Introduction and Aim of The Work

The term allergy was introduced by **Von Priquet, (1906)** as having the meaning of altered reactivity to all substances foreign to the host, **Bryan and Bryan, (1980)**.

Allergic rhinitis is a symptom complex including nasal pruritis, watery rhinorrhae, sneezing and nasal congestion resulting from exposure to specific antigen **Salvin, (1982)**.

Delozier, (1974), found that nasal troubles account for more than 33 million office visits a year. About one-third of the visits are for allergic rhinitis.

It has been also reported that allergic rhinitis, particularly the seasonal variety involves about 15 % of the entire population in Europe and in the United States of America, **Mygind, (1978)**.

The management of hay fever and perennial allergic rhinitis can be considered in terms of allergen avoidance, hyposensitization and anti-allergic drugs which can be subdivided into those for prevention (topical steroids and disodium cromoglycate) and those for relief (antihistaminic), **Kay et al., (1984)**. Topical steroids had proved to be the drug of choice when the symptoms of allergic rhinitis are troublesome, **Brouwn, et al., (1977)**.

Corticosteroids have been used extensively for 19 years without reports of serious side-effects and so, it can be concluded that topical steroids are the drugs of first choice in treatment of allergic rhinitis in adults, **Pipkorn et al., (1981)**.

The aim of the present study is to evaluate the protective effects of topical steroids as applied in a single dose three hours before nasal challenge as compared with two weeks of treatment with corticosteroids before nasal challenge.

This will be of value for allergic patients to protect themselves from an expected or an unavoidable exposure to their specific antigens.

It is worth mentioning that, nasal ***challenge tests*** are said to be more accurate in the diagnosis of allergic rhinitis than other methods of diagnosis. The test is also needed for monitoring the effect of therapy because of the considerable variations in the individual sensitivity and response to treatment, **Clarke, (1988)**.

Allergic Rhinitis

Definition : **Terr, (1978)** simply defined allergic rhinitis as type I allergy localized to the nasal mucosa and the conjunctiva. **Bickmore, (1974)** reported that, the term nasal allergy should only be used if there is a convincing evidence of true antigen-antibody reaction responsible for the nasal condition. This is based on the study of case history, clinical finding and the results of special tests. **Parker, (1980)** defined allergic rhinitis, on an immunological and clinical bases, as IgE mediated inflammation of the nose producing rhinorrhae, itching, sneezing and obstruction. According to **Norman and Litchenstein, (1987)** the characteristic symptom complex of allergic rhinitis include sneezing, nasal congestion, watery discharge as well as conjuctival itching. Bronchoconstriction may accompany these symptoms.

Clinical types:

1. Seasonal allergic rhinitis (Pollinosis) :

The term is applied to allergic rhinitis condition with seasonal incidence so, purely seasonal rhinitis is usually due to pollen and hence, the commonly used terms (Pollinosis-Hay fever), but also it could be due to fungal spores **Golding-wood, (1961) and Mygind, (1978)**. The development of hay fever depends on an inherited atopic disposition and on the degree of exposure to pollens with high sensitizing capacity (Grass, ragwee, birch, mug wort) and so, the incidence of hay fever vary according to the place **Schachter and Higgins, (1978)**. According to **Weir, (1979)**, pollinosis usually commences during the first half of life.

2. Perennial allergic rhinitis :

In contrast to the seasonal type, the symptoms of perennial allergic rhinitis vary in severity throughout the year, often with indistinct onset and cessation **Taylor, (1975); Mygind, (1978) and Bellanti, (1979).** The majority of cases are due to exogenous allergens; in adults, the cause is usually due to inhalants but in childhood, foods are the most common causative factor. According to **Taylor, (1975)**, the allergen may be single but usually there are multiple allergens which may be responsible for the condition of perennial allergic rhinitis such as :

1-Inhalants : e.g house dust, mattress, animal danders etc...

2-Ingestants : e.g milk, fish, egg, some fruits etc...

3-Contactants : e.g nasal drops and sprays.

4-Bacterial antigens : usually those of staph., strept., and pneumococci.

5-Drugs : Commonly allergy may occurs with acetyl salicylic acid. iodides, quinines and sulphonamides.

Predisposing factors for nasal allergy :

The clinical picture of allergic rhinitis is aggravated or precipitated by many predisposing factors. these are:

I-Environmental factors :

1) Humidity : **Griep, (1976)**, stated that increased humidity and fog influence respiratory allergy adversely probably because of the increased breathing resistance produced by the particles of moisture of air, however, **Andersen, (1974)** has failed to demonstrate the effect of air humidity on nasal symptoms as the normal nose can deal with any load of dry air and he has stated that, humidity probably affect the dust level and so the degree of allergy.

