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Nasal mucosal reactivity after long-time exposure to building dampness

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Photo on the front page:
Measurement of nasal mucosal swelling with rhinostereometry after histamine provocation.

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ABSTRACT

An association between working and/or residing in damp buildings and respiratory health has been reported in a number of studies. A major limitation has been difficulty in objectively verifying any effects on the mucous membranes of the respiratory tract in order to explain symptoms of irritated eyes, nasal congestion and cough that are often reported by occupants in buildings with indoor air problems. The main aim with this thesis was to objectively study changes in the nasal mucosal reactivity after long-time exposure to a deteriorated indoor climate.

Twenty-eight teachers who had worked for at least five years in a recently renovated school, which for years had had severe moisture problems, were randomly selected to participate in this study. Eighteen teachers randomly selected from another school, with no known moisture problems, formed the control group (in 1995). Although remedial measures had been taken, an increased prevalence of mucous membrane irritations was still reported by the teachers from the target school. A nasal challenge test with three concentrations of histamine (1, 2 and 4 mg/ml) was used. Recordings of the swelling of the nasal mucosa were made using rhinostereometry. The analysis of the mucosal swelling induced by the three concentrations of histamine showed a significant difference in the growth curves of the two groups, indicating that long-time exposure to indoor environments with moisture problems may contribute to mucosal hyperreactivity of the upper airways.

A study comparing students who began their high-school studies at both schools in 1995 and the teachers was performed regarding mucosal reactivity, frequency of atopy and symptoms. A nasal histamine provocation test and a skin-prick test were administered to 45 students from each school. They also answered a standardized questionnaire.

The teachers had significantly greater mucosal histamine reactivity than the students, compatible with an age-related pattern of mucosal reactivity. The students had significantly higher frequency of allergic sensitization.

In 1997 the nasal histamine provocation test was repeated among the teachers. This showed that the teachers from the repaired water-damaged school still demonstrated an increased reactivity to histamine compared to those in the control school, but the differences between the growth curves of the provocation tests were less than in 1995. No major differences were observed in the technical investigation between the two schools and the measurements were all within the range of values usually seen in schools in northern countries.

In a longitudinal study the students were followed during their high school studies. They underwent a nasal histamine provocation test and answered a questionnaire on three occasions, in 1995, 1996 and 1997. No significant differences in the nasal histamine provocation curves between the students at the target school and those at the control school could be shown from the start to the end of the study period. Nor were there any differences concerning perceived indoor air or mucosal symptoms between the target group and the control group. Based on both technical and objective medical measures, this study indicated that the indoor air in the remediated moisture-damaged school did not exert an irritant effect on the upper airway mucosa of the students.

In 2000, six years after remedial measures had been taken, the teachers underwent a nasal histamine provocation test. In addition to using mucosal swelling as a measure of mucosal reactivity, we also examined the mucosal microcircular reaction to histamine provocation with Laser-Doppler flowmetry (LDF). We found that the difference in nasal histamine reactivity between the two study groups, measured as mucosal swelling, was no longer significant. However, Laser-Doppler flowmetry showed a significant difference between the two teacher groups regarding microcircular perfusion and CMBC (concentration of moving bloodcells), indicating a more pronounced plasma leakage and oedema from the nasal mucosa upon histamine provocation among the target school teachers.

In conclusion, we found a restored nasal histamine reactivity, measured as the mucosal swelling reaction, among the teachers six years after long-time exposure to building dampness. LDF showed remaining changes in the microcircular pattern of the target school teachers. Consequently, long-time exposure to building dampness may increase the risk for hyperreactivity of the upper air-ways. This aquired hyperreactivity may last for years and decrease only slowly, even after the indoor climate has been properly improved. A possible explanation for this slowly decreasing reactivity might be a slow but ongoing restoring process in the mucosa of the upper air-ways.
It is of importance to determine if residing in bad indoor environment implies a risk of future health problems. Following a group of people exposed to building dampness with objective mucosal tests over several years provides knowledge about how long and in what way the increased mucosal reactivity persists. It is important to identify both predisposed people and particular risk environments.
Key words: indoor environment, histamine provocation, nasal mucosa, mucosal reactivity, rhinostereometry, moisture, Laser-Doppler.

The difficulty in most scientific work lies in framing the questions rather than in finding the answers.
(*A.E. Boycott*)

We should make things as simple as possible, but not simpler.

(*Albert Einstein)*

LIST OF PAPERS

This dissertation is based on the following original publications, which will be referred to in the text by their Roman numerals:

I. Rudblad S, Andersson K, Juto JE, Bodin L. Nasal hyperreactivity among teachers in a school with a long history of moisture problems. Am. J. Rhinology 2001;15:135-41.

II. Rudblad S, Andersson K, Stridh G, Bodin L, Juto JE. Slowly decreasing mucosal hyperreactivity years after working in a school with moisture problems. Indoor Air 2002;12:138-44.

III. Rudblad S, Andersson K, Bodin L, Stridh G, Juto JE. Nasal mucosal histamine reactivity among young students and teachers, having no or prolonged exposure to a deteriorated indoor climate. Allergy 2002; 57(11):1029-35.

IV. Rudblad S, Andersson K, Stridh G, Bodin L, Juto JE. Nasal histamine reactivity among adolescents in a remediated moisture-damaged school - a longitudinal study. Indoor Air 2004 (In press).

V. Rudblad S, Andersson K, Stridh G, Bodin L, Juto JE. Nasal mucosal histamine reactivity among teachers six years after working in a moisture damaged school. Submitted for publication.

CONTENTS

ABBREVIATIONS

ANOVA	Analysis of variance
CI	Confidence interval
CMBC	Concentration of moving blood cells
FEV_1	Forced expiratory volume (during 1 second)
LDF	Laser Doppler flowmetry
NO	Nitric oxide
PEF	Peak expiratory flow
RSM	Rhinostereometry
SAR	Seasonal allergic rhinitis
SBS	Sick building syndrome
SPT+	Skin prick test positivity
SPT-	Skin prick test negativity
TVOC	Total concentration of volatile organic compounds
VOC	Concentration of volatile organic compounds

INTRODUCTION

Background

Poor indoor air quality has been discussed, but also rejected by some authors, as one of the factors related to the increased prevalence of allergies and asthma in the Western world [1, 2, 3]. Allergens from furry pets are ubiquitous in public buildings, including schools [4, 5], and the amount of allergens in school dust is sufficient to cause increased symptoms in sensitized persons [6]. However, there are no obvious indications that exposure to these environments actually increases the incidence of atopic diseases [1, 3].

General symptoms such as headache, mental fatigue and difficulties concentrating as well as non-specific airway symptoms are frequently reported by residents and/or employees in polls regarding indoor environments. This variety of inconveniences is often referred to as symptoms of "sick building syndrome" (SBS) [7, 8].

Many occupants of buildings attribute irritative mucosal airway symptoms, such as eye irritation, nasal blockage and cough, to a bad indoor climate [9]. These complaints frequently emanate from people working in non-industrial buildings such as offices, schools and day-care centres [10, 11, 12]. In an overhaul of 220 Swedish schools during the period 1978-1997, obvious maintenance defiencies were demonstrated, with poorly functioning and polluted ventilation systems, water leakages and building dampness [13]. Taking measures to rectify verified insufficient indoor ventilation when SBS-symptoms have been reported has sometimes resulted in a rapid reduction of perceptions and symptoms attributed to SBS [14]. However, there are also indications that an increased nasal mucosal reactivity due to long time exposure to a deteriorated indoor climate may last for years even after moving out of the problem area, although residents no longer complain of irritative symptoms [15, 16]. An association between working and/or residing in damp buildings and symptoms of mucosal irritation from the upper and lower airways has been reported in a number of studies [17, 18, 19, 20].

Symptoms included in SBS are common in the general population, and are of multifactorial origin related to personal, occupational, and residential factors [21]. However, in many of these environments with reported SBS-symptoms, there have been difficulties in verifying a relationship between measured low-level indoor air pollution and reported symptoms [22, 23, 24]. The indoor climate is complex and symptoms are influenced by physical factors, such as emissions from damp building materials, ventilation, and variation in temperature, as well as by different psychosocial factors [21, 25, 26]. The prevalence of reported symptoms is also related to age, sex and allergic constitution of the occupants [27].

Studies on work-related symptoms in non-industrial buildings have i.a. shown a high frequency of reported nasal mucosal symptoms [28, 29, 30]. Nasal symptoms, such as nasal irritation, stuffiness and runny nose are, however, common among otherwise healthy individuals, and there is no clear-cut boundary between normal physiology and inflammatory disease such as rhinitis [31].

There is a growing interest in objectively verifying the effects of a deteriorated indoor climate on the mucous membranes of the respiratory tract. Furthermore, there seems to be a need for increased knowledge about the physiological and pathophysiological changes that take place in the mucosa of the airways during these conditions. The nose, as compared to the lungs, is easily accessible, but it is also a quite complicated organ.

Nasal mucosal reactivity

Behind the nasal valve, the site with the narrowest cross-sectional area of the nose, the cavity of the nose expands and the turbinates hang down from the lateral wall (**figure 1**). Approximately 12 m^3 of air passes through the nose each day. The turbinates increase the mucosal surface and, together with the narrow valve, contribute to a turbulent flow of inspired air that results in extensive contact between the inspired air and the mucosal surface. This contact makes it possible for inspired air to reach proper moisture and temperature conditions on its way into the lower airways. The nose also has the function of a filter where inhaled foreign particles are deposited (mainly >10µm) and prevented from passing to the lower airways [32].

Upon exposure to irritants, the nasal mucosa react with symptoms like itching, sneezing, nasal discharge and/or nasal congestion. Irritant stimuli give the experience of itching, propagated afferently by trigeminal nerves and resulting in a spasmodic inhalation that is followed by an explosive expiration caused by contraction of the accessory respiratory muscles [33]. Sneezing clears the throat, nose and mouth. Nasal discharge is primarily caused by a mixture of plasma exudation and glandular secretion and serves as an important defence mechanism upon inflammatory stimulation in the airway mucosa [34, 35].

An inflammatory reaction in the nasal mucosa also results in nasal congestion due to dilatation of the deeper situated sinusoidal vessels, which increases the blood volume in the nasal mucosa [36, 37]. Another factor that contributes to nasal congestion might be extravasation of fluid and the consequent interstitial oedema

[38]. Studies on nasal inflammatory conditions have predominately focused on allergic rhinitis [39, 40], which is the most common allergic manifestation [41]. However, it was found in a questionnaire study, that 21% of a rural and urban population in Sweden was suffering from non-allergic nasal complaints [42]. Furthermore, among persons who develop symptoms of chronic rhinitis the proportion with a non-allergic aetiology increases steadily with age and exceeds 60% after the fifth decade of life [43]. Besides the obvious association between allergic rhinitis and asthma there also seems to be a strong association between non-allergic rhinitis and asthma [44, 45, 46].

The term nasal hyperreactivity is often used to describe hyperreactive symptoms caused by various non-specific irritants such as smoke, odours and dust. Hyperreactivity is of central importance and is usually present in allergic as well as non-allergic rhinitis, although with variable intensity [47]. The pathogenesis of nasal hyperreactivity is not known but a greater permeability of the nasal mucosa has been discussed as a contributing factor [48]. An increased sensitivity of the mucosal sensory nerve endings may also play a role [49, 50].

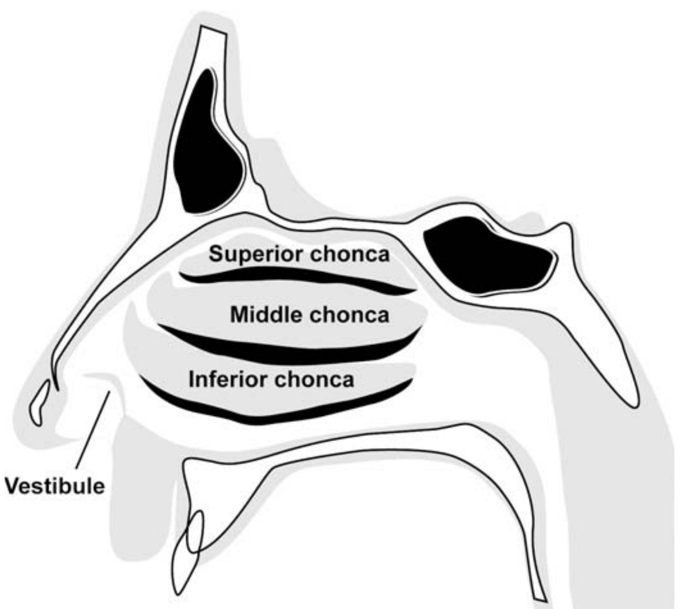


Figure 1. Schematic drawing of the lateral wall of the nasal cavity showing the narrow nasal valve and the extension of the turbinates.

Assessment of nasal mucosal reactivity

Inflammation of the nasal mucosa evokes nasal obstruction, and measurements of nasal patency constitute an objective measure of how open the nose is. Rhinomanometry, a method which indirectly measures nasal airway resistance, has previously been the main objective method of quantitating nasal obstruction [51]. Acoustic rhinometry, which uses acoustic reflection to assess the geometry of the nasal cavity, is a method that has been increasingly used in environmental studies [52, 53]. This method has, for example, been applied to show that a low air exchange rate in schools may affect the airways and cause a swelling of the nasal mucosa [54].

An airway- provocation test is a method to study the dynamic course of mucosal reactivity when exposed to allergens or non-specific irritants. In the field of bronchial pulmonology clinical methods are well established for estimating the degree of bronchial hyperreactivity. These methods include provocation tests with histamine and methacholine followed by spirometric recordings of forced expiratory volume (FEV_1) or measurement of peak expiratory flow (PEF) [55, 56].

Nasal provocation tests, using histamine or methacholine, have been used in different surveys to study nasal mucosal reactivity [57, 58]. However, these provocation tests have not been particularly suitable for routine clinical work because the nasal mucosa is very sensitive and easily affected by internal and external disturbances. Nevertheless they have been helpful as a research tool in selected investigative set-ups [59, 60].

Histamine, a major mediator in the allergic reaction, exerts a broad action on the nasal mucosa causing congestion, rhinorrhea and sneezing in atopic as well as non-atopic subjects [61]. Histamine acts directly on cellular histamine receptors, which cause vasodilation, oedema formation and exudation of plasma to the airway lumen and indirectly, via reflexes, which accounts for sneezing and watery hypersecretion [62]. In one study it was shown that unilateral nasal histamine provocation caused ipsi-lateral obstruction and increased the patency of the contra-lateral nostril, the latter possibly by a neural reflex [63]. However, in other studies the nasal mucosal swelling reaction upon histamine provocation has been shown to be ipsi-lateral with no effect on the contra-lateral side [15, 64, 65].

