Nasal provocation testing: a review

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**Objective:** This review focuses on the uses of nasal provocation testing (NPT) for scientific investigations of the mechanisms of allergic and nonallergic rhinitis. It also describes the use of NPT as a diagnostic tool in clinical practice. The indications, contraindications, advantages, and limitations of different techniques for evaluation of nasal responses are reviewed. The paper familiarizes investigators with particulars of different nasal delivery systems, provocation agents, nasal patency measurements, secretion collection, and nasal lavage techniques.

**Data Sources:** Relevant publications obtained from a literature review.

**Study Selection:** Relevant publications on the topics of NPT, allergic, and nonallergic rhinitis were critically evaluated.

**Results and Conclusions:** To date, NPT has been used primarily as a research tool for the investigation of allergic and nonallergic rhinitis with a wide variety of techniques depending on the specific scientific purposes. NPT will continue to provide useful information about the pathogenesis of airway diseases. Standardized nasal provocation testing has the potential to become a more frequently used clinical test in the diagnosis of allergic and occupational rhinitis and for determination of the appropriate and focused therapy.

**INTRODUCTION**
Nasal provocation testing (NPT) has been crucial for the scientific investigation of the pathophysiology, immunology, and pharmacotherapy of allergic and nonallergic rhinitis. These studies also offer insights into the pathophysiology of hyperreactivity in lower airways because of the similarity of the response to allergen challenge of the upper and lower airways. Several techniques of NPT have been used depending on purpose of the investigation. Each method has its own advantages and disadvantages. Limitations include the wide variety of test techniques, the absence of standardization for methods and some reagents, and lack of validated direct comparisons between methods. The absence of data regarding inter- and intra-subject variability needs to be addressed to standarize allergen NPT so that it may become a more widely accepted diagnostic method.

**INDICATIONS**
NPT is mainly used for scientific purposes in the United States, but in several European countries, it is used for clinical evaluation. NPT is an office procedure range from diagnosis of complicated clinical cases to selection of optimal therapy (Table 1). Nasal allergic reactions are thought to be predictive of bronchial responses. This can occur only if both target organs are sensitized and responsive to the same allergen. Under this frequent circumstance, nasal provocations will likely be predictive of bronchial, asthmatic effects. The possibility that an allergen may cause a positive nasal response, but not be relevant to a subject’s asthma must be considered. The same dilemma occurs with allergen skin testing for prediction of bronchial responses to allergen. Despite these concerns NPT generally offers a safer alternative to bronchial provocation when evaluating the role of specific allergens in a patient’s asthma. Indications for scientific investigations have been described (Table 2) because NPT allows ready access to respiratory mucosa for sampling of mediators, cells, and secretions.

**CONTRAINDICATIONS**
Acute bacterial or viral mucosal inflammation is accompanied by rhinorrhea, stuffy nose, and nonspecific hyperreactivity, which preclude NPT (Table 3). In accordance to the general approach in allergy, generalized allergic reactions, including anaphylactic shock and severe bronchospasm and status asthmaticus can occur in patients during the acute phase or exacerbation of their allergic disease (rhinitis, food allergy, drug allergy, insect allergy, urticaria) or in patients with previous anaphylactic reactions to the allergen of interest. NPT should not be conducted in patients with restricted lung capacity. The danger of miscarriage due to anaphylaxis prohibits NPT during pregnancy. A wide variety of drugs can cause false-negative NPT and should be withdrawn before testing (Table 4). Nasal congestion may also result from oral contraceptives and preparations containing sulfite preservatives such as bronchodilator solutions (metaproterenol, isoproterenol, isoetharine), analgesics (meperidine),...
changes in nasal reactivity and may lead to chronic rhinitis from nonallergic rhinitis. Differentiation of allergic perennial rhinitis or seasonal allergic rhinitis. To 2 to 4 weeks after any acute allergic challenge is not clear. NPT should be delayed to 2 to 4 weeks after an infection. Nasal reactivity is also decreased for 4 to 8 weeks after nasal or sinus surgery since atypical reactions may be induced. Nasal pathology such as polyps, atrophic rhinitis, and septal deviation can give false-positive or false-negative results in NPT depending on their severity.