2) Temperature : The response of patients suffering from allergy to temperature conditions varied but the greatest effect is noticeable when there are marked variations in temperature. In general patients are better in summer than winter provided that they are not sensitive to pollens. This may be due to physiologic capillary vasodilation that occurs in winter due to warm-cold air exposure that lead to nasal and bronchial congestion and so, the allergic state, **Griep, (1976)**.

Mygind, (1979), stated that cold air inhalation causes decrease in nasal blood flow, venous congestion and stimulation of the anterior serous glands leading to watery hypersecretion. These physiological changes are exaggerated in allergic patients.

3) Geography and altitude : **Foxen, (1971)**, reported that places in which the atmosphere is damp and stagnant particularly where trees are numerous are bad for cases of nasal allergy. The attacks of allergic rhinitis are less severe in altitude over 1500 M.

4) Air pollution : Conditions that produce high concentrations of particulate contiminants, will aggravate and precipitate the allergic symptoms. These contaminants include industrial irritants, dusts of all kinds, pollens and molds, **King and Norman (1978)**.

Andersen, (1974) and Mygind, (1979), stated that synthetic materials in the surrounding environment may cause allergy such as formaldehyde, sulphur dioxide, inert dust, smoke, fumes and irritant smell that provocate symptoms in hyper-reactive nose.

5) Seasonal conditions : **Broder et al., (1974)**, reported that seasonal conditions play an important role in cases of pollen allergies, the small

number of species of air-born plant pollens which are significant in nasal allergy are produced in definite season characteristic for each plant which may vary a week or two from year to year in the same locality.

II-Infection :

Foxen, (1971), reported that , the attacks of nasal allergy may be initiated or precipitated by direct action of bacteria, viruses or their products on the tissue cells. This action may be confined to the infected tissue or may has a general effect through the absorption of toxins into the circulation. Of particular importance in this respect are the epidemic acute infectious diseases, whooping cough, measles and influenza.

Pepys et al., (1969), stated that airways infection precipitates the attacks of allergic rhinitis probably due to direct tissue damage, increasing the sensitivity to chemical mediators such as histamine and bradykinin, or secretion of enzymes such as that of bacillus subtilis that sensitizes exposed subjects giving rise to type I allergic reaction.

III-Endocrinal factors :

According to **Foxen (1971)**, menstruation, menopause and ovarian dysfunction all tend to augment the allergic reactions. Pregnancy also increases nasal allergy. In hyperthyroidism, there is an increased sensitivity of sympathetic nervous system and tendency to exudative reaction and allergic manifestation. In contrast, nasal allergy is very rare in patients with diabetes mellitus, this effect is probably due to the relative acidosis.

IV-Psychological factors :

Urbach (1946), reported that these factors play a part in the majority of the allergic subjects. They may act as a sole cause, as a predisposing

factor, as an exciting factor or they may be the result of the allergic disease itself.

V-Genetic factors :

Mygind, (1978), stated that an atopic subject inherits both a common predisposition for atopic manifestation and a tendency to react against it in specific organ.

Urbach, (1946), found that 50% of allergic patients give family histories of allergy, children with bilateral inheritance develop allergy in 75 % of cases, those with unilateral inheritance develop allergy in 50% of cases, but those without family history develop allergy in 7-12 % of cases.

Not all authorities, however, agree that heredity unquestionably plays an important role where **Frankland, (1968)**, observed that there seem to be no good evidence that atopic diseases are inherited and suggested that what occurs is a somatic mutation which may or may not be inherited.

VI-Drugs :

Szczeklik et al., (1976), stated that acetyl salicylic acid may produce allergic rhinitis, asthma and urticaria. Intolerance to asprin is common in patients with nasal polypi, asthma and urticaria. Indomethacin, antipyrin and some dyes have a similar effect.