Nasal hyperreactivity can be demonstrated by a nasal histamine provocation test. However, these tests cannot differentiate a normal from a diseased population as efficiently as an inhalation test in asthma. Therefore, the descriptive term increased nasal reactivity seems more adequate than nasal hyperreactivity in order to differentiate a more reactive group of subjects from a control group. The main problem is the recording of the mucosal reaction. Recordings have been made using symptom scores, counts of sneezes, or quantitative or qualitative analyses of nasal discharge [60, 61].

Rhinomanometry and acoustic rhinometry have also been used in nasal histamine provocation tests measuring nasal obstruction as an indirect measure of mucosal reactivity [58, 59]. In a study of methods for assessment of nasal histamine reactivity these two methods were found comparable for measuring mucosal changes [66]. In the same study nasal peak flowmetry, a simple and clinically useful method, was found more sensitive to mucosal changes than the other methods studied.

Another method, rhinostereometry, has lately been used to record the degree of mucosal swelling after nasal histamine provocation. It is an optical, non-invasive and direct method that exclusively studies changes in the nasal mucosa [67, 68]. In our studies rhinostereometry has been used for recordings of mucosal swelling after histamine provocation.

Nasal mucosal blood flow

Arterial blood enters the nasal mucosa via arteries forming anastomoses along their course [69, material and methods: fig 4.]. The arteries ramify into smaller arterioles controlling the blood flow of the mucosa. [70] Because they control nasal blood flow, the arteries are referred to as resistance vessels. The arterioles end in a capillary network arranged in subepithelial and glandular zones.

The blood from the capillaries is drained via postcapillary venules, which seem to be the site of the inflammatory, mediator induced, increase in permeability to macromolecules [71]. Larger collecting veins then drain into the deeper situated sinusoides, which are especially well developed in the mucosa of the turbinates [69].
The venous sinusoids drains primarily through specialized throttle veins in bony canals in the turbinate bone. Arterial blood can also reach the sinusoids by way of arteriovenous anastomoses, and there are indications that control of nasal mucosal congestion may depend on the balance between filling of the tissue via arteriovenous anastomoses and drainage of the tissue through the throttle veins [72].

Nasal mucosal blood flow during histamine provocation

Vascular changes in the nasal mucosa occur during various pathophysiological conditions. Histamine locally injected into the mucosa of the inferior turbinate increases the blood flow, measured with the 133 Xe wash-out method, in allergic as well as non-allergic subjects [73]. Histamine solution applied locally on the nasal mucosa also increases the blood flow in healthy volunteers, as recorded with laser Doppler flowmetry (LDF), extending the previously established vasodilating properties of the substance [74].

Another effect of histamine on the nasal mucosa is to increase the permeability of microvessels [75]. The sites of plasma leakage have been determined to be in the small postcapillary venules. In an animal study using the hamster cheek pouch model, histamine provocation was found to provide a rapid onset of increased vascular permeability peeking at 5 minutes and returning to normal after 25 minutes [76]. These observations roughly correspond to a study where allergic and healthy subjects were exposed out of season to nasal histamine provocation [77]. The mucosal microcirculation was recorded with LDF and the vascular leakage (interstitial oedema) was calculated as the fall in the parameter CMBC (= concentration of moving blodcells). Following provocation there was a significant decrease in CMBC in the allergic subjects with the minimum at 8 minutes which was not seen in the normal subjects. This was interpreted as the development of a transient interstitial oedema by the allergic subjects in response to the histamine provocation. In our fifth paper we used the combination of rhinostereometry (RSM, see above) and LDF making it possible to record nasal mucosal congestion and microcirculation simultaneously.

Mucosal signs and symptoms in relation to building dampness

The importance to respiratory health of building dampness and mould growth in houses has been the focus of substantial interest, and it has been concluded that there is a consistently increased risk of respiratory symptoms among people living in houses with dampness problems and mould growth [78, 79, 80]. It is usually possible to classify the severity of the problem simply by local inspection [81]. There is evidence in the literature, that building dampness increases the prevalence of asthmatic symptoms [82, 83, 84]. However, there are no reliable indications that exposure to moisture and/or mould in damp buildings leads to sensitization and development of immunoglobulin E (IgE) mediated mould allergy [85].

Some studies indicate that microbial or chemical exposure related to building dampness could influence the nasal mucosa. Increases in inflammatory biomarkers in nasal lavage were observed in occupants of a building with pronounced microbial growth in the building structure [86].

The relation between mould exposure in schools and respiratory symptoms has been investigated in some studies. Attending a school with moisture damage and mould growth was found to be related to asthmatic symptoms in the pupils [17, 87]. Among school employees, exposure to building dampness at school has been associated with lower respiratory tract disorders [88, 89] and pathophysiological effects on the nasal mucosa [89, 90]. In a study on school personnel, a lower degree of nasal patency and increases in inflammatory biomarkers in nasal lavage were found when there were higher concentrations of total moulds in classroom air [91].

There are indications that the water content in building materials may have an effect on the emission in the air, either due to microbial growth or to chemical degradation of the material [92, 93]. This is in accordance with an increased risk of respiratory tract symptoms among occupants in houses with moisture problems with or without the presence of mould [94, 95]. Furthermore, a thorough renovation in moisture-damaged schools has resulted in a decrease in the prevalence of respiratory symptoms among personnel and pupils [96, 97].

In summary, there is reliable evidence that exposure to building dampness is associated with mucosal signs and symptoms from the upper and lower respiratory tract.

Atopy and allergy

A revised nomenclature for allergy was presented in a position paper [98]. Atopy is defined here as a personal or familial tendency to produce IgE antibodies in response to low doses of allergens and to develop typical symptoms such as asthma and rhino-conjunctivitis. This means that *IgE sensitization* per se (e.g. skin prick positivity) is not a criterion for atopy. The term *atopy* should be reserved for the combination of IgE sensitization and typical allergic symptoms. Furthermore, *allergy* is defined as a hypersensitive reaction initiated by immunological mechanisms and can be either IgE-mediated or non-IgE-mediated.

In our first two papers we used skin prick test positivity and atopy as synonyms, which is frequently the case in many studies [99, 100]. However, this new nomenclature was applied starting with the third paper.

Hyperreactivity in allergic rhinitis during and out of season

Nasal non-specific hyperreactivity is an important feature of allergic rhinitis [101]. However, there is some controversy regarding the way in which this hyperreactivity changes during and out of season. Konno et al. found no differences in nasal histamine reactivity among seasonal allergic rhinitis (SAR) subjects during off season compared with normal subjects [102].

In two consecutive studies on SAR patients 19 to 43 years of age, increased and unchanged nasal histamine reactivity was found during and out of season compared to controls [103, 104]. This was interpreted as an indication of continuos mucosal inflammation regardless of season in these patients. In another study, where the degree of nasal mucosal inflammation was estimated by the concentration of exhaled nitric oxide (NO), an increased inflammatory reaction was found during the non-pollen season among allergic rhinitis subjects as compared to controls that further increased during the pollen season [105]. Reasons for the discrepancies in these studies might depend on the sensitivity of the measuring method, the intensity and duration of the allergic disease and/or the inclusion criterias for the allergic subjects. Thus there seems to be a need for further studies in this field.

Indoor air quality questionnaires

If information is to be gathered from a large number of employees or residents, a questionnaire is a useful aid. Indoor air problems are of multifactorial origin, and methods facilitating the diagnosis phase are of vital importance in solving indoor air problems. When investigating SBS, questionnaires should be used to collect structured information from occupants concerning their perception of environmental conditions, psychosocial factors and symptoms [106].

A questionnaire widely used in the Nordic countries, which also includes items concerning the psychosocial work environment, is the MM-questionnaire [107]. The MM-questionnaire is used for studying the respondent´s experience of the quality of the indoor air and the conditions at the workplace, as well as SBS symptoms attributed to the work environment. The respondent´s experience of the indoor environment and reported SBS-symptoms can be used to help determine necessary technical measurements as well as remedial measures to improve the environment in buildings with problems. The usefulness of this questionnaire has been confirmed in some recent studies [108, 109]. We used two different versions of the MM-questionnaire in our studies, MM040NA for the teachers and MM 060NA for the students. Both versions have identical questions about perceived indoor climate and symptoms.

AIMS OF THE INVESTIGATIONS

The overall aim of this thesis was, by using objective methods, to elucidate if long-time exposure to building dampness may lead to an increased mucosal reactivity of the upper airways. The purpose was also to study the dynamic changes in the nasal mucosa when exposed to repeated histamine provocations.

The specific aims were the following:

1. to study if long-time exposure to building dampness contributes to an increased nasal mucosal reactivity measured as mucosal swelling upon repeated histamine provocations

2. if so, to examine if this increased reactivity remains after remedial measures have been taken

3. to elucidate if nasal mucosal histamine reactivity among students attending senior high school differs from that of adult teachers

4. to determine if there is a difference in the frequency of IgE sensitized ("skin prick test positive") subjects between the students and the adult teachers

5. to evaluate if nasal mucosal histamine reactivity increases among the students at the target school during their three years of study compared to students at the control school

6. to investigate if there is a difference in nasal histamine reactivity among atopic compared to non-atopic students out of season

7. to study the changes in mucosal microcirculation, measured with laser Doppler flowmetry, in response to nasal histamine provocation and find out if there is a difference between teachers at the target school and teachers at the control school

8. to examine if there is a correlation between the nasal mucosal swelling reaction and the nasal microcirculation, measured with laser Doppler flowmetry, when subjects are exposed to repeated nasal histamine provocations

MATERIAL AND METHODS

The study schools

The target school was constructed in the 1960s as a single storey building with flat roofs and an inlet and exhaust ventilation system and was situated close to a river that usually overflowed in the spring. Moisture damages were reported shortly after the construction period. Technical investigations performed in the beginning of the 1990s showed very severe moisture problems because of inadequate drainage and numerous water leaks from the flat roof causing growth of mould and discolouring of building materials. Measurements from insulation material in the ventilation system showed a substantial growth of mould of different species (e.g. claudosporium , penicillium, alternaria, and paecilomyces).

No systematic measuring programme was followed, but available measurements during the wintertime of relative air humidity (22-27%), airborne microorganisms (low levels) and chemicals in the air (total volatile organic compounds, TVOC ≈ 50 $\mu g/m^3$) showed no deviations from what is usually seen in Swedish schools [110]. The ventilation flows were within the range stipulated by the Swedish regulations and most CO2-measurements showed concentrations below 1 000 ppm (parts per million).

The control school was composed of four 3-4-storey buildings built between 1890 and 1930. Most classrooms were naturally ventilated during the 1980s, with very low air exchange rates, and carbon dioxide levels during the lessons occasionally exceeded 2 500 ppm. No moisture problems were reported. Extensive remedial measures were taken in both schools in 1993-94.

Study populations

1. **Studies I, II** and **V** represent different phases of a longitudinal study of teachers. A random sample of teachers who had worked at least five years at the water-damaged school (target school) before the renovation (39 persons), and all teachers in the control school who fulfilled the same inclusion criteria (30 persons), were invited to participate in the study. **Study I** was performed in the spring of 1995. Twenty-eight and 18 teachers, respectively, agreed to take part and formed the two study groups. Those who did not participate usually indicated lack of time for the examination during the limited period of the study as their reason for not doing so. In **study II**, which was performed in the spring of 1997, 26 teachers from the target school (one woman had died and one declined to participate because she was breast-feeding her baby) and all 18 teachers from the control school participated in the investigations. **Study V** was carried out in the

spring of 2000.Twenty-four teachers from the target school and 16 from the control school agreed to participate. Reasons for not participating were mainly practical, i.e. a change of school.

2. In **study IV** a random sample of 180 students (90 from each school) who were beginning their high-school studies were asked to participate in the study. Forty-five students from each school agreed and formed the study groups from the target school and the control school.

In order to estimate the possibility of a selection bias, all of the initially randomly selected 100 students (50 from each school) who refused participation were offered a simplified test procedure. As a result of this measure, a total of only eight students in this initially selected group provided no information at all. The first investigations were performed in the fall of 1995 (about two months after the start of the term). The next two investigations were done in the fall of 1996 (38/38 participated) and the fall of 1997 (38/35 participated). In 13 cases the reason for non-participation was that the students no longer attended the school in question. In no case were health reasons reported as the reason for leaving school or changing schools. One student who had participated in 1995 but not in 1996 also took part in 1997.

Thus, 37 students from the target school (37/45, 82%) and 35 students from the control school (35/45, 78%) participated in all investigations during the study period including nasal histamine provocation tests.

3. **Study III** comprised a comparison between the study populations of teachers and students in 1995 (presented above).

Questionnaires

Surveys of all teachers in the target school and the control school were conducted, using a standardised questionnaire (MM040NA [107]), before (1989) and after (January 1995) the renovation. The same MM-questionnaires were answered in February/March 1995 by all teachers (about six weeks before the start of the study) and used for analysis of the representativity of the test groups. The questionnaire contained questions about the perceived indoor climate, symptoms often referred to in indoor climate research, allergic manifestations, and some background factors.

In the tables in our papers, perception of *poor indoor air quality* means often troubled (at least once a week) by dry air, stuffy bad air, or unpleasant smell. In some tables we have used the single factors (dry air, stuffy bad air and unpleasant smell).

In January 1995 (**table 1**) the teachers in the target school still reported an increased frequency of mucous membrane irritations, while there was a slight decrease in the perception of stuffy bad air and a marked reduction of perceived unpleasant smell and complaints about dust compared to the outcome of the survey of 1989. The prevalence of dry air was high in 1989 and even higher in 1995. The teachers in the control school reported improved indoor air after the ventilation system was changed.

In all our studies, participating subjects answered a questionnaire in direct connection with the investigation. The teachers answered the same standardized questionnaire mentioned above and the students a somewhat modified one (MM060NA, [107]). In 1996 (study IV) the students answered two additional questions in order to determine the current prevalence of allergic symptoms (Have you had allergic eye or nose symptoms (itching, sneezing, runny eyes/nose) during the past twelve months? Have you had asthmatic symptoms during the past twelve months?).

Table I. The frequency of perceived indoor air quality, mucosal symptoms and general symptoms among teachers in the target- and control schools in 1989 and in January 1995.