TECHNIQUES

Rhinoscopic examination should precede any nasal provocation to inspect the baseline condition of nasal mucosa and evaluate structural pathology such as polyps, septal deviation, atrophic rhinitis or sinusitis. If significant pathologic changes are found, NPT may not be required. Subjects should have previous skin tests or/and RAST performed to evaluate the likely atopic sensitivities. For clinical purposes, the most practical method is simple, safe, and easily repeatable (Fig 1). Most of the clinical protocols are consistent with European practice, but are not accepted for clinical use in the United States. Testing should be performed by well-trained personnel in a well-equipped unit under standard conditions to readily identify and limit nonspecific irritant effects, and treat allergic side effects as soon as they appear. The best time for NPT is in the morning, before lunch time because this limits effects of daily-life stimuli (fumes, cold air, spicy food, physical exercise). After adaptation to room temperature for 30 minutes, clinical symptom score and nasal function should be evaluated. Basal nasal function can be measured by nasal peak expiratory flow rate [NPEFR], or nasal peak inspiratory flow rate [NPIFR], anterior or posterior rhinomanometry, or acoustic rhinometry (gives volume of nasal cavity). Method of NPEFR is not accepted by experts in the United States. These measures are repeated three times and the mean value is recorded. Each measurement should differ from the mean by less than 10% to 15%.

Table 1. Clinical Indications for NPT

| 1. To identify a role of an individual, nonstandardized, novel, or unique specific allergen in the nasal target organ using allergen preparations. |
| 2. To confirm the role of a special occupational agent, such as baker's yeast and dusts, carpenter's saw dusts, or latex. |
| 3. To confirm the clinical relevance of a specific allergen in patients with multiple positive allergy skin tests. |
| 4. To assess the role of allergens implicated by a patient's history when allergy skin test and/or RAST are negative or when the reactions of the nasal mucosa to an allergen are more pronounced than those of skin. |
| 5. To investigate food-induced rhinorrhea. |
| 6. To determine if nasal application of allergen can induce symptoms in the conjunctiva, middle ear, sinus, and lower respiratory airways. |
| 7. To confirm the allergic nature of asthma, since positive nasal reactions may be obtained when the corresponding bronchial provocation tests are negative or can not be safely performed. |
| 8. To confirm nasal reactivity before starting local nasal immunotherapy. |

Table 2. Indications for the Scientific Investigations

| 1. To investigate the spectrum of allergen-induced immediate and late phase responses and the dose dependent nature of these reactions. |
| 2. To identify the morphological and cellular responses to inhaled allergens using nasal lavage, biopsy, and brushing. |
| 3. To detect chemical mediators, markers of glanular exocytosis, and vascular permeability in nasal lavage following allergen provocation. |
| 4. To assess the response of nasal airways to allergens and nonallergic provocative agents and following changes in bronchial responsiveness. |
| 5. To examine the therapeutic effects of drugs such as antihistamines, corticosteroids, cromoglycate, anticholinergic medications, and vasoconstrictors on acute, late phase, nonspecific, and other aspects of airway diseases. |