The Immune system of the nose

Mygind et al., (1989), stated that most of the nasal cavity and the nasopharynx are covered by thin specialized epithelium that constitute a week mechanical barrier. Adequate surface protection, therefore, depended on an intimate cooperation between natural non-specific defense

mechanisms and the acquired specific immunity that is mainly mediated by secretory antibodies. According to **Mygind et al., (1986)**, the human nasal mucosa does not seem to contain typical lymphoepithelial structures, however, small aggregates of B-Lymphocytes are present in the superficial stroma but they are apparently not covered by specialized follicle-associated epithelium, in contrast to the situation in Gut associated lymphoid tissue (GALT), Bronchus associated lymphoid tissue (BALT) and the tonsil. B-cells responsible for mucosal immunity in the nose, therefore, are most likely derived from the latter structures in which priming of the subsequent immune responses at the secretory sites takes place.

Role of IgE in nasal allergy

According to **Raif, (1984)**, the presence of reagenic antibodies in the serum of allergic rhinitis patients was first demonstrated by **Prausnitz and Kustner (1921)**. The nature of these antibodies remained unknown for 40 years until IgE was found in the serum of hay fever patients and identified as a carrier of reagenic antibody activity by **Ishizaka and Ishizaka, (1967)**. This antibody has the unique property to bind reversibly with high affinity to specific membrane receptors on basophils and mast cells. The combination of a specific cell-bound IgE antibodies with an antigen triggers a series of events that ultimately leads to the release of vasoactive amines and other pharmacologically active substances responsible for the clinical manifestations of hypersensitivity. **Hallpren, (1974)**, reported that IgE is the first antibody to be produced during the immune response to be followed by IgM and IgG. The determination of IgE in the serum has established a standard for the degree of hypersensitivity of the allergic patients.

The mechanism of IgE-mediated hypersensitivity

The most important biologic property of IgE antibody is the ability to sensitize homologous tissues for allergic reactions. The sensitizing effect can be observed at the cellular level as well, where histamine release can be observed from isolated leucocytes of atopic patients on exposure to an allergen **Lichtenstein and Osler, (1964)**. It is now possible to demonstrate the target cells to which IgE is fixed. If one treats leucocytes with I^{125}-labelled anti-IgE, the readioactive antibody is demonstrated only on basophil granulocytes. At the tissue level IgE is found on mast cells but not other cells and only mast cells combine with I^{125} -labeled IgE. Thus, it appears that the target cells for IgE are mast cells and basophil granulocytes. the human basophils of normal and atopic individuals posses 10,000 to 40,000 receptor sites per cell for IgE and it may increase up to 90,000 receptor sites per cell. The bridging of cell-bound IgE molecule by a divalent antigen or anti-IgE antibody brings two receptors into a close proximity leading to activation of membrane-associated enzymes which induce the release of histamine and other vasoactive amines such as 5-HT, SRS-A, acetylcholine and bradykinines in various combinations **Raif, (1984)**.

According to **Patterson (1974)**, histamine is the most important chemical mediator involved in the pathogenesis of allergic rhinitis. **Stanworth, (1971)**, stated that, in the nose, the action of histamine is greatly influenced by the characteristic structure and autonomic regulation of the lining tissues, for example its action is markedly potentiated in the highly vascularized areas such as the nasal mucosa. **Mygind et al., (1987)** stated that, the manifestations of IgE mediated hypersensitivity in the nasal mucosa are inflammatory in nature and principally of protective value where eosinophilia associating the allergic reaction exerts antiphlogistic function by taking immune complexes

present in the nasal mucosa and secretion and also release histamine which modulate the effect of mast cell degranulation. This function will reinforce mucosal immunity.

Diagnosis of Allergic Rhinitis

I- Case history : Careful history taking is the most important investigation in the allergic case. **Bickmore, 1974; Missal, 1971; Williams 1966 and Mygind 1979**, concluded that the examiner questions to the allergic patient should fulfill the following :

1. Personal history : Age, Sex, Occupation, residence, any general disease as DM or hormonal defects.
2. Detailed inquiry about the patient's symptoms of allergic rhinitis and related conditions.
3. The possible aetiological factors e.g diet, pets, fumes, dust at home and at work, cosmetics, soap and powders.
4. A mention of the general medical history.
5. Environmental survey.
6. Childhood allergic history.
7. Family history.

II-Rhinoscopy : According to **Murray, 1972**, anterior rhinoscopy should be done in all patients with sneezing discharge and nasal obstruction not only to reveal polyps and other abnormalities but also to exclude tumour and foreign bodies. The nasal mucosa of the allergic patients particularly on the turbinates is usually swollen, wet and pale bluish in colour.

Anterior rhinoscopy is important for :

1-Grading of nasal blockage which can be clinically evaluated as (-,+,++,+++) and disclosing to what extent the nasal blockage is due to the vasodilatation (by examination before and after vasoconstrictor application) **Mygind, 1978**.