	Target school		**Control school**	
	1989 n = 131	1995 n = 138	1989 n = 75	1995 n = 69
Perception of dry air (%)	33	54	27	7
Perception of stuffy bad air (%)	37	30	45	9
Perception of unpleasant smell (%)	17	6	13	1
Perception of dust and dirt (%)	47	25	16	20
General symptoms (%)*	34	36	41	33
Mucous membrane irritation (%)**	28	27	15	15

* The frequency of teachers often (every week) troubled by tiredness, feeling heavy-headed, headache, nausea, vertigo or concentration problems.

** The frequency of teachers often troubled by irritation from eyes, nose, throat or cough.

Rhinostereometry

Rhinostereometry (RSM) evolved primarily as a method for direct measurement of changes in nasal mucosal congestion with special reference to the reactivity of the vascular bed of the mucosa [**Figure 2,** 67]. The method is non-invasive and permits standardization of the nasal swelling reaction, without interference from secretion or anatomical disparities. The rhinostereometer (RHINOMED, Sweden) consists of a surgical microscope, with a small depth of focus, placed on a micrometer table fixed to a frame. The microscope can be moved in three orthogonal directions defining a three-dimensional co-ordinate system. The nasal cavity is placed in the co-ordinate when the subject bites down on an individually adapted tooth splint fixed to the frame. In this way the nasal cavity resumes the same position with a high degree of precision in repeated measurements. The nasal mucosa is examined via the eyepiece of the microscope. The ocular is equipped with a horizontal mm scale making it possible to measure changes in the congestion of the nasal mucosa. The accuracy of the method is 0.18 mm, that is to say the apparatus measures any movement of the mucosa exceeding 0.18 mm.

RSM permits measurements of all visible parts of the nasal mucosa. The structure mainly responsible for the perception of nose blockage is the head of the inferior turbinate which can undergo large variations in the degree of swelling. This region is part of the valve area, which is considered to play a major role in the development of nasal obstruction [111, 112]. Moreover, the inferior turbinate (or choncha) represents a highly reactive part of the nasal mucosa [64, 113].

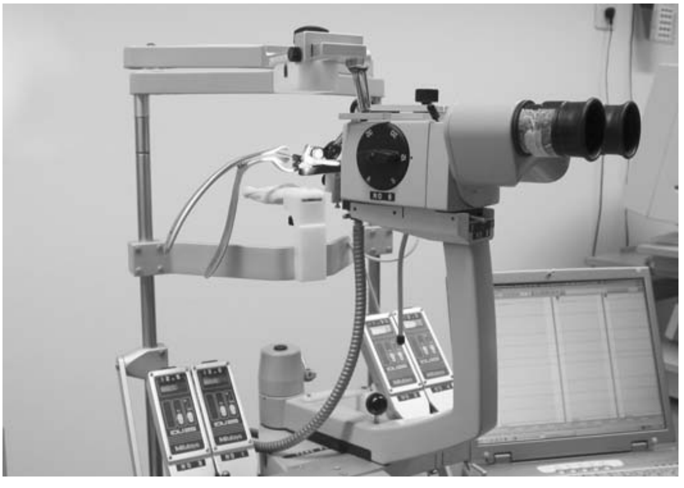


Figure 2. Rhinostereometer. The surgical microscope in front of the self-retracting nasal speculae and the individually formed tooth-splint.

Laser Doppler flowmetry

Laser Doppler flowmetry admits continuous registrations of relative changes in tissue blood flow in a non-invasive manner [114, 115]. The method utilizes the reflection of laser light from various components of the tissue studied. Light reflected from moving structures, such as blood cells, undergoes a frequency shift (the Doppler effect). By analysing the frequency distribution in the reflected light, one can make relative calculations of blood flow in the tissue. The concentration of moving blood cells (CMBC) can be calculated by analysing the amount of Doppler-shifted light. The average velocity of the moving blood cells can also be calculated from the degree of frequency shift. The product of CMBC and velocity of flow is the perfusion or flow.

The LDF probe, specially designed (PERIMED, Sweden), emitting the laser light and collecting the reflected light, is introduced into the nasal cavity and placed close to the surface (0,1-0,3 mm) of the mucosa of the inferior turbinate (**figure 3, figure 4**). The measuring volume (depth) is influenced by tissue properties and light source wavelength [116]. The wave-length of the laser beam was 780 nm. LDF was performed using a PERIFLUX 4001 (PERIMED, Sweden) and the signal was fed into an IBM compatible computer using PERISOFT software program.

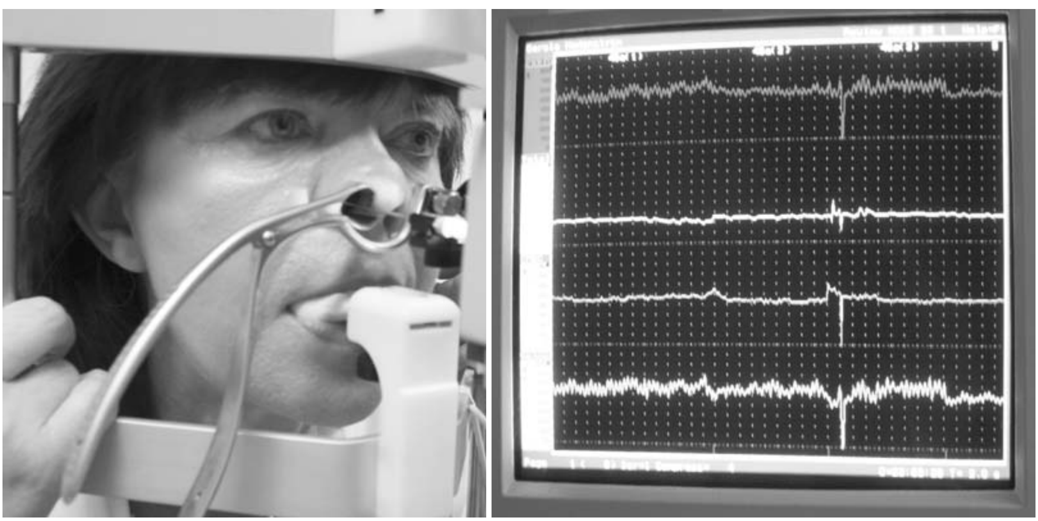
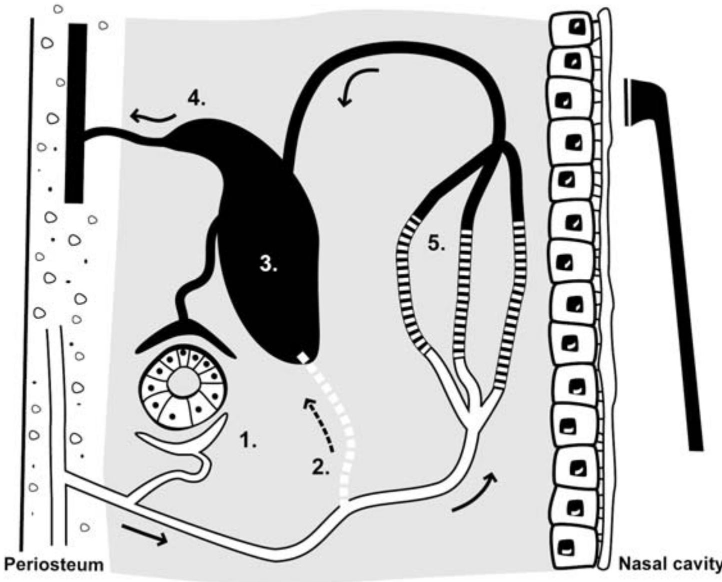


Figure 3. Rhinostereometry and laser Doppler flowmetry. The probe is introduced into the right nasal cavity (left). The microcircular flow (from top to bottom): perfusion, total back scatter (= a control function), CMBC and velocity is registered on a computer screen (right).



1. Glandular capillaries
2. Arteriovenous anastomosis
3. Venous sinusoid
4. Throttle vein
5. Subepithelial capillaries

Figure 4. Schematic drawing of the vessels in the nasal mucosa of the inferior turbinate. Arterioles and capillaries superficially and the sinusoids in the deeper mucosal layer. The probe is placed ≈ 0.1 mm from the mucosal surface.

The provocation test

We selected histamine as the provocation substance because of its documented ability to evoke mucosal swelling in rhinostereometric studies of nasal mucosal reactivity [15, 64]. We used a histamine dihydrochloride solution with no preservatives to avoid the potential risk of causing a double challenge effect [117].

The provocation test in **study I** was performed as a single blind procedure at a near-by hospital. In **studies II, IV** and **V** the provocations were carried out in a reception room at the respective schools. The subjects were allowed to acclimatize during 30 minutes, after which they were challenged every 10 minutes with 0.14 ml of histamine dihydrochloride in rising concentrations (1, 2 and 4 mg/ml), using the same standard nasal provocation procedure as described by Hallén and Juto [65, 118]. The challenge substance was applied to the medial side of the right inferior concha with a syringe, while the left inferior concha was unprovoked and served as a control. Only if the initial rhinoscopic investigation showed pronounced right septal deviation was the left inferior turbinate used for the provocation.

Recordings of the mucosal swelling were made with rhinostereometry in both nasal cavities 5 and 10 minutes after each challenge (in **study V** recordings were also made 2 minutes after challenge with the lowest histamine concentration and only the right nasal cavity was recorded as earlier studies showed only marginal mucosal changes on the contralateral side during provocation). In **study V**, directly after histamine provocation and recording of the mucosal congestion with rhinostereometry the LDF probe was placed in position. As soon as there were stable recordings of perfusion, CMBC and velocity on the computer screen, these were saved for later analysis. Each time, a 10 to 20-second recording was saved. Laser Doppler registrations were made 2, 5 and 10 minutes after provocation with the lowest histamine concentration (1mg/ml), and 5 minutes after provocation with the remaining histamine concentrations (2 and 4 mg/ml).

In **study I** the subjective perceptions of nasal blockage during histamine provocation (not specified to the provocation side) were recorded on a four-point scale where zero meant no blockage and three severe blockage. The amount of secretion observed by the investigator on the provoked side was rated as none, sparse, covering the medial part of the anterior choncae, or covering the choncae with wide septal contact, also on a four-point scale. Number of sneezes were recorded by the investigator.

Skin prick test

In 1995 (**studies I, III** and **IV**) a skin prick test with a standardized panel of allergens, often used in Scandinavia (ALK, Copenhagen), was performed after the histamine challenge.

The following allergens were tested: pollen (birch, timothy and mugworth), mites (d. pteronyssinus and d. farinae), furry animals (cat, dog and horse) and moulds (claudosporium, alternaria and aspergillus fum.). Skin prick test positivity (SPT+) was defined as a wheal with a diameter of at least 3 mm [119] (for further information see previous heading "Atopy and allergy").

Exposure measurements in the study schools

Exposure measurements were performed, although not systematically, before remedial measures had been taken in the study schools (and also before the start of our studies), and these were mentioned earlier (under the heading "The study schools").

After the renovations, exposure measurements were performed in both schools on three occasions. To reflect the possible influence of outdoor climate on the indoor conditions technical measurements were done at different times of the year. The first series of measurements were performed in spring 1996, the second in autumn 1996 and the third in winter 1997.

Representative rooms were chosen and the measurements performed were identical on the three occasions. The following factors were studied (described in more details in **study II**):

- total concentration of airborne dust (sampling time 7 am to 5 pm during three consecutive work-days)
- particle size distribution of airborne dust
- indoor air temperature
- relative humidity in indoor air
- concentration of carbon dioxide (continuously during at least three days)
- concentration of formaldehyde (24 hours)
- concentration of volatile organic compounds (14 days)

Technical investigations of the students´ home environments

In the longitudinal student study (**study IV**) 81 of the 90 homes were examined (39/42, respectively, of the target group and control group environments) by experienced building engineers. Dropouts were due mainly to a recent move to a new home, difficulty in finding a suitable time during the limited time of the investigation or, in a few cases, unwillingness to participate. Moisture- and mould damage in different rooms and spaces was noted, and a question was posed as to whether there was condensation on the inside of bedroom windows in the wintertime, which is an indication of insufficient ventilation.

Room temperatures and relative humidity were measured in 76 of the homes (36/40, respectively). The additional dropout here was because of technical problems. The average indoor temperature in each student´s home was measured during the heating season over a period of approximately 30 days. Relative humidity in the indoor air was determined in parallel with the temperature.

Statistical methods

For the continuous outcome variables we used an analysis of variance model for repeated measurements (an ANOVA model) in **studies I, II, III, IV and V**. The basic formulation of this model aimed at modelling the growth curves for the variables as a function of the provocation concentrations of 1, 2 and 4 mg/ml of the histamine solution. The model was applied with somewhat different specifications but the core specification had one main exploratory factor or 'between subjects' factor, i.e. the study group factor. This factor was school (target school or control school) that classified the individuals (teachers or students) in the two groups. In **study III** a further classification was used since both school and person group (teachers or students) were analysed simultaneously.

In addition to the group factor there were 'within subjects' factors, i.e. factors for which there were repeated measurements for the subjects. These factors were dose (1, 2 and 4 mg/ml of histamine solution), time (5 and 10 minutes after provocation), and in **studies II, IV and V** also year of investigation (1995, 1997 and in study V 2000).

Some additional factors to control for a potential confounding were also tested in the model: age, sex, smoking, and status of allergy or atopy. To facilitate the understanding of the rather complex ANOVA model we used a slight reformulation that enabled the estimation of the average increase in swelling per ^{2}log mg/ml histamine (actual doses 1, 2 and 4 which give the logarithmic values 0, 1 and 2) in **studies II, III and V.** This is equivalent to an estimate of the slope in the linear regression of mucosal swelling on ^{2}log provocation level, restricted to the interval 1-4 mg/ml histamine solution.

Correlation analysis of the continuous variables was done with Pearson's as well as Spearman's correlation coefficients in **study V.**

The binary outcome variables were analysed with Fisher's exact test in **study II**, the chi-square test in **study IV**, logistic regression in **study IV,** and two reformulations of the common logistic regression model into a generalised version with repeated measurements in **studies I and V**.

The statistical models were implemented in the statistical packages SAS, version 8.1 (modules GENMOD and MIXED), BMDP, version 7 (procedure 5V), EPILOG, version 3 and StatXact, version 5.

RESULTS

The main results in the studies (**studies I-V**) are briefly summarized as follows.