Table 3. Absolute Contraindications

| 1. Acute bacterial or viral rhinitis or sinusitis |
| 2. Acute period or exacerbation of allergic disease (rhinitis, food allergy, drug allergy, insect allergy, urticaria) |
| 3. Previous anaphylactic reaction to an allergen |
| 4. Severe general diseases or acute period of diseases, especially severe asthma, obstructive bronchial diseases, cardiopulmonary diseases with restricted lung capacity |
| 5. Pregnancy |
buffered saline with 0.4% phenol, lactated Ringer’s solution, or normal saline into one or both nostrils using a metered dose delivery device. This challenge will detect nonspecific responses. Over the next 15 minutes, sneezes are counted, nasal discharges are collected, and pruritus, rhinorrhea, nasal blockage, and ocular symptoms are scored. Symptom scoring systems including 10-cm linear analog scales, 4-point severity scales, and other ordinal methods have been used. If there are no clinical symptoms or significant changes of rhinomanometric measurements (reduction < 20% by baseline), then allergen is deposited into the nose. An approximate guide for the starting dose is determined before NPT (see “Outcomes”). During allergen application the patient must hold his breath to avoid inhaling allergen into the larynx or lower airways. If the initial nasal allergen response is negative after 15 minutes, then the extract concentration can be increased 3-fold. These sequential increments can be given at 15-minute intervals. Doses are increased in step-wise fashion until a positive result is obtained, a maximum concentration is given without any significant reaction, or concentrations of 1:500 wt/vol or higher are reached that cause nonspecific irritant effects in nonallergic control subjects, and especially at levels above 1:100 with house dust and fungus extracts.35

OUTCOMES
Clinical symptoms of sneezing, itching, rhinorrhea, and obstructed nasal airflow, and measures of nasal patency are evaluated before administration of each dose of allergen. NPT is stopped when a positive response occurs. The intensity of the response is evaluated by dose of allergen given to patient and by total system score. True positive response occurs at an allergen concentration causing at least two of the following three criteria: 5 sneezes, 50% fall in NPEFR, or rhinorrhea.7 Other symptom scoring systems have also been used.4,38 For example, one previously validated system38 scores the number of sneezes (0 to 2 = 0 points; 3 to 4 = 1 point; 5 or more = 3 points), pruritus (nose, palate or ear = 1 point each), rhinorrhea (0 to 3 points), blockage (1 to 3 points), and ocular symptoms (1 point). The endpoint is the amount of antigen required to produce a total symptom score of 5 of a maximum of 13. The severity of each sensation can also be evaluated by 10-cm linear visual analog scale: mild, 1 to 3 cm; moderate, 4 to 7 cm; and severe, 8 to 10 cm at the dose that caused a positive response.38 According to German guidelines, positive test criteria should include flow reduction > 40% and/or more than three score points: secretion, 0 to 2 points (moderate, 1 point; severe, 2 points); sneezing, 0 to 2 points (0 to 2 sneezes = 0 point; 3 to 5 sneezes = 1 point; >5 sneezes = 2 points); additional symptoms such as tearing, itching (eyes, throat) = 1 point; conjunctivitis, cough, urticaria, and/or dyspnea = 2 points.39 Another investigators considered the positive NPT with a decrease of 20% or more in NEFPR and occurrence of nasal symptoms such as sneezes, rhinorrhea, nasal blockage and itching.3,37 Changes in the nasal temperature (using thermography) and the pH of nasal secretions have also been proposed as endpoints. Allergen challenge makes the pH more alkaline, while the temperature increases.40,41 These latter methods are not widely used.

False-positive results can be caused by preservatives in extracts such as phenol, glycerol, benzalkonium chloride; extremes of extract pH, temperature, and osmolarity; evaluation within 2 to 4 weeks of allergic, viral or bacterial rhinitis; and when allergen extract concentrations reach 1:500 wt/vol or higher.28,34,35 Appropriate vehicle control solutions are essential to identify nonspecific irritant reactions and prevent false-positive test results. Extracts should be used at room temperature and pH of 5 to 8.28 The allergen should be diluted in isoosmolar solution such as 0.9% saline or lactated Ringer’s solution. These issues are especially important if the allergen extracts are prepared by the investigator. Latex solution provides a good illustration of these problems.42

