prevent haemorrhage.

This study shows that nasal biopsy using small forceps under local anaesthetic is a highly successful (98%) technique for obtaining samples of nasal mucosa, in a manner which is pain-free in 94% of cases. Moreover, in those subjects who do suffer pain, it is only momentary.

Research possibilities involving small samples of nasal mucosa have been outlined earlier, and the figures for the complications support the view that taking biopsies from volunteers is ethically justified. The low complication rate and minimal discomfort ensure that in longitudinal studies, volunteers will be willing to return for a repeat biopsy. Failure to return can render an otherwise good study, suspect.

For those who are considering embarking on a research study involving nasal biopsy, the data presented may help applications for approval by ethical committees. It is stressed that there is a learning curve to the procedure, and for those studies conducted outside an otolaryngology department, an otolaryngologist who is interested in rhinology is a valuable asset.

References