Nasal hyperreactivity among teachers in a school with a long history of moisture problems (Study I)

Personal characteristics and symptoms

Analysis of personal characteristics (**table II**) showed that the test groups were fairly representative of the total populations of personnel at the two schools. The teachers at the target school complained more about the quality of the indoor air than those at the control school and also reported a higher prevalence of mucous membrane symptoms.

Table II. Personal characteristics and mucosal and general symptoms in the two groups of teachers and the total populations of employees in the two schools answering the questionnaire in 1995. The frequency of positive skin-prick tests in the two study groups is also shown.

	Target school		**Control school**	
	Study group	Total[1]	Study group	Total[1]
	n = 28	n = 129	n = 18	n = 69
Sex (% men)	46	41	67	49
Age (mean)	51	48	51	49
Smoker (%)	7	16	6	13
Allergic disease (%)[2]	25	26	11	21
Employment (years)	15	11	13	9
Poor Indoor air quality[3]	57	66	28	28
General symptoms (%)[4]	43	37	39	33
Mucous membrane irritation (%)[5]	25	27	17	15
Positive prick test (%)	18	-	17	-

[1]Total means the whole group of personnel answering the questionnaire in Feb./March1995.
[2]Reported cumulative incidence of hay fever and asthmatic symptoms.
[3]The prevalence of teachers often troubled by dry air, stuffy bad air, or unpleasant smell.
[4]The frequency of teachers often troubled by tiredness, headache, feeling heavy-headed, nausea, vertigo or concentration problems
[5]The prevalence of teachers often troubled by irritation from eyes, nose, throat or cough.

The provocation test

The results of the provocation test are shown graphically in **figure 5.** The mucosal congestion was calculated as the deviation from the baseline. The ANOVA model showed significantly different growth curves in the two study groups ($p < 0.01$) with respect to the provoked side of the nose. On the control side, only slight mucosal congestion was recorded around the baseline.

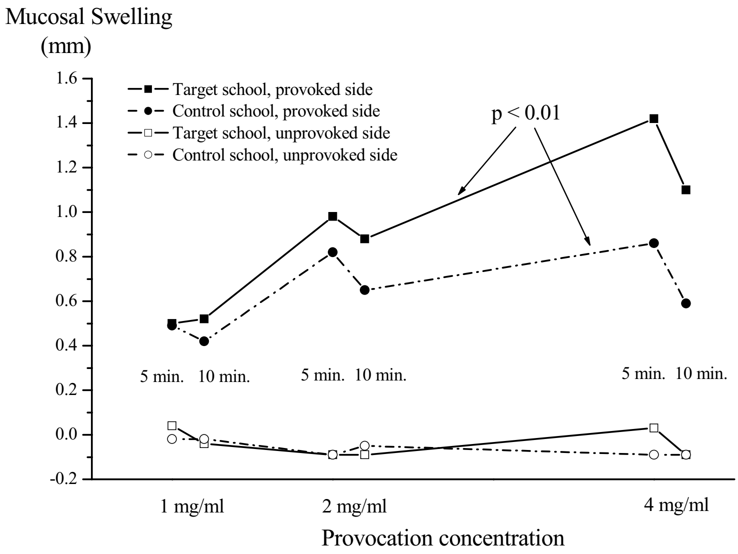


Figure 5. Histamine provocation curves (the mean of net change in mucosal swelling from baseline on provoked and unprovoked sides) in target-school and control school. The significance of the difference in slope between the two provocation curves is shown ($p<0.01$).

Local reactions

The prevalence of local reactions (nasal blockage, secretion and sneezing) during the histamine provocations was registered. For nasal blockage we obtained no differences in trend but there was a borderline statistical significance for the two groups with respect to the general level of perceived nasal blockage, $p=0.06$, with higher scores for the target school. With respect to secretion we observed no difference in level of the scores but there was a difference in trend for the target school as compared to the control school, $p=0.03$. (The scores between 2 and 4 mg/ml did not increase in the control school.) For sneezing, no statistically significant results were found. If the analysis is done on the whole group of teachers there is a statistically significant increase in the perception of nasal blockage and registered nasal secretion with increasing histamine concentration ($p<0.01$, not shown in the paper).

Skin prick test

Eighteen percent of the teachers at the target school and seventeen percent of those at the control school had a positive skin prick test (**table 2**). Allergy to birch pollen was most common (13%), while no allergy to mites or moulds was detected in the two schools.

Slowly decreasing mucosal hyperreactivity years after working in a school with moisture problems (Study II)

Perceived indoor climate and symptoms

Differences in the outcome for the two test groups analysed separately for each year (1995 and 1997) resulted in significance only for perception of dry air in 1995 where the target school had a significantly higher prevalence (Fisher´s exact test, $p=0.0002$).

There was a significant improvement for the target school compared to the control school (Fisher´s exact test, $p=0.03$), although 31% of the teachers still complained about perceived dryness of the air. No symptoms showed significant improvement and most individuals reported the same outcome in 1995 and 1997.

Provocation test

The mean congestion of the nasal mucosa for the two provocation tests (1995 and 1997) and the two groups are presented graphically in **figure 6.** Using the ANOVA model we estimated the slope in the regression of mucosal swelling on the provocation level under two different hypotheses: the first assuming that the difference in slopes was constant between 1995 and 1997, and the second that a change had occurred. Based on the results of these two hypotheses we concluded that there was still a difference between the two schools, but the difference appeared to be decreasing. It will later be shown that this finding also fits well into the corresponding findings in **study V**.

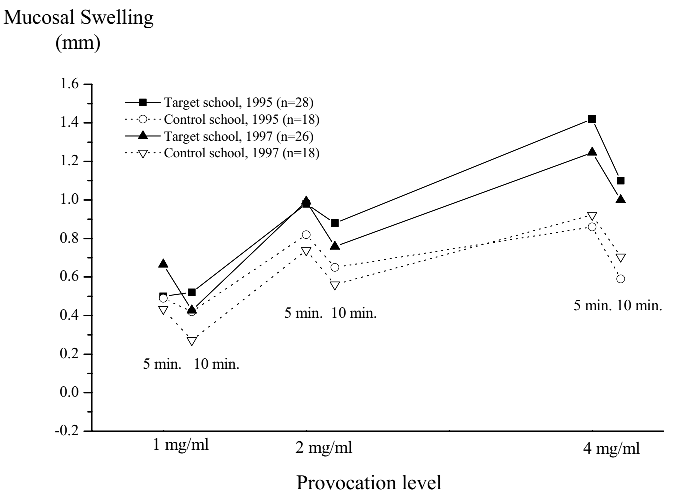


Figure 6. The histamine provocation curves (mean values) for the two groups in 1995 and 1997. Readings for 5 as well as 10 minutes after provocation are shown.

Technical measurements

The total concentration of airborne dust was found to be low in all classrooms and at the same level as found in dwellings. Continuous measurements during several days showed that the concentration could vary considerably during the day. When the classroom was unoccupied the concentration was very low, less than 5 $\mu g/m^3$, whereas the concentration momentarily could reach values of approx. 100 $\mu g/m^3$ when persons entered or left the classroom.

The concentration of compounds in the air that are generally associated with water-damages in the construction (n-butanol and 2 ethyl-1-hexanol) were below the detection level (1$\mu g/m^3$).

The ventilation systems were not equipped with humidifiers and therefore the relative humidity indoors was mainly a function of temperature and relative humidity outdoors. The highest values (55%) were recorded in the autumn and the lowest (30%) in the winter. When a classroom was occupied, the steady state concentration of carbon dioxide during a lesson exceeded the recommended highest level, 1000 ppm (AFS, 1993), in 25% of the classrooms in the target school and in 33% of the classrooms in the control school. The concentrations of volatile organic compounds (VOCs), of total volatile organic compounds

(TVOC), and of formaldehyde were low and well within expected levels. Individual organic compounds were also those that would be expected considering the type of construction and surface materials used.

Nasal mucosal histamine reactivity among young students and teachers, having no or prolonged exposure to a deteriorated indoor climate (Study III)

Study population

Table III shows a few characteristics of the students and teachers in the two schools. The proportion of boys was higher in the target school than in the control school, but this simply reflected the gender ratio in the two schools (47.9% versus 33.4% boys in the target and control schools, respectively).

Table III. Some personal characteristics of the students and the teachers at the two schools.

	Target school (students) n = 45	**Control school (students)** n = 45	**Target school (teachers)** n = 28	**Control school (teachers)** n = 18
Gender (% males)	46.7	28.9	46.4	66.7
Age (mean)	16.1	16.1	51.4	50.6
Smoker (%)	15.6	13.3	7.1	5.6

A description of the randomly selected teachers (**study I**) and students (**study IV**) has been reported in the papers. There was no bias in the selection of teachers or students to participate in the histamine provocation study according to reported allergy, mucosal symptoms or positive skin prick test.

Reported allergy and symptoms

The reported prevalence of allergic disease was similar in students and teachers in the target school, but the teachers in the control school reported a somewhat lower prevalence. However, the overall difference between students and teachers was not significant, p=0.52. Teachers had a higher frequency of mucosal symptoms (21.9%) than students (10.0%), but the difference was of only borderline significance, p=0.07.

Skin prick test

The frequency of skin prick positivity (SPT+) and the prevalence of mucosal symptoms are shown in table IV. The total frequency of SPT+ among the students was much higher than in the adult teachers (35.6% versus 17.4%, p=0.03) and in good accord with results from other studies of young people [120]. Allergens from pollen and furry animals dominated.

Table IV. The prevalence of symptoms and frequency of atopy (positive skin prick test) in students and teachers at the two schools.

	Target school (students) n = 45	**Control school (students)** n = 45	**Target school (teachers)** n = 28	**Control school (teachers)** n = 18
Symptoms (according to questionnaire):				
Asthma/hayfever (%)	27.9	24.4	25.0	11.1
Mucosal symptoms (%)	8.9	11.1	25.0	16.7
SPT+ (%)	35.6	35.6	17.9	16.7

The provocation test

The results of the histamine provocation test on the provoked side of the nasal cavity in the students and teachers are given in **figure 7**. Only small oscillations around the baseline were seen on the control side. The ANOVA analysis showed a statistically significant difference of the main factor teachers versus students, p=0.0001, with students having much lower values than teachers (on average, about half the teachers´ values).

The first ANOVA model with all main factors and interactions showed that the interaction group*concentration level was highly significant, p=0.008, which indicated that the four groups had different provocation curves. **Figure 7** shows that the statistical significance is due to two features, i.e., the curves are different in the two groups of teachers, and those of the students are much lower than those of the teachers.

Since we found no difference in any respect between students in the two schools, they can be viewed as a homogenous group. Our analysis of each school showed that the provocation curve of the target school teachers had consistently higher values than that of the students, p=0.0001, but its slope and shape were similar, p=0.15. In the control school, however, there was a difference between the slopes of the curves that was of borderline significance, interaction (category)* (provocation concentration), p=0.07.

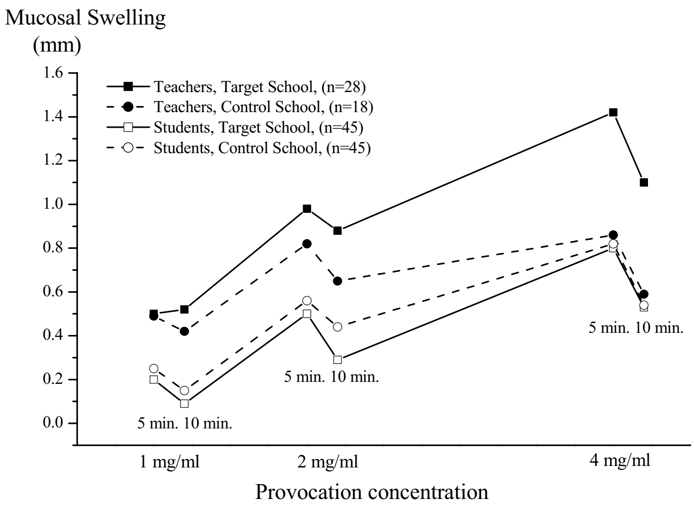


Figure 7. Histamine provocation curves of the teachers and students at both schools.

A separate analysis of differences between atopic and non-atopic teachers as well as between atopic and non-atopic students showed no differences in the provocation curves.

The rhinoscopic examination of the teachers showed that 15 had a dry and crusty mucosa and 31 did not. No significant difference was found between teachers in the target school and those in the control school (10/28 and 5/18 respectively, p>0.50). Among the students less variation was noted in the rhinoscopic findings and only one had such a dry and crusty appearance on rhinoscopic examination.
Among the teachers we found a definite statistical significance for the crusty appearance, p=0.002, in the analysis of baseline values and in the analysis of the provocation curves (p=0.0004) **(figure 8).** However, and more importantly, the significant difference between the target and control schools in the latter analysis did not disappear with the introduction of a crusty appearance in the statistical model since we obtained p=0.002 for difference in slopes. Furthermore, in a later analysis (Fisher´s exact test), not included in the primary study, we found that the teachers with a rhinoscopically dry and crusty mucosal appearance complained more frequently of irritative mucosal symptoms (33%/16% respectively) and skin symptoms (53%/7%, respectively) than those without this appearance. The difference between the two groups is significant regarding skin symptoms (p=0.004).

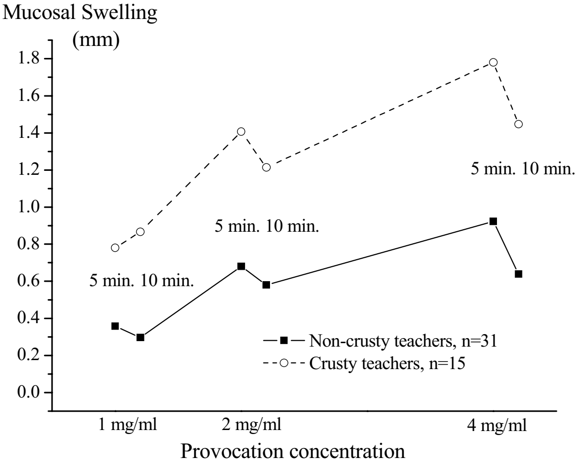


Figure 8. Histamine provocation curves for teachers with a rhinoscopically dry and crusty appearance compared with those without this appearance.

Nasal histamine reactivity among adolescents in a remediated moisture-damaged school – a longitudinal study (Study IV)

Study population

Of the initially randomly selected 100 students in 1995, 54 took part in the histamine provocation study and 46 declined to participate. Data (skin prick test and questionnaire) were obtained from 38 of these 46 students who refused the provocation test. There was no bias in the selection of students who participated in the histamine provocation study according to reported allergic manifestations (24.5% (13/53) and 28.9% (11/38), respectively), mucosal symptoms (11.1% (6/54) and 7.9% (3/38), respectively) or positive skin prick test (33.3% (18/54) and 28.9% (11/38), respectively). The participation rate was higher for girls than for boys (61% (33/54) and 29% (11/38), respectively).