The NPT is considered to be true negative if the patient has no clinical symptoms and no changes of nasal patency after receiving the 1:1,000 wt/vol extract or maximum allergen dose.35 False-negative NPT occur after the use of contraindicated medications; within 8 weeks of nasal surgery, in patients with atrophic rhinitis, nasal polyps, or occasionally after specific immunotherapy. Subjects with chronic sinusitis may also have abnormal results since they have high levels of baseline mucous secretion, but do not respond to secretagogues such as methacholine.31

ALLERGEN DOSING
As a safety measure, it is recommended to begin with a low allergen concentration. For skin test-negative patients, the initial dose of allergen should be in the range of 1:10,000 to 1:5,000 wt/vol, or 50 to 100 PNU (overall pollen protein concentration).35 If the initial allergen applica-
tion is negative, then the extract concentration can be increased in 3-fold sequential increments at 15-minute intervals (1:10,000, 1:3,000, 1:1,000 wt/vol). For subjects with positive scratch and puncture tests, skin titration is performed with 3-fold dilutions of extracts. The concentration causing a 3-mm wheal can be used for nasal provocation. For intradermal tests, the lowest concentration generating a wheal can be determined, and a concentration 10 times more dilute used for NPT. Identification of a role of *Blomia tropicalis* as a cause of allergic rhinitis was performed with concentrations of 1:125,000, 1:25,000, 1:5,000 vol/vol, 1:1,000, and 1:200 vol/vol. Comparisons of nasal reactions to house dust and dust mite allergen extracts in skin positive subjects with perennial rhinitis were performed with 10, 100, 1,000, and 2,000 PNU (house dust) and 5, 50, and 500 PNU (dust mites). Allergic patients varied considerably in nasal sensitivity but all reacted to the final dose. Identification of latex allergy by NPT was performed with a 0.0005% latex solution. As can be seen, the different methods of allergen standardization such as allergy units (AU) or biologic units (BU) and measures of overall pollen protein concentration (PNU, wt/vol) make comparisons between studies difficult.

**DELIVERY SYSTEMS**

For clinical purposes the most acceptable simple techniques with good reproducibility involve delivering aqueous allergen extract by syringe, bottle dropper, micropipette or pump action nasal spray devices. Additional techniques for research purposes include: a powder and pollen grain insufflator; a “nasal pool” device for aqueous allergen extracts and soluble agents; saturated wads of cotton wool that are placed under the medial concha of the nose; impregnated paper discs placed on the inferior turbinate or nasal septum with forceps; and modified airbrush techniques. Each method has its own advantages and limitations.

**Figure 1. Protocol of NPT with allergens.**
The area of distribution of solutions deposited via syringes and droppers cannot be readily predicted. These bulk application methods have the risk that, in some cases, fluid may be aspirated into the larynx, inducing cough, laryngeal irritation, edema, or bronchospasm. These unwanted side effects are very rare if care is taken to instruct the patient not to inhale forcefully or bend their head backwards after the allergen is placed. Carriage of the allergen posteriorly by mucociliary clearance past the orifice of the Eustachian tube and into the pharynx may lead to nasopharyngeal swelling, itch, or middle ear discomfort or dysfunction. The use of 5- to 10-μL pipettes allows the deposition of small, exact volumes of the allergen directly onto the turbinate under direct rhinoscopic control.

Nasal pump spray devices improve contact of the provocative agent with the nasal mucosa by distributing it over the exposed anterior nasal cavity surfaces. Precise volumes on the order of 100 μL are applied that generally do not lead to bronchospastic reactions. Unfortunately, the popular beclomethasone (Vancenase, Schering-Plough, Kenilworth, NJ and Beconase, Glaxo Wellcome, Research Triangle Park, NC) spray bottles have become difficult to obtain because these products have been largely replaced in the market place. Hand-held automizers generate large-diameter particles, which helps to avoid the delivery of allergens to the lower airways. Volumes of 0.2 to 0.5 mL per nostril are arbitrarily but commonly used. The materials suspended in the mist may be more readily absorbed by the mucosa than with the bulk application methods mentioned previously. Allergen meter-dose pump spray was recommended for clinical routine and research in Europe.