Technical investigation of home environments

Students at the target school more often came from the suburbs and lived more often in multi-family houses. Their homes less often had natural ventilation, condensation on the bedroom windows in wintertime and a high internal moisture supply (difference between the absolute water content in indoor and outdoor air), all of which are indicators of better ventilation than in the homes of students at the control school.

There were, however, no important differences in the homes of the students at the target and control schools with respect to room temperatures or relative humidity.

Questionnaires

Complaints about variable and low room temperatures were more frequent among the students at the target school during the years of the study (1995, 1996 and 1997), while the perception of air quality was similar at the two schools. The prevalence of mucosal and dermal symptoms was low and fairly similar in the two schools and did not change during the study period. No significant differences regarding the perceived indoor air climate or mucus membrane irritation were seen between atopic and non-atopic students, and we did not observe any statistical interaction between school and atopy.

Skin prick test

The frequency of skin prick test positivity among the students was 36% at each school (16/45). In 1996, 70% (19/27) of the SPT+ students reported symptoms of nasal allergy and/or asthma during the past year. During the same time, 18% (9/49) of the SPT- students reported symptoms of nasal allergy, while there were no reports of asthma.

Provocation test

The results of the provocation tests are shown in **figure 9**. In the figure, the swellings for 5 and 10 minutes after provocation are averaged so that the figure is easier to interpret, and therefore the time factor is not shown. The ANOVA with outcome values for 1995, 1996 and 1997 gave a borderline significance for school*dose*year ($p=0.06$), indicating that the provocation curves for the two schools shifted over the three years. This was due to the different curve in 1996 for the target school.

For all factors where school was included (school*dose*time, school*time, school*dose and school), no statistically significant results were found, and all p-values were in fact >0.25. At the end of the three-year study period there seemed to be no substantial difference in mucosal swelling induced by histamine provocation for the students at the two schools when differences at baseline were accounted for.

We could find no evidence for differences between atopic and non-atopic students during these three years of study.

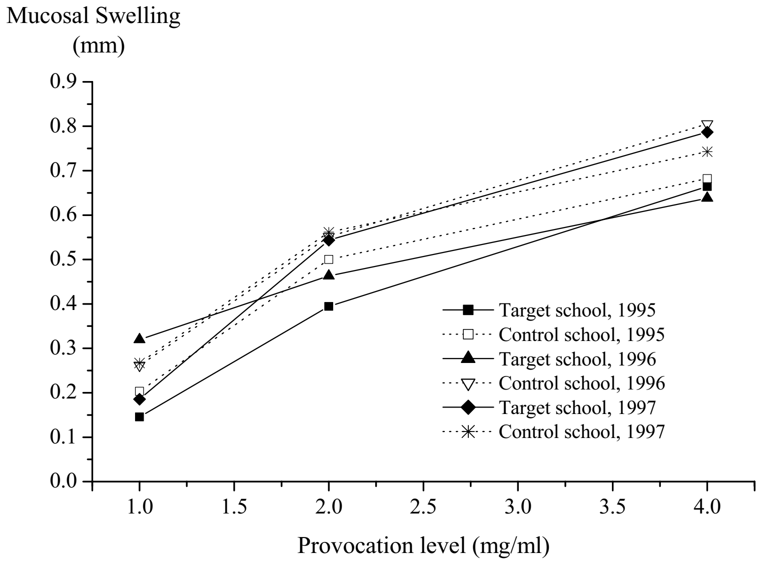


Figure 9. Histamine provocation curves (the mean net change in mucosal swelling from baseline) for students from the target and control schools measured on three occasions, in 1995, 1996 and 1997. The curve for the target school in 1996 deviates somewhat from the other curves (p=0.06).

Nasal mucosal histamine reactivity among teachers six years after working in a moisture damaged school (Study V)

Reported complaints and symptoms

As shown in **table V**, there were more complaints of varying and low room temperatures among the teachers in the target school as compared to the teachers in the control school. The analysis of varying room temperature and low room temperature showed a significant difference between the two schools, p=0.01 and p=0.04, respectively. The odds ratios for complaints, with the control school teachers as referents, were 5.7 (95% CI 1.2 – 27.7) and 5.4 (95% CI 1.1 – 25.6), respectively, indicating a much higher risk for complaints at the target school.
For poor indoor air quality there was also a significant difference between the two schools, p=0.01, and the odds ratio was 5.3 (95% CI 1.2 – 22.3) for the target school, but no significance for the factor year or interaction school*year.
For the symptoms none of the investigated factors, showed statistical significance. However, there was a decreasing tendency for general, mucosal and skin symptoms during the years of investigation among the teachers in the target school, which was not seen in the control school.

Table V. Prevalence of complaints and symptoms in Target and Control Schools in 1995, 1997 and 2000.

	Year	Target school (n = 24)	Control school (n = 16)
		Yes / n of answers (%)	
COMPLAINTS:			
Varying room-temperature	1995	5/23 (21.7)	0/16 (0.0)
	1997	9/22 (40.9)	2/15 (13.3)
	2000	5/20 (25.0)	1/14 (7.1)
Low room-temperature	1995	1/24 (4.2)	0/16 (0.0)
	1997	7/22 (31.8)	1/16 (6.3)
	2000	5/20 (25.0)	1/15 (6.7)
Poor indoor air quality[1]	1995	13/24 (54.2)	2/16 (12.5)
	1997	8/24 (33.3)	2/16 (12.5)
	2000	10/24 (41.7)	2/16 (12.5)
SYMPTOMS:			
General symptoms[2]	1995	12/24 (50.0)	7/16 (43.8)
	1997	10/24 (41.7)	8/16 (50.0)
	2000	8/24 (33.3)	7/16 (43.8)
Mucosal irritative symptoms[3]	1995	7/24 (29.2)	3/16 (18.8)
	1997	8/24 (33.3)	1/16 (6.3)
	2000	4/24 (16.7)	3/16 (18.8)
Skin symptoms[4]	1995	5/24 (20.8)	3/16 (18.8)
	1997	3/24 (12.5)	3/16 (18.8)
	2000	2/24 (8.3)	3/16 (18.8)

[1]The percentage of teachers often troubled (= at least every week) by stuffy bad air, dry air or an unpleasant smell the preceding three-month period.
[2]The frequency of teachers often troubled by tiredness, feeling heavy-headed, headache, nausea, vertigo or concentration problems.
[3]The frequency of teachers often troubled by irritated eyes, nose, throat or cough.
[4]The frequency of teachers often troubled by facial dryness- or redness, scaly and itchy scalp/ears or dry itchy skin on the hands (eczema of the hands).

Provocation test

RSM/mucosal swelling reaction

The ANOVA analysis showed that in 1995 there was a statistically significant difference in the responses of teachers in the two schools to increased provocation levels, (p=0.001 for the 5-minute readings). In 1997 the difference had decreased compared to 1995 (the difference was still statistically significant). In 2000 (**figure 10**) there were no statistically significant differences (p=0.35). The swelling reaction 2 minutes (in 2000) after provocation with the lowest histamine concentration was more pronounced in the two study groups than after 5 or 10 minutes.

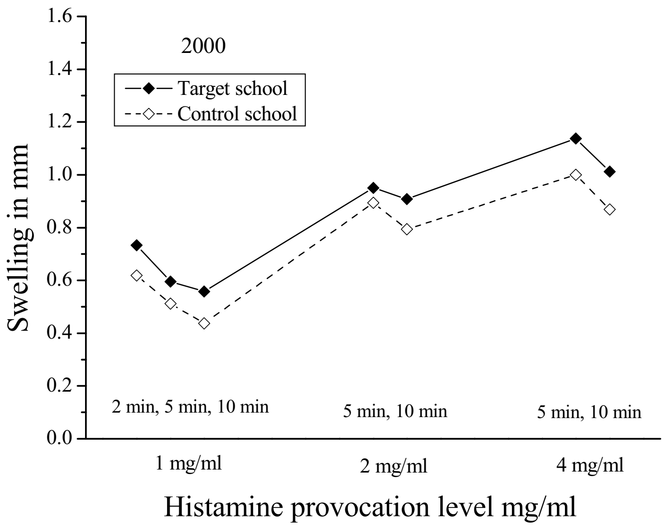


Figure 10. Histamine provocation curves (the mean net change from baseline) for teachers in the target and control schools in 2000.

Laser Doppler flowmetry

An analysis of variance of repeated measurements of perfusion for various dose levels in schools, based on 5-minute readings, showed a significant difference for school*dose (p=0.0022) indicating a difference in reaction patterns between the two teacher groups during the provocation procedure. This is well illustrated in **figure 11** where the microcircular perfusion in the nasal mucosa steeply increases from baseline 2 minutes after the first provocation with the lowest histamine concentration in the two teacher groups. The control group then seems to restore the level of perfusion rapidly and reacts more strongly to the following provocations compared to the weaker reaction from the teachers in the target school. There was also a significant difference over time (2, 5 and 10 minutes) ($p=0.0064$) when considering the lowest histamine concentration (1mg/ml).

Figure 12 shows the changes in CMBC during the histamine provocation procedure. The teachers in the target school, in contrast to those in the control school, show a decrease in their CMBC after the first histamine provocation and this remains low during the whole provocation procedure. There is a significant difference based on the 5-minute readings for the factor school ($p=0.0009$), but not for the factor school*dose ($p=0.25$), indicating that the provocation curves are well separated with a similar reaction pattern during the provocation procedure. As with perfusion, there was also a significant difference over time ($p=0.0048$) when considering the lowest histamine concentration.

There was no correlation between measured mucosal swelling and Laser-Doppler flowmetry (perfusion/CMBC values) during the histamine provocation procedure, with almost all correlation coefficients in the order of –0.10 to 0.10. On the other hand, correlations within the measured mucosal swelling as well as within flowmetry were much higher, in the order of 0.6 – 0.7, clearly indicating the need for the analysis of these measurements with allowance for correlations between repeated measurements, i.e. our chosen method of analysis.

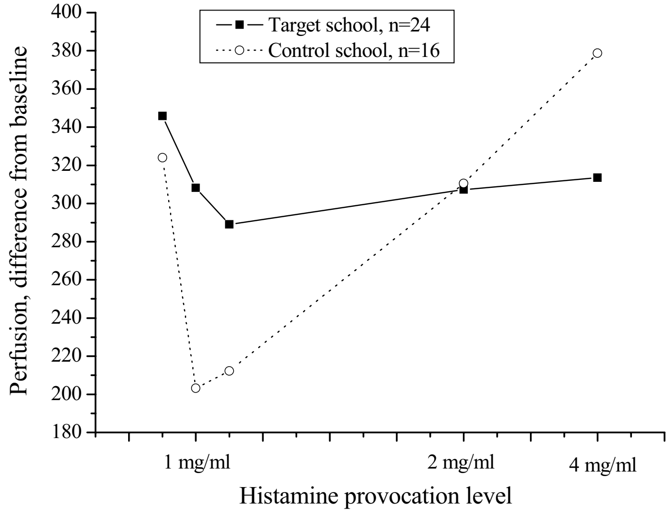


Figure 11. Perfusion, difference from baseline. Values read at 2, 5, and 10 minutes after provocation for the 1 mg/ml histamine provocation level, and at 5 minutes for the 2 and 4 mg/ml levels.

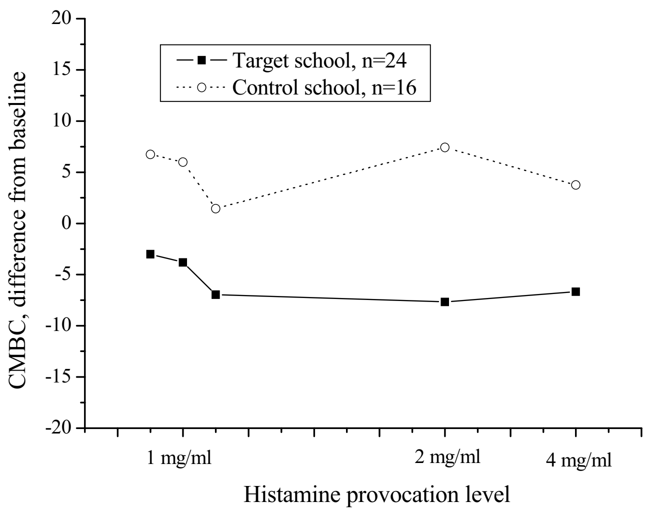


Figure 12. CMBC, difference from baseline. Values read at 2, 5, and 10 minutes after provocation for the 1 mg/ml histamine provocation level, and at 5 minutes for the 2 and 4 mg/ml levels.

DISCUSSION

Decreasing Nasal histamine reactivity among the teachers in the target school

In 1995, one year after the renovations, the provocation tests showed significantly higher nasal mucosal reactivity to histamine among teachers working at the earlier water-damaged school than among teachers in the control school (**study I**). In 1997 the difference was less pronounced but still statistically significant (**study II**) and in 2000, six years after remedial measures had been taken, the statistical analyses showed no significant differences regarding nasal histamine reactivity between the two teacher groups (**study V**). These findings strengthens the assumption that long-time exposure to building dampness may induce mucosal hyperreactivity of the upper air-ways. This acquired hyperreactivity may then last for years and decrease only slowly even after the indoor climate has been properly improved. A possible explanation for this slowly decreasing reactivity might be a slow but ongoing restoring process in the mucosa of the upper air-ways.

Nasal histamine reactivity among the students

The statistical analysis showed no significant differences regarding nasal histamine reactivity between the previously unexposed students at the target school and the control school from start to endpoint of the time of observation (**study IV**). Furthermore, there were no differences in nasal histamine reactivity between the usually more sensitive atopic and non-atopic subjects during the years of study. Accordingly, persistent symptoms and increased nasal mucosal reactivity among personnel (teachers) in a remediated moisture-damaged school building does not necessarily imply an inadequate renovation.

This longitudinal study with registration of subjective (questionnaires) and objective (nasal histamine reactivity) data concerning this earlier unexposed group in the same building further contributed to the assumption that the renovation was successful.