Pollen grain insufflations can be used to imitate natural exposures. This technique is simple and the dose of pollen grains can be well controlled. However, most investigators prefer to use aqueous extracts because of the hydroscopic properties of pollen. Very high doses of pollens are generally required to obtain large magnitude responses in subjects who are studied out of the pollen season. Hydration of dried, defatted pollen grains leads to the explosive release of a pollen eluate with high osmolarity that may be sufficient to cause irritation reactions in patients with nonspecific nasal hyperreactivity. Similarly, some patients may have nonspecific reactions to the lactose that is used to pack the pollen grains into inert capsules. Generally, the dose of lactose is insufficient to cause symptoms in lactose-intolerant subjects.

The “nasal pool” device, a compressible plastic container with a nasal adapter, offers significant improvements of provocation and lavage technique. The device can hold a soluble agent of known volume and concentration. The adapter is pressed to the nostril and the container compressed to push the fluid into the nose for a precise time and in the defined space of the anterior nasal cavity. The lavage fluid is collected when the container is re-expanded. Any soluble agent can be tested. Even children can use the device correctly. A disadvantage of this technique is the unknown dilutional effect of nasal secretions by lavage fluid. The devices are no longer available in the United States.

Topical application of allergenic extracts by means of cotton wool swabs in the middle meatus under the medial concha, impregnated paper discs, or a modified airbrush technique for application onto the inferior turbinate have been used mostly for scientific investigations. The site of provocation is relatively small, but changes in mucosal appearance can be observed at both the local site and more distant mucosal locations. Placing allergens in the middle meatus seems dangerous and potentially could lead to sinusitis.

Filter paper discs (3-mm diameter) impregnated with allergen solution can be placed bilaterally by forceps on the anterior part of the inferior turbinate or nasal septum. Doses can be increased in step-wise fashion, but the concentrations used may need to be individualized based upon the extract potency. Larger discs (8-mm diameter) that are dry can be placed to collect small, undiluted samples of nasal fluid. For example, the osmolarity of the absorbed secretions was evaluated after nasal provocation with cold dry air and after stimulation with hypertonic saline and mannitol solutions (800 to 1,000 mOsmol/kg H2O). The discs may preferentially sample the sol phase of the epithelial lining fluid, but may also promote transepithelial exudation of interstitial fluid from the upper lamina propria.

The option of using either unilateral or bilateral challenges is a great advantage over bronchial provocations. After unilateral challenge, ipsilateral responses are due to local, direct effects and recruited parasympathetic reflex effects whereas responses in the contralateral nostril represent “pure” parasympathetic reflex effects (Fig 2).

Nasal patency measurements

Nasal patency is extremely dependent on structures such as the septum and nasal valve. The degree of swelling of venous sinusoids deep in the mucosa regulates mucosal thickness, air space volume and nasal patency. Other factors that may also participate are mucosal edema, cellular infiltration, and the presence of luminal secretions. Several methods are available to measure nasal airflow resistance: NPIFRs, NPEFRs, nasal spirometry, passive anterior rhinomanometry, active anterior rhinomanometry, active posterior rhinomanometry, balloon method/infra-nasal pressure measurements, and oscillometry. The nasal volume can be measured by acoustic rhinometry. The nasal peak flow method is easy to perform, inexpensive, and reasonably well correlated with rhinomanometry, but is less reproducible. Passive anterior rhinomanometry is a suitable technique for recording air pressure and airflow during breath-holding and has been used in children, patients with problematic dental prostheses, or with an overactive gag reflex. In contrast, this technique does not truly represent the physiologic breathing process. Active anterior rhinomanometry eval-
uates the pressure/volume or pressure/flow relationship for the nostril during tidal breathing. It is the most widely used technique. However, the active inspirations cause significant changes in the nasal valve, resulting in breath-to-breath variability in measurements. This technique cannot be used for patients with fragile and bleeding nasal mucosa or with frequent sneezing, because the insertion of nasal adapter of device can alter the nasal valve. Changes in resistance may be limited when there is severe occlusion of a nostril by turbinate hypertrophy, polyps, septal deviation, or severe rhinorrhea at the onset of the study. Active posterior rhinomanometry also records pressure, volume and flow rates during tidal breathing. This technique is not suitable for children, patients unable to tolerate the close-fitting masks, and patients who cannot satisfactorily coordinate the required nasal, palate, glottic, and breathing maneuvers.

Acoustic rhinometry is a newer technique that measures the cross-sectional area of the nasal cavity. Pulsed sounds are broadcast into the nose. Signals are reflected from the mucosal walls back to a microphone. After spectral analysis, the cross-sectional area is plotted as a function of distance from the tip of the instrument. Changes in the minimum cross-sectional area and volume of the cavity can be determined.

Nasal microcirculation has been used as an endpoint. Laser Doppler velocimetry evaluates capillary blood flow in the superficial mucosa. Radioactive xenon washout and clearance of hydrogen (3H2) into exhaled nasal air are limited to research institutions. Colorometric evaluation of mucosal erythema has also been used.

**COLLECTION OF NASAL SECRETIONS AND LAVAGE FLUID**

The amount, viscosity, and spinability of the nasal mucus discharge, and quantity of the mediators, cytokines, plasma proteins, glandular secretory products, extracellular matrix molecules and cells in lavage fluids vary in different forms of rhinitis and in response to different provocation agents and methods of collection. In clinical practice, secretions may be collected by blowing directly onto a plastic film or into a funnel, cup, or tube. However, interpretation may be difficult if the fluid is viscous or swallowed, collections are incomplete, or the volumes of secretions are small. Secretion of 0.5 mL (0.5 g) with 5 or more sneezes and >20% decrease in peak flow is considered a positive test.

Introduction of nasal lavage fluid promotes collection for biochemical analysis, but raises the problem of secretion dilution. Naclerio pioneered the method of instilling 4 to 5 mL of lavage fluid directly into the nose using a pipette. Subjects are required to hyperextend their necks and obstruct their posterior nasopharynx by palatal closure. Lavage fluid is recovered by anterior flexion of the head combined with nasal exhalation. This method samples nasal and nasopharyngeal airways. α-Adrenergic agonists have been used to improve fluid recovery. Druce and Raphael began using pump spray devices and collected secretions by placing a small, soft, red, rubber 8F urethral catheter along the floor of the nostril. Unilateral provocations could be performed with secretions continuously collected from both sides. As described above, the nasal pool device is a further refinement for challenge, lavage, and collection.

These techniques sample large surface areas of mucosa, and can quantify vascular, glandular, neuronal, and cellular events simultaneously. Nasal lavages with isoosmolar saline can be performed repeatedly without causing nasal mucosal irritation. The disadvantages of repeated nasal lavages are the