Comparison of nasal histamine reactivity between students and teachers

The nasal histamine provocation tests differed markedly between teachers and students as regards nasal mucosal histamine reactivity. The fact that even the teachers from the control school showed more marked mucosal swelling in response to the lowest histamine provocation concentrations than the students suggests that age and/or various types of environmental exposures are of importance. Such a mucosal reaction pattern may be due to a reduced secretory ability with age [121] and the lack of a protective mucus layer, which would make the mucosal sensory nerve endings more sensitive to non-specific stimulation.

The teachers in the control school had only a moderate increase in mucosal swelling when exposed to the highest histamine concentration as compared to the students. The marked mucosal reaction to the lowest histamine concentration may induce tachyphylaxis of the neural response during repeated stimulation. This is unlike the response of the teachers in the target school who reacted most to the highest histamine concentration. Their curve for mucosal swelling closely resembled that of the students, but at higher levels.

Exposure measurements before and after the renovation

The investigations performed by professional consultants before renovation of the target school showed a substantial increase in mould growth in the ventilation system and severe moisture problems caused by water leakage for many years. However, measured indoor air parameters in the target school before renovation, including relative air humidity, concentrations of moulds and volatile organic compounds in indoor air, were not higher than what is usually measured in Swedish schools without indoor climate problems [110]. Indoor concentrations of airborne viable fungi vary extensively, mostly depending on differences in climate conditions, and mainly follows the outdoor concentrations [122, 123, 124]. In colder climates, such as in Scandinavia and Canada, the prevalence of moisture and mould damage in the building construction but "normal" levels of pollutants, including moulds, in the indoor air has been described [125, 126, 127]. Furthermore, the outdoor humidity largely determines the relative humidity levels in the indoor air. In the Nordic countries, the relative humidity indoors is usually low (mostly below 45%), even in mould contaminated buildings [128, 129].

The control school had had severe ventilation problems before renovation. In spite of this, significant differences in nasal histamine provocation curves were seen between the two schools after the renovations, which might indicate that specific pollutants were causing a prolonged effect on the mucous membranes of the exposed teachers in the water-damaged school. Indeed, the relationship between working and/or residing in edifices with building dampness and increased mucosal reactivity seems to be due to emissions in the air from the moisture-damaged foundation by microbial growth or chemical degradation of the material [130, 131, 132]. The lack of remaining signs of water damage in the building construction and the fact that, according to the technical measurements performed after the renovations, the physical environments in both schools were essentially of the same quality also indicated a successful renovation of the previous moisture-damaged school.

Complaints and symptoms

The high frequency of experienced poor indoor air among the teachers in the target school in 1995 only marginally decreased during the years of observation. A contributing factor might be difficulties in maintaining a uniform temperature in a single-storey building, leading to a significantly higher prevalence of complaints of varying and low room temperature among the target school teachers. Uniformity of temperature and well adapted ventilation are important for comfort and seem to be associated with a lower incidence of experiencing air dryness [133], which was a dominating complaint in the experience of poor indoor air climate among the target school teachers.

The frequency of reported mucosal irritative symptoms and skin symptoms decreased among the teachers in the target school during the time of observation. However, there were no statistically significant differences regarding these symptoms over time between the teachers in the target school and the teachers in the control school, probably because the study was not fully dimensioned to evaluate differences in these parameters.

The assumption that the renovation was adequate is also strengthened by the fact that the students at both the target and the control school reported a similar low frequency of perceived bad indoor climate and mucosal symptoms during the time of observation. Furthermore the perception of bad indoor climate as well as general and mucosal symptoms among the students did not differ much from those of the teachers in the control school.

Sample size

It should be mentioned that these studies were designed primarily to analyse differences in histamine reactivity and for that purpose the sample size was considered well in line with experiences of earlier investigations [15, **study I**].

The secondary aim was to analyse the questionnaire data, where the variables were measured on a nominal or ordinal scale with few categories. For that purpose, it would have been better to increase the sample somewhat, but for practical reasons that was not possible. However, the number of participating students in **studies III and IV** was quite high, allowing for the possibility of differentiating moderate differences in reported complaints and symptoms.

Atopy/skin prick test positivity

The prevalence of *IgE sensitization*, defined as a positive skin prick test (SPT+), was not higher among the teachers in the target school compared to the teachers in the control school, indicating that the increased reactivity of the nasal mucosa in the target group was of a non-specific type.

The frequency of SPT+ was at least twice as high among the students as compared to the teachers (36% versus17%). This is in accord with the increasing frequency of atopy in the Western world [1, 134]. The exposure measurements did not show any deviation from what is usually seen in Swedish schools [110]. However, exposure to indoor air pollutants in moderate concentrations has been shown to be related to airway symptoms, particularly among atopic individuals [6, 135, 136]. We found no significant differences between SPT+ and SPT- students or between atopic and non-atopic students at the two schools regarding nasal histamine reactivity, perception of indoor climate or mucosal irritative symptoms, indicating a decent indoor air quality in both schools. In 1996, the majority of the SPT+ students (70.4%) reported allergic symptoms during the preceding year. Consequently, a positive skin prick test in this age group seems to indicate an active atopic disease. None of the SPT- students reported asthmatic symptoms, indicating that asthma in this age group (16-18 years) is predominately a manifestation of atopy.

Mucosal appearance (rhinoscopically)

Among the teachers in the two schools with a rhinoscopically dry and crusty appearance the histamine provocation curves for mucosal swelling showed a marked significant increase compared to those for the remaining teachers. The prevalence of this dry and crusty mucosa did not differ significantly between the teachers in the two schools. The development of such a dry mucosa may be constitutional, but it may also be age dependent and predispose to an increase in mucosal reactivity to histamine.

One explanation could be an age dependent lower mucosal water content and the lack of a protecting mucus layer, which would make the mucosal sensory nerve endings more sensitive to unspecific stimulation. However, we think that the dry and crusty mucosal appearance is a constitutional variant that may indicate an increased risk for developing nasal hyperreactivity when exposed to various mucosal irritants. It is also interesting that the teachers with a dry and crusty mucosal appearance and increased mucosal histamine reactivity also presented a higher frequency of mucosal irritative symptoms and skin symptoms. This leads us to believe that there is a relationship between measured mucosal reactivity and mucosal and skin symptoms, but a larger study population is needed in order to demonstrate this.

Nasal mucosa/sensitivity/swelling/secretion

The nasal mucosa is very sensitive and easily affected by external and internal disturbances. By using histamine, a potent substance with a broad action on the nasal mucosa, the influence of these background factors is reduced. Histamine directly affects sensory c-fibres of the nasal mucosa as well as receptors of the vessels [137]. The induced mucosal swelling is apparently due to a combination mainly of dilatation of mucosal vessels and to some extent, leakage from the microcirculation [138, 139].

Both the mucosal swelling and the perception of nasal blockage and nasal secretion increased with increasing histamine concentrations in the provocation test **(study 1**). This is in accordance with a study by Hallén and Juto, where a significant correlation between symptom score and recorded mucosal swelling was shown [140]. Regarding nasal blockage the scores (symptoms) were higher among the target school teachers, which is in line with an increased mucosal swelling reaction upon histamine provocation. The teachers in the control school did not increase their secretory response to the highest histamine concentration, which might be in accordance with an acquired tachyphylaxis to provocation in this "normal adult group of people" (**study III**). The appearance of sneezes did not follow this pattern.

Rhinostereometry

Rhinostereometry (RSM) permits standardization of the nasal mucosal swelling reaction, without interference from secretion or stenosis [67]. RSM measures the congestive status of the mucosa, probably mainly reflecting the degree of filling of the deeper situated venous sinusoids [141]. Its high sensitivity makes it possible to measure small changes in mucosal congestion, which is probably necessary when studying groups of people with moderate symptoms of mucosal disease.

Laser Doppler flowmetry (LDF)

LDF is the method of choice for measuring microcirculation in combination with RSM as it is non-invasive and continuous recordings can be made of the microcirculation.

It is suggested that LDF measures the superficial layers of the nasal mucosa, containing arterioles and a dense capillary network, and does not reflect the status of the deeper situated venous sinusoids [69,142, **figure 4**].

The combination of RSM and LDF makes it possible to accurately regulate the distance between the probe and mucosal surface.

The CMBC (the concentration of moving blod cells) is probably affected by changes in the amount of interstitial fluid [143]. Therefore, an increase in vascular permeability resulting in oedema would appear in the LDF recordings as a reduction in CMBC.

In our study (**study V**), both study groups initially reacted to nasal histamine provocation with an increase in perfusion ("blood flow"), but there was a somewhat flatter provocation curve among the teachers in the target school indicating a somewhat slower reaction pattern. This is in accordance with the decreasing CMBC during the provocations among the teachers at the target school which indicates plasma leakage and to some extent interstitial oedema.

The absence of correlation between mucosal congestion and the microcircular pattern was probably due to the measurements of different parameters. The RSM measures changes in mucosal congestion which is due to dilation of the deeper situated sinusoids in the nasal mucosa while LDF measures the superficial microcircular pattern.

Allergic rhinitis in the non-pollen season

The studies were conducted during the non-pollen season and no significant differences in mucosal swelling due to histamine provocation were seen between atopic and non-atopic or between SPT+ and SPT- students.

Although some studies show an increase in nasal mucosal reactivity to histamine challenge among atopic subjects out of season [103, 105], our study indicates that the ongoing mucosal inflammation among young atopic subjects during the pollen season may disappear almost entirely in the non-pollen season.

CONCLUSIONS

In conclusion we have shown:

that long-time exposure to building dampness contributed to an increased nasal mucosal reactivity measured as mucosal swelling upon repeated histamine provocations

that this increased reactivity lasted for years, even after remedial measures had been taken

that there was an increased nasal histamine reactivity among the adult teachers as compared to the adolescent students

that the frequency of IgE sensitization (SPT+) was about twice as high among the students as compared to the teachers

that there was no increase in nasal mucosal reactivity among students in the target school as compared to those in the control school during their three years of study

that there were no significant differences in nasal histamine reactivity among atopic students as compared to non-atopic students in the non-pollen season

that there was a highly significant increase in nasal histamine reactivity among teachers with a dry and crusty nasal mucosa as compared to the remaining teachers

that there were indications of a slower reacting nasal mucosal circulation and increased interstitial vascular leakage among the teachers in the target school upon repeated histamine provocations as compared to those in the control school six years after the renovation of the target school

that there was no correlation between the nasal swelling reaction measured with RSM and nasal microcirculation measured with laser Doppler flowmetry upon repeated nasal histamine provocations

General considerations

The association between residing in moisture damaged buildings and adverse health (especially increased risk for health effects regarding the airways) is apparent, but the factors responsible for the symptoms are not at all clear [144]. To gain more information about possible mechanisms, future research should test new hypotheses such as those dealing with effects of specific chemicals and microbial agents.

Evidence that elevated levels of airborne fungi in school buildings are a causal factor for health complaints remains inconclusive [145, 146]. In a Danish school study there was a positive association between building-related symptoms and viable moulds in floor dust, but not between symptoms and the extent of moisture and mould growth in the school buildings [147]. Furthermore, there are no generally accepted standards for interpretation of fungal levels in indoor and outdoor air [148]. Another possible mechanism resulting in inflammation of the airway mucosa is a synergistic effect between certain emitted chemicals and dust [149].

Although the mechanisms are unclear, the best approach today to indoor microbial control is moisture control in the indoor environment. Assuming that the health effects are reversible, renovation of the moisture damage should lead to improvement in mucosal symptoms, which was seen in one school study from Denmark [150]. In our study the teachers had been exposed to severe building dampness for several years and we found a gradually and slowly decreasing nasal mucosal reactivity after remedial measures had been taken. This was interpreted as a slow but ongoing restoring process in the mucosa of the upper airways. However, six years after the renovation signs of persistent microcircular leakage and oedema upon nasal histamine provocation were shown among the target school teachers. These long-standing effects on the air-way mucosa seem to be mostly subclinical and represent no actual clinical disease.

The role of sensory nerves and psychological factors in the generation and perception of symptoms has been relatively neglected compared to the large amount of research on inflammatory mediators [86, 151, 152]. For instance, subjects can acquire somatic symptoms and altered respiratory behaviour in response to harmless, but odorous chemical substances, if these odours have been associated with a physiological challenge that originally caused these symptoms [153, 154].

There is much evidence that the sensory nervous system in the nasal mucosa plays an important role in normal and pathological nasal reactions [155, 156].

Triggering of sensory-efferent nerves (for instance with histamine provocation) can initiate systemic reflexes such as sneezing, as well as central cholinergic reflexes [157]. These reflexes cause release of mediators that stimulate blood vessels and glands, resulting in vasodilatation and secretion. Local reactions are also caused by release of neuropeptides from the sensory nerves.

Thus neurogenic inflammation involves interaction between nerves and inflammatory cells. The observation that reflex mechanisms of neurogenic inflammatory origin can be relatively easily investigated in the nasal mucosa indicates that the nose is a useful instrument in studying and understanding inflammatory processes in the respiratory tract [158]. It is quite possible that unspecific hyperreactivity of the nasal mucosa can be caused by chemical irritants with a resulting change in the neuropeptide-contents of mucosal nerve fibres [159].

In addition to agents used for provocation, the sensitive nasal mucosa reacts to other stimuli such as odours, temperature changes and touch. RSM allows direct inspection of the nasal mucosa and introduction of probes for stimulation of different receptor areas of the nasal cavity with a very high precision. We think that this technique will be a valuable future tool for learning about the physiological and pathophysiological mechanisms of airway mucosal reactions.

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REFERENCES

1. Björkstén B. Environmental Risk Factors for Allergy. Clin Rev Allergy Immunol 1997;15:125-143.

2. Heinrich J, Holscher B, and Wjst M. Housing condition and allergic sensititation in children. Zentralbl Hyg Unweltmed, 1998 (in German);201:211-228.

3. Strannegård Ö, Strannegård IL. The cause of the increasing prevalence of allergy: is atopy a microbial deprivation disorder? Allergy 2001;56:91-102.

4. Perzanowski MS, Rönmark E, Nold B, Lundbäck B, Platts-Mills TAE. Relevance of allergens from cats and dogs to asthma in the northernmost province of Sweden: School as a major site of exposure. J Allergy Clin Immunol 1999;103:419-424.

5. Custovic A, Green R, Taggart SCO, Smith A, Pickering CAC, Chapman MD, Woodcock A. Domestic allergens in public places II: dog (Can f 1) and cockroach (Bla g 2) allergens in dust and mite, cat, dog and cockroach allergens in the air in public buildings. Clin Exp Allergy 1996;26:1246-1252.