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![Figure 2. Nasal Provocation. Unilateral administration of allergen or other materials may lead to local, ipsilateral responses, and parasympathetic reflex effects. Allergen leads to mast cell degranulation with the release of histamine, LTC4/D4/E4, tryptase, and other mediators. Histamine acts upon H1-receptors on endothelium to cause vascular permeability and exudation of an albumin-rich, watery discharge. H1-receptors on nociceptive nerves lead to the sensation of itch. The neural mechanism leading to the sensation of nasal congestion is not clearly understood. Nociceptive nerves may release neuropeptides when activated (“axon response” mechanism). Substance P may cause glandular secretion, whereas calcitonin gene-related peptide may cause vasodilation. Vasodilation with swelling of venous sinusoids leads to thinning of the mucosa and obstruction to nasal airflow. Histamine, as well as other mediators and cytokines, plays a key role in regulating cellular infiltration as seen in the late phase response and clinical allergic rhinitis. Activation of nociceptive nerves recruits bilateral parasympathetic reflexes that cause acetylcholine-mediated glandular exocytosis.](image-url)
dilution of samples, the removal of important target cells such as adherent eosinophils or metachromatic cells during the initial provocations, and alterations in the dynamics of fluid flux across the mucosal barrier. In each method, the degree of dilution of the original epithelial lining fluid cannot be determined. However, the addition of exogenous radiolabeled albumin or lithium to the lavage fluid permits calculation of the percentage of recovery in research studies. These techniques have provided useful information about the amount of secretions, but they do not define their source, physical properties, or composition. Measurement of urea in plasma and lavage fluid provides an estimate of the volume of epithelial lining fluid sampled. These methods are impractical for office practice. Dry filter paper discs collect only small quantities of undiluted secretions, limiting the number of analytes that can be assayed with precision.

NASAL CYTOLOGY
Cellular changes during NPT can be evaluated by nasal smear, blown secretions, cotton swabs, imprints, nasal scraping, nasal brushes, and biopsy. Multiple methods of biochemical, histochemoical, immunochemoical, and electron micrographic can then be applied. Collection of cells with cotton swabs is a simple but low reproducibility technique. The advantage of imprints and scrapings is that monocytes and lymphocytes can be enumerated. Nasal biopsy is rarely used for diagnostic purposes in rhinitis, but it has provided valuable information about the ciliary dysfunction, role of lymphocytes and cytokines in allergic reactions. Biopsies are the only means to study the structural elements. The nature of cellular infiltrates can be evaluated, but persistent bleeding may follow the trauma of the biopsy.

LATE-PHASE RESPONSE
The immediate allergic response is characterized by itch, sneezing, rhinorrhea, plasma exudation, and glandular secretion attributable to the release of mast cell mediators. The clinical symptoms of the late phase response are limited to nasal congestion, posterior drainage of secretions, and sinus or facial pressure. Cell, mediators, cytokines, and neurohormones in the nasal secretions of the late phase response are different from those of acute response. The clinical implications of having a late phase response after NPT are still debated. The European Academy of Allergy and Clinical Immunology’s recommendations for investigation of late-phase reactions entail assessments at 0.5, 10, 20, 30, 45, and 60 minutes, then every hour to 10 hours after provocation. If a positive allergen response occurs, then the subject should be challenged with the diluent to determine whether it had induced a false-positive response. The times for evaluation after the vehicle challenge should be exactly as after the allergen. Both placebo reactors and subjects with nonspecific hyperresponsiveness will be detected.