6. Munir AKM, Einarsson R, Shou C, Dreborg SKG. Allergens in school dust. J Allergy Clin Immunol 1993;91:1067-1074.

7. Finnegan JJ, Pickering CAC, Burge PS. The sick building syndrome: prevalence studies. BMJ 1984;289:1573-1575.

8. Hodgson M. The sick-building syndrome. Occup. Med. State of Art Rev 1995;10:167-175.

9. Mölhave L. Indoor climate, air pollution, and human comfort. J Expo Anal Environ Epidemiol 1991;1(1):63-81.

10. Skov P, Valbjörn O, and DISG (The Danish Indoor Study Group). The sick building syndrome in the office environment: The Danish town hall study. Environ Int 1987;13:339-349.

11. Norbäck D. Subjective Indoor air quality in schools- the influence of high room temperature, carpeting, fleecy wall material and volatile organic compounds (VOC). Indoor Air 1995;5:237-246.

12. Ruotsalainen R, Jaakkola N, Jaakkola JJ. Dampness and molds in day-care centers as an occupational health problem. Int Arch Occup Environ Health 1995;66(6):369-74.

13. Hilling R. [220 schools; Damage and defects in school buildings] (in Swedish). SP Swedish National Testing and Research Institute. SP Rapport 1998:34, Borås, Sweden.

14. Pejtersen J, Brohus H, Hyldgaard CE, Nielsen JB, Valbjörn O, Hauschildt P, Kjaersgaard SK, Wolkoff P. Effect of renovating an office building on occupants' comfort and health. Indoor Air 2001;11:10-25.

15. Ohm M, Juto JE, Andersson K, Bodin L. Nasal histamine provocation of tenants in a sick-building residential area. Am J Rhinol 1997;11:167-175.

16. Ohm M, Juto JE, Andersson K. Does the nasal reactivity change after removal from SBS domestic area to areas without SBS problems? In: Morawska L, Bofinger ND, Maroni M. (eds.) Indoor Air – An integrated approach, Brisbane, Australia. Elsevier 1995:197-200.

17. Taskinen T, Meklin T, Nousiainen M, Husman T, Nevalainen A, Korppi M. Moisture and mould problems in schools and respiratory manifestations in schoolchildren: clinical and skin test findings. Acta Paediatr 1997;86:1181-1187.

18. Bornehag CG, Sundell J, Bonini S, Custovic A, Malmberg P, Skerfving S, Sigsgaard T, Verhoeff A. Dampness in buildings as a risk factor for health effects, EUROEXPO: a multidisciplinary review of the literature (1998-2000) on dampness and mite exposure in buildings and health effects. Indoor Air 2004;14:243-257.

19. Ebbehoj NE, Hansen MO, Sigsgaard T, Larsen L. Building-related symptoms and molds: a two-step intervention study. Indoor Air 2002;12:273-277.

20. Taskinen T, Hyvarinen A, Meklin T, Husman T, Nevalainen A, Korppi M. Asthma and respiratory infections in school children with special reference to moisture and mold problems in the school. Acta Paediatr 1999;88:1373-1379.

21. Norback D, Edling C. Environmental, occupational, and personal factors related to the prevalence of sick building syndrome in the general population. Br J Ind Med 1991;48:451-462.

22. Peat J, Dickerson J, Li J. Effects of damp and mould in the home on respiratory health: a review of the literature. Allergy 1998;53:120-128.

23. Husman T. Health effects of indoor-air microorganisms. Scand J Work Environ Health 1996;2:5-13.

24. Dales RE, Miller D, McMullen E. Indoor air quality and health: validity and determinants of reported home dampness and moulds. Int J Epidemiol 1997;26:120-125.

25. Ooi PL, Goh KT. Sick Building Syndrome: An emerging stress-related disorder? Int J Epidemiol 1997;26:1243-1249.

26. Redlich CA, Sparer J, Cullen MR. Sick-building syndrome. Lancet 1997;349:1013-1016.

27. Skov P, Valbjörn O, Pedersen BV and DISG (the Danish Indoor Study Group). Influence of personal characteristics, job-related factors and psychosocial factors on the sick building syndrome. Scand J Work Environ Health 1989;15:266-295.

28. Burge S, Hedge A, Wilson S, Bass JH, Robertsson A, Bach B, et al. Sick building syndrome: a study of 4373 office workers. Ann Occup Hyg 1987;31:493-504.

29. Jaakkola JJK, Heinonen OP, Seppäinen O. Mechanical ventilation in office buildings and the sick building syndrome. An experimental and epidemiological study. Indoor Air 1991;2:115-128.

30. Wålinder R, Wieslander G, Norbäck D, Erwall C, Venge P. Influence of personal factors on nasal patency and lavage biomarkers in white-collar workers. Rhinology 2000;38(3):130-135.

31. International Rhinitis Management Working Group (IRMWG). International consensus report on the definition and classification of rhinitis. Allergy 1994;49(S19):1-34.

32. Niland J. Industrial Hygiene. In: Zenz C, Dickerson OB, Horvath EP, editors. Occup Med. St. Louis, Missouri: Mosby-Year Book, inc.; 1994. pp. 1012-1060.

33. Angell James JE, Daly Mde B. Nasal reflexes. Proc Roy Soc Med 62 1969:1287-1293.

34. Brofeldt S, Mygind N, Sorensen CH, Readman AS, Marriot C. Biochemical analysis of nasal secretion induced by methacholine, histamine, and allergen provocations. Am Rev Respir Dis 1986;133:1138-1142.

35. Svensson C, Baumgarten CR, Pipkorn U, Alkner U, Persson CG. Reversibility and reproducibility of histamine induced plasma leakage in nasal airways. Thorax 1989;44:13-18.

36. Widdicombe J. Microvascular anatomy of the nose. Allergy 1997;52:7-11.

37. Eccles R, Reilly M, Eccles KS. Changes in the amplitude of the nasal cycle associated with symptoms of acute upper respiratory tract infection. Acta Otolaryngol 1996;116:77-81.

38. Persson CG. Plasma exudation in the airways: mechanisms and function. Eur Respir J 1991;4:1268-1274.

39. Juliusson S, Holmberg K, Karlsson G, Enerbäck L, Pipcorn U. Mast cells and mediators in the nasal mucosa after allergen challenge. Effects of four week´s treatment with topical glucocorticoid. Clin Exp Allergy 1993;23:591-599.

40. Lopuhaa CE, de Riemer MJ, Out TA, Sjamsoedin DH, Aalberse RC, Jansen HM, van der Zee JS. Comparison of allergen-induced late inflammatory reactions in the nose and in the skin in house dust mite-allergic patients with or without asthma. Int Arch Allergy Immunol 2003;130:266-274.

41. Kaliner M. Allergic rhinitis. In: Mygind N, Nacleiro RM, editors. Allergic and Non-Allergic Rhinitis, Copenhagen: Munksgaard; 1993.

42. Jessen M, Janzon L. Prevalence of non-allergic nasal complaints in an urban and a rural population in Sweden. Allergy 1989;44(8):582-587.

43. Togias A. Age relationships and clinical features of nonallergic rhinitis. J Allergy Clin Immunol 1990;85:182.

44. Koh YY, Kim CK. The development of asthma in patients with allergic rhinitis. Curr Opin Allergy Clin Immunol 2003;3:159-164.

45. Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: An independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. J Allergy Clin Immunol 1999;104:301-304.

46. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol 2000;106(5 Suppl):201-205.

47. Gerth van Wijk RG, de Graaf-in ´t Veld C, Garrelds IM. Nasal hyper-reactivity. Rhinology 1999;37:50-55.

48. Andersson M, Greiff L, Svensson C, Persson C. Mechanisms of nasal hyper-reactivity. Eur Arch Otorhinolaryngol 1995;252:22-26.

49. Bernstein JM. The role of autonomic nervous system and inflammatory mediators in nasal hyperreactivity: a review. Otolaryngol Head Neck Surg 1991;105:596-607.

50. Stjärne P. Sensory and motor reflex control of nasal mucosal blood flow and secretion; clinical implications in non-allergic nasal hyperreactivity. Acta Physiol Scand Suppl 1991;600:1-64.

51. Hirschberg A. Rhinomanometry: an update. ORL 2002;64:263-267.

52. Hilberg O, Jackson AC, Swift DL, Pedersen OF. Acoustic rhinometry: Evaluation of nasal cavity geometry by acoustic reflection. J Applied Physiol 1989;66:295-303.

53. Wålinder R, Norbäck D, Wieslander G, Smedje G, Erwall C, Venge P. Acoustic rhinometry in epidemiological studies – nasal reactions in Swedish schools. Rhinol Suppl 2000;16:59-64.

54. Wålinder R, Norbäck D, Wieslander G, et al. Nasal mucosal swelling in relation to low air exchange in schools. Indoor Air 1997;7:198-205.

55. Hargreave FE, Ryan G, Thomson N.C, O´Byrne P.M, Laatimer K, Juniper E.F. Bronchial responsiveness to histamine or methacoline in asthma: measurement and clinical significance. Eur J Respir Dis 1982;63:79-88.

56. Yan K, Salome C, Woolcook AJ. Rapid method for measurement of bronchial responsiveness. Thorax 1983;38:760-765.

57. Gert Van Wijk R, Dieges PH. Comparision of nasal responsiveness to histamine, methacholine and phentolamine in allergic rhinitis patients and controls. Clin Allergy 1987;17:563-570.

58. Hilberg O, Grymer LF, Pedersen OF. Nasal histamine challenge in nonallergic and allergic subjects evaluated by acoustic rhinometry. Allergy 1995;50:166-173.

59. van Wijk RG, Mulder PG, Dieges PH. Nasal provocation with histamine in allergic rhinitis patients: clinical significance and reproducibility. Clin Exp Allergy 1989;19:293-298.

60. Simola M, Malmberg H. Nasal histamine reactivity; relationships to skin-test responses, allergen provocation and symptom severity in patients with long-continuing allergic rhinitis. Acta Otolaryngol 2000;120:67-71.

61. Doyle WJ, Boehm S, Skoner DP. Physiologic responses to intranasal dose-response challenges with histamine, methacholine, bradykinin, and prostaglandin in adult volunteers with and without nasal allergy. J Allergy Clin Immunol 1990;86:924-935.

62. Mygind N. Essential Allergy. Copenhagen-Munksgaard 1996.

63. Birchall MA, Schroter RC, Pride NB. Changes in nasal mucosal blood flux and air-flow resistance on unilateral histamine challenge. Clin Otolaryngol 1993;18:139-44.

64. Hallen H, Juto JE. A model for mucosal reaction during challenge. Rhinology 1992;30(2):129-133.

65. Hallén H, Juto JE. A test for objective diagnosis of nasal hyperreactivity. Rhinology 1993;31:23-25.

66. Hellgren J, Jarlstedt J, Dimberg L, Toren K, Karlsson G. A study of some current methods for assessment of nasal histamine reactivity. Clin Otolaryngol 1997;22:536-541.

67. Juto JE, Lundberg C. An optical method for determining changes in mucosal congestion in the nose in man. Acta Otolaryngol 1982;94:149-156.

68. Graf P, Hallen H. Clinical and rhinostereometric assessment of nasal mucosal swelling during histamine challenge. Clin Otolaryngol 1996;21:72-75.

69. Cauna N. Blood and nerve supply of the nasal lining. In: Proctor DF, Andersen I, eds. The nose. Upper airway physiology and the atmospheric environment. Elsevier Biomed Press, Amsterdam 1982;45-69.

70. Mellander S, Johansson B. Control of resistance, exchange and capacitance functions in the peripherial circulation. Pharmacol Review 1968;20:117-196.

71. Majno G, Palade GE, Schoefl GL. Studies on inflammation. II. The site of action of histamine and serotonin along the vascular tree: a topografic study. J Biochem Cytol 1961;11:571-605.

72. Cauna N, Cauna D. The fine structure and innervation of the cushion veins of the human nasal respiratory mucosa. Anat Rec 1975;181:1-16.

73. Bende M, Elner A, Ohlin P. The effect of provoked allergic reaction and histamine on nasal mucosal blood flow in humans. Acta Otolaryngol 1984; 97:99-104.

74. Bisgaard H, Olsson P, Bende M. Effect of leukotriene D4 on nasal mucosal blood flow, nasal airway resistance and nasal secretion in humans. Clin Allergy 1986;16:289-297.

75. Svensson C, Baumgarten CR, Pipkorn U, Alkner U, Persson CG. Reversibility and reproducibility of histamine induced plasma leakage in nasal airways. Thorax 1989;44:13-18.

76. Svensjö E, Joyner WL. The effects of intermittent and continous stimulation of microvessels in the cheek pouch of hamsters with histamine and bradykinin on the developoment of leaky sites. Micro Endothel Lymphat 1984;14:381-396.

77. Grudemo H, Juto JE. Intranasal histamine challenge in normals and allergic rhinitis before and after intranasal budesonide studied with rhinostereometry and micromanipulator-guided laser Doppler flowmetry. ORL 2000;62:33-38.

78. Peat J, Dickerson J, Li J. Effects of damp and mould in the home on respiratory health: a review of the literature. Allergy 1998;53:120-128.

79. Yang CY, Chiu JF, Chiu HF, Kao WY. Damp housing conditions and respiratory symptoms in primary school children. Pediatr Pulmonol 1997; 24:73-77.

80. Jaakkola JJ, Jaakkola N, Ruotsalainen R. Home dampness and molds as determinants of respiratory symptoms and asthma in pre-school children. J Expo Anal Environ Epidemiol 1993;3 Suppl 1:129-42.

81. Hutter HP, Moshammer H, Kundi M, Wallner P, Neuberger M. Moulds in housing: visual inspection and spore counts comparison - implications for future strategies in the public health setting. Cent Eur J Public Health 2002;10:93-96.

82. Engvall K, Norrby C, Norback D. Asthma symptoms in relation to building dampness and odour in older multifamily houses in Stockholm. Int J Tuberc Lung Dis 2001;5:468-477.

83. Norback D, Bjornsson E, Janson C, Widstrom J, Boman G. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. Occup Environ Med 1995;52:388-395.

84. Norback D, Bjornsson E, Janson C, Palmgren U, Boman G. Current asthma and biochemical signs of inflammation in relation to building dampness in dwellings. Int J Tuberc Lung Dis 1999;3:368-376.

85. Immonen J, Meklin T, Taskinen T, Nevalainen A, Korppi M. Skin prick test findings in students from moisture- and mould-damaged schools: a 3-year follow-up study. Pediatr Allergy Immunol 2001;12:87-94.