OTHER PROVOCATION AGENTS
Histamine produces the triple response of nerves in the skin and causes an analogous pattern in the nose: stimulation of a population of H1-receptor bearing type C neurons that mediate itch that recruit cholinergic parasympathetic reflexes that induce glandular exocytosis; stimulation of plasma extravasation with stimulation of endothelial H1-receptors leads to exudation of plasma into the lamina propria leading to edema with hydrostatically driven exudation across the epithelium into the nasal cavity to cause watery rhinorrhea and vasodilatation of deep venous sinusoids leading to mucosal thickening, reduced nasal patency, and obstruction to airflow. All of these mechanisms are seen on the ipsilateral side after unilateral histamine provocation, whereas only the reflex-induced glandular secretion is seen in the contralateral nonchallenged nasal cavity. Methacholine induces glandular secretion only. Challenge with histamine and methacholine have been widely carried out for exploring of nonspecific nasal hyperreactivity. Capsaicin stimulates nociceptive type C fibers and neuropeptide release from their sensory nerve endings. Capsaicin provocations stimulate excessive glandular secretion in a subset of vasomotor rhinitis subjects. Capsaicin also damages C fibers, and has been proposed as a treatment for nonallergic rhinitis. Bradykinin (BK) induces vasodilatation and vascular permeability because of the stimulation of vascular BK-B2 receptors. BK receptors on sensory nerves are upregulated in severe allergic rhinitis and lead to activation of cholinergic reflexes. Nicotine and serotonin also induce sensory nerve stimulation with presumed axon responses and cholinergic reflexes. Irritants such as ozone, sulfur dioxide, formaldehyde, cigarette smoke, organic-solvent fumes, and cold air (or re-warming after cold exposure) induce nasal obstruction and rhinorrhea that may be attributable to mast or epithelial cell damage, the stimulation and depolarization of trigeminal sensory nerves, and the induction of axon responses and parasympathetic reflexes. Nasal and bronchial inhalations of hypertonic solutions of saline, mannitol or other solutes have been used to investigate nonspecific irritant and neural sensitivity, and may offer insights into exercise-induced asthma. NPT with acetylsalicylic acid and lysyl-acetylsalicylic acid is a helpful procedure for diagnosis of aspirin-sensitive asthma, but is less sensitive than oral challenge. Lysyl-aceetylpirin-sensitive asthma is not approved for use in the United States.

CONCLUSION
As the methods of NPT become more standardized, we anticipate that NPT may become a more frequently used clinical tool. Its place will be to define the presence of allergic rhinitis when the history is highly suggestive but skin testing and RAST testing are negative, for the evaluation of unique or occupational allergens, and to demonstrate nonallergic, irritant, or nasal hyperresponsiveness mechanisms. In these instances, the NPT responses
may lead to more appropriate and focused therapy. These tests may also be useful to determine whether allergen-specific IgE that can be detected in nonallergic nasal polyp and sinusitis subjects are relevant to the development of these “nonatopic” diseases. The nasal mucosa will also be of value as a surrogate for bronchial testing, and will continue to provide useful information about the pathogenesis of airway diseases.

REFERENCES

CME Test Questions

1. Indications for the use of NPT in clinical practice include all of the following EXCEPT:
   a. To confirm the role of allergen in cases of disagreement of patient’s history and skin testing and/or RAST
   b. For the diagnosis of occupational allergic rhinitis
   c. To identify a novel allergen causing allergic rhinitis
   d. To confirm nasal reactivity to allergen before starting immunotherapy
   e. To prove the allergic nature of asthma when corresponding bronchial allergen provocation tests are positive

2. Which of the following is NOT an absolute contraindication for NPT?
   a. Acute period of allergic rhinitis
   b. Mild asthma in remission
   c. Previous anaphylactic reaction to an allergen
   d. Acute viral or bacterial rhinitis and sinusitis
   e. Pregnancy
3. Which of these statements is false?
   a. NPT can be done 4 weeks after the episode of allergic or infectious rhinitis
   b. Polyps, atrophic rhinitis, and deviated nasal septum are absolute contraindications for NPT
   c. NPT can be done 6 weeks after nasal or sinus surgery
   d. Nasal congestion can result from oral contraceptives and preparations containing sulfite preservatives
   e. NPT should not be done in patients with restricted lung capacity (TLC <60%)

4. A positive NPT is determined by:
   a. The maximum allergen dose that patient received
   b. Self-report scoring of clinical symptoms
   c. 10-cm linear visual analog scales of symptoms
   d. Measures of nasal patency
   e. The assessment of clinical symptoms scores, nasal secretion, and nasal patency measurements

5. Which of these statements is false?
   a. NPT is a well standardized method and is frequently used in clinical practice in the United States
   b. NPT has shown promise for the diagnosis of allergic and occupational rhinitis
   c. The analysis of mechanisms of NPT responses may lead to a more appropriate and focused therapy
   d. There is a wide variety of NPT test techniques for research
   e. NPT provides useful information about the pathogenesis of airway diseases

Answers found on page 386.