86. Walinder R, Norback D, Wessen B, Venge P. Nasal lavage biomarkers: effects of water damage and microbial growth in an office building. Arch Environ Health 2001;56:30-36.

87. Rylander R, Norrhall M, Engdahl U, Tunsater A, Holt PG. Airways inflammation, atopy, and (1--> 3)-beta-D-glucan exposures in two schools. Am J Respir Crit Care Med 1998;158(5 Pt 1):1685-1687.

88. Thorn A, Lewne M, Belin L. Allergic alveolitis in a school environment. Scand J Work Environ Health 1996;22:311-314.

89. Hirvonen MR, Ruotsalainen M, Roponen M, Hyvarinen A, Husman T, Kosma VM,Komulainen H, Savolainen K, Nevalainen A. Nitric oxide and proinflammatory cytokines in nasal lavage fluid associated with symptoms and exposure to moldy building microbes. Am J Respir Crit Care Med 1999;160: 1943-1946.

90. Norback D, Walinder R, Wieslander G, Smedje G, Erwall C, Venge P. Indoor air pollutants in schools: nasal patency and biomarkers in nasal lavage. Allergy 2000;55:163-170.

91. Norback D, Wieslander G, Nordstrom K, Walinder R. Asthma symptoms in relation to measured building dampness in upper concrete floor construction, and 2-ethyl-1-hexanol in indoor air. Int J Tuberc Lung Dis 2000;4(11):1016-1025.

92. Gustafsson H. Moisture induced chemical degradation and emission from flooring materials on damp concrete. (in Swedish). Swedish National Testing and Research Institute; report 1996:25.

93. Cooley JD, Wong WC, Jumper CA, Straus DC. Correlation between the prevalence of certain fungi and sick building syndrome. Occup Environ Med 1998;55:579-584.

94. Koskinen OM, Husman TM, Meklin TM, Nevalainen AI. The relationship between moisture or mould observations in houses and the state of health of their occupants. Eur Respir J 1999;14:1363-1367.

95. Wieslander G, Norback D, Nordstrom K, Walinder R, Venge P. Nasal and ocular symptoms, tear film stability and biomarkers in nasal lavage, in relation to building dampness and building design in hospitals. Int Arch Occup Environ Health 1999;72:451-461.

96. Meklin T, Husman T, Pekkanen J, Hyvärinen A, Hirvonen MR, Nevalainen A. Effect of moisture damage repair on microbial exposure and health effects in schools. Proceedings: Indoor Air 2002;416-420.

97. Åhman M, Lundin A, Musabasic V, Soderman E. Improved health after intervention in a school with moisture problems. Indoor Air 2000;10:57-62.

98. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, Kowalski ML, Mygind N, Ring J, van Cauwenberge P, van Hage-Hamsten M, Wuthrich B. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001;56:813-824.

99. Carey OJ, Cookson JB, Britton J, Tattersfield AE. The effect of lifestyle on wheeze, atopy, and bronchial hyperreactivity in Asian and white children. Am J Respir Crit Care Med 1996;154(2 Pt 1):537-540.

100. Remes ST, Iivanainen K, Koskela H, Pekkanen J. Which factors explain the lower prevalence of atopy amongst farmers' children? Clin Exp Allergy 2003;33:427-434.

101. Gerth van Wijk RG, de Graaf-in 't Veld C, Garrelds IM. Nasal hyperreactivity. Rhinology 1999;37:50-5.

102. Konno A, Togawa K, Nishihira S. Seasonal variation of sensitivity of nasal mucosa in pollinosis. Arch Otorhinolaryngol 1981;232:253-261.

103. Kolbeck KG, Ehnhage A, Juto JE. Nasal and bronchial histamine reactivity in patients with allergic rhinitis out of season. Ann Allergy Asthma Immunol 1999;82:55-60.

104. Ehnhage A, Kolbeck KG, Mossberg B, Juto JE. Nasal and bronchial histamine responsiveness in pollen-exposed patients with seasonal rhinitis. ORL 2002;64:191-199.

105. Henriksen AH, Sue-Chu M, Lingaas Holmen T, Langhammer A, Bjermer L. Exhaled and nasal NO levels in allergic rhinitis: relation to sensitization, pollen season and bronchial hyperresponsiveness. Eur Respir J 1999;13:301-306.

106. Schneider T. Measuring strategies and monitoring of the indoor environment. J Environ Monit 1999;1:427-34.

107. Andersson, K. Epidemiological Approach to Indoor Air Problems. Indoor Air 1998;4:32–39.

108. Reijula K, Sundman-Digert C. Assessment of indoor air problems at work with a questionnaire. Occup Environ Med 2004;61:33-38.

109. Lahtinen M, Sundman-Digert, K Reijula. Psychosocial work environment and indoor air problems: a questionnaire as a means of problem diagnosis. Occup Environ Med 2004;61:143-149.

110. Smedje G, Norbäck D, Edling C. Subjective indoor air quality in schools in relation to exposure. Indoor Air 1997;7:143-150.

111. Haight JS, Cole P. The site and function of the nasal valve. Laryngoscope 1983;93:49-55.

112. Jones AS, Wight RG, Stevens JC, Beckingham E. The nasal valve: a physiological and clinical study. J Laryngol Otol 1988;102:1089-1094.

113. Birchall MA, Phillips I, Fuller RW, Pride NB. Intranasal histamine challenge in normality and allergic rhinitis. Otolaryngol Head Neck Surg 1993;109:450-456.

114. Oberg PA, Tenland T, Nilsson GE. Laser-Doppler flowmetry--a non-invasive and continuous method for blood flow evaluation in microvascular studies. Acta Med Scand Suppl 1984;687:17-24.

115. Holloway GA Jr, Watkins DW. Laser Doppler measurement of cutaneous blood flow. J Invest Dermatol 1977;69:306-309.

116. Principles of laserDoppler flowmetry, Bonner & Nossal, in Laser Doppler Blood Flowmetry, pp 17-45, eds. Sheperd & Öberg, Kluwer Academic Publishers, 1990.

117. Grant JA, Bilodeau PA, Guernsey BG, Gardner FH. Unsuspected benzyl alcohol hypersensitivity. N Engl J Med 1982;14;306(2):108.

118. Hallen H, Juto JE. Evaluation of a test for objective diagnosis of non allergic nasal hyperreactivity. Am J Rhinol 1993;7:117-121.

119. Dreborg S. The skin prick test: Methodological studies and clinical applications. Thesis (Linköping, Sweden), 1987.

120. Bråbäck L, Breborowicz A, Dreborg S, Knutsson A, Pieklik H, Bjorksten B. Atopic sensitization and respiratory symptoms among Polish and Swedish school children. Clin Exp Allergy 1994;24:826-35.

121. Sanico A, Togias A. Noninfectious nonallergic rhinitis (NINAR): Considerations on possible mechanisms. Am J Rhinol 1998;12:314-318.

122. Fradkin A, Tarlo SM, Tobin RS, Tucic-Porretta M, Malloch D. Species identification of airborne molds and its significance for the detection of indoor pollution. JAPCA 1987;37:51-53.

123. Su HJ, Wu PC, Lin CY. Fungal exposure of children at homes and schools: a health perspective Arch Environ Health 2001;56:144-149.

124. Gots RE, Layton NJ, Pirages SW. Indoor Health: Background Levels of Fungi. AIHA Journal 2003;64:427-438.

125. Nevalainen A, Pasanen A-L, et al. The indoor air quality in Finnish homes with mold problems. Envir Int 1991;17:299-302.

126. Meklin T, Husman T, Vepsalainen A, Vahteristo M, Koivisto J, Halla-Aho J, Hyvarinen A, Moschandreas D, Nevalainen A. Indoor air microbes and respiratory symptoms of children in moisture damaged and reference schools. Indoor Air 2002;12:175-183.

127. Hyvarinen A, Reponen T, Husman T, Nevalainen A. Comparison of the indoor air quality in mould damaged and reference buildings in a subarctic climate. Cent Eur J Public Health 2001;9:133-139.

128. Norlén U, Andersson K. Indoor climate in Swedish dwellings. In: Maroni, M (eds). Healthy buildings ´95, Milano 1995:393-401.

129. Chelelgo J, Haverinen U, Vahteristo M, Koivisto J, Husman T, Nevalainen A, Jaaskelainen E. Analysis of moisture findings in the interior spaces of Finnish housing stock. J Air Waste Manag Assoc 2001;51:69-77.

130. Norback D, Wieslander G, Nordstrom K, Walinder R. Asthma symptoms in relation to measured building dampness in upper concrete floor construction, and 2-ethyl-1-hexanol in indoor air. Int J Tuberc Lung Dis 2000;4:1016-1025.

131. Walinder R, Norback D, Wessen B, Venge P. Nasal lavage biomarkers: effects of water damage and microbial growth in an office building. Arch Environ Health 2001; 56:30-36.

132. Engvall K, Norrby C, Norback D. Ocular, airway, and dermal symptoms related to building dampness and odors in dwellings. Arch Environ Health 2002;57:304-310.

133. Jalas J, Karjalainen K, Kimari P. Indoor air and energy economy in school buildings. Proceedings of Healthy Buildings 2000, 2000;4:273-278.

134. Ceuppens J. Western lifestyle, local defences and the rising incidence of allergic rhinitis. Acta Otorhinolaryngol Belg 2000;54:391-395.

135. Smedje G, Norback D, Edling C. Asthma among secondary schoolchildren in relation to the school environment. Clin Exp Allergy 1997;27:1270-1278.

136. Peroni DG, Piacentini GL, Alfonsi L, Zerman L, Di Blasi P, Visona' G, Nottegar F, Boner AL. Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. Clin Exp Allergy 2003;33:1349-1354.

137. Baraniuk JN. Sensory, parasympathetic and sympathetic neural influences in the nasal mucosa. J Allergy Clin Immunol 1992;90:1045-1050.

138. Grudemo H, Juto JE. Rhinostereometry and laser doppler flowmetry in human nasal mucosa: Changes in congestion and microcirculation during intranasal histamine challenge. ORL 1997;59:50-56.

139. Grudemo H, Juto JE. The impact of the measuring distance on laser-doppler measurements of the microcirculation in human nasal mucosa. ORL 1997;59:280-285.

140. Hallén H, Juto JE. Correlation between subjective and objective assessment of nasal hyperreactivity. ORL 1994;56:51-54.

141. Malm L, Druce HM, Holgate ST. Vasoconstrictors and antihistamins. In Allergic and Vasomotor rhinitis: Clinical Aspects. Mygind N, Weeks B, Eds. Munksgaard, Copenhagen, 1985, pp. 140-150.

142. Olsson P. A comparison between the 133Xe washout and laser Doppler techniques for estimation of nasal mucosal blood flow in humans. Acta Otolaryngol 1986;102:106-112.

143. Grudemo H, Juto JE. The effect of saline-induced edema in the human nasal mucosa on laser Doppler flowmetry. Rhinology 1999; 37:104-107.

144. Bornehag CG, Blomquist G, Gyntelberg F, Jarvholm B, Malmberg P, Nordvall L, Nielsen A, Pershagen G, Sundell J. Dampness in buildings and health. Nordic interdisciplinary review of the scientific evidence on associations between exposure to "dampness" in buildings and health effects (NORDDAMP). Indoor Air 2001;11:72-86.

145. Daisey JM, Angell WJ, Apte MG. Indoor air quality, ventilation and health symptoms in schools: an analysis of existing information. Indoor Air 2003;13:53-64.

146. Hardin BD, Kelman BJ, Saxon A. Adverse human health effects associated with molds in the indoor environment. J Occup Environ Med 2003;45(5):470-478.

147. Meyer HW, Wurtz H, Suadicani P, Valbjorn O, Sigsgaard T, Gyntelberg F; Members of aWorking Group under the Danish Mould in Buildings program (DAMIB). Molds in floor dust and building-related symptoms in adolescent school children. Indoor Air 2004;14:65-72.

148. Burge HA. An update on pollen and fungal spore aerobiology. J Allergy Clin Immunol 2002;110:544-552.

149. Pan Z, Molhave L, Kjaersgaard SK, Sigsgaard T, Juto JE, Andersson K, Stridh G. Spiking of office dust with beta-(1,3)-D-glucan and aldehydes increases nasal inflammation in volunteers. In R. Luhrman (ed.), Bioaerosols, fungi, bacteria, mycotoxins and human health. Conference book. Saratoga springs, pp. 47-57 2003.

150. Sigsgaard T, Jensen H, Nichum E, Gravesen S, Larsen L, Hansen MO. Decrease in symptoms after rebuilding a water damaged school building. In Proceedings of Healthy Buildings 2000, Espoo, Finland 2000;3:409-414.

151. Purokivi M, Hirvonen MR, Roponen M, Randell J, Vahteristo M, Tukiainen H. Comparison of inflammatory elements in nasal lavage and induced sputum following occupational exposure to moldy-building microbes. Inhal Toxicol 2002;14:653-662.

152. Purokivi MK, Hirvonen MR, Randell JT, Roponen MH, Meklin TM, Nevalainen AL, Husman TM, Tukiainen HO. Changes in pro-inflammatory cytokines in association with exposure to moisture-damaged building microbes. Eur Respir J 2001;18:951-958.

153. Van den Bergh O, Stegen K, Van Diest I, Raes C, Stulens P, Eelen P, Veulemans H, Van de Woestijne K P, Nemery B. Acquisition and extinction of somatic symptoms in response to odours: a Pavlovian paradigm relevant to multiple chemical sensitivity. Occup Environ Med 1999;56:295-301.

154. Shusterman D. Review of the upper airway, including olfaction, as mediator of symptoms. Environ Health Perspect 2002;110:649-653.

155. Bernstein JM. The role of autonomic nervous system and inflammatory mediators in nasal hyperreactivity: a review. Otolaryngol Head Neck Surg 1991;105:596-607.

156. Rogers DF. Reflexly runny noses: neurogenic inflammation in the nasal mucosa. Clin Exp Allergy 1996;26:365-367.

157. Ramnarine SI, Rogers DF. Non-adrenergic, non-cholinergic neural control of mucus secretion in the airways. Pulm Pharmacol 1994;7:19-33.

158. Persson CGA, Svensson C, Greiff L et al. The use of the nose to study the inflammatory response of the respiratory tract. Thorax 1992;47:993-1000.

159. Heppt W, Peiser C, Cryer A, Dinh QT, Zweng M, Witt C, Fischer A, Groneberg DA. Innervation of human nasal mucosa in environmentally triggered hyperreflectoric rhinitis. J Occup Environ Med 2002;44:924-929.