2-Taking a smear for cytological examination.

3-Taking biopsy for histopathological examination.

Posterior rhinoscopy is important for :

1-Detection of post-nasal discharge and its character, **Hansel, 1975**.

2-Detection of polypi in the nasopharynx, **Hansel, 1975**.

3-Detection of any hypertrophy and hyperplasia of the lymphoid tissue of the nasopharynx caused by the allergic state.

According to **Missal, (1974)**, ophthalmic, oral, pharyngeal and laryngeal examination should be carried out in correlation with rhinoscopy to detect any allergic manifestations in the area.

III-Radiological examination : It is a routine practice to take the standard occipitomental view to demonstrate the maxillry sinuses and the occipitofrontal view to demonstrate both ethmoid and frontal sinuses **Wright, 1979**.

In cases of allergy of the nasal sinuses radiography may reveal the following changes, **Seebohm, (1978)**.

1-Generalized mucosal thickenings giving a veiled or clouded appearances. The depth of mucosal thickening may vary from day to day.

2-Localized swelling of one area will appears as a localized shadow but generalized irregular swelling will show as mottled shadow.

3-Complete opacity, which is seen when mucosal swelling is extreme or when the lumen is completely filled with fluid.

4-Fluid levels which are differentiated from mucosal swelling by comparing the levels in the upright and tilted positions.

According to **Wright, (1979)**, the opacity of the sinus must be investigated to determine if the sinus is full of pus or show gross mucosal thickening.

IV-Special tests for allergy:

1) Nasal cytology : Cytological examination of nasal smear help to provide quick information about different types of rhinitis and also useful in planning the diagnostic work-up and treatment. By cytologicl examination **Bryan et al. 1968** and **Radford, 1978** can differentiate between different types of rhinitis which are difficult to be diagnosed clinically. The significant cells in allergic disease are goblet cells, eosinophils and mast cells. In some cases the increase in lymphocytes is noted **Bryan and Bryan (1959)**. They also reported that eosinophils may or may not be present at the time of the smear, So finding of goblet cells or mast cells may be the chief factor in the diagnosis of nasal allergy. According to **Kay et al., (1977)**, eosinophils migrate towards certain chemical stimuli usually of high histamine concentrations. The most important of these stimuli is the eosinophil-chemotactic factor of anaphylaxis (ECF-A). This factor is liberated from the mast cells and basophils during allergen challenge of sensitized cells, **Mygind, (1978)**.

Hansel, (1975), stated that , in cases of non-allergic patients, nasal cytology shows eosinophils in a scattered manner and in small number with no clumping, but in allergic patients, a large number of eosinophils appear and they are often in clumps. According to **Mygind, (1979)** nasal eosinophilia is considerably reduced by systemic steroid treatment but only to slight degree by topical steroid therapy.

2) Histopathological study: The biopsy can be obtained easily under local anaethesia from the lateral or the middle part of the inferior turbinate with small pitting cup forceps or punch biopsy forceps. It gives further information about the histological changes occurring in the nasal mucosa **Gat's et al., 1977**.

3) Immunoglobulin study : **Peter and Viggo, 1978**, reported that the identification of allergen specific IgE antibodies in the serum is of limited value in perennial rhinitis, probably due to the small size of the target organ, However, radioallergosorbent test (RAST) investigation of nasal secretion is of great value in determining in which patients the allergic mechanisms are of importance (Allergic rhinitis) and in which a non-specific vasomotor instability is of importance (Vasomotor rhinitis). **Weir, (1979)**, reported that serum IgE determination is of value in research work but is not necessary in the diagnosis and management of allergic rhinitis. High levels are associated with multiple positive skin tests but again the individual case of allergic rhinitis may have level within normal limits, particularly if there is no associated asthma. **Miadonne et al., (1983)**, concluded that RAST analysis on nasal secretion is useful in clinical diagnosis of allergy especially for dermatophagoides, epidermal derivatives and moulds. it has been positive in most cases in which the serum RAST was negative. **Olive et al., (1981)** found that IgE levels in nasal secretions were significantly greater in allergic form than vasomotor form of rhinitis. The levels of IgE in nasal secretion serves as a useful but not pathognomonic parameter in differential diagnosis of different aetiologic forms of rhinitis and it should be considered within the context of all clinical and analytic data before a conclusive diagnosis is made. **Ortolani et al., (1981)**, had correlated the specific IgE in the serum and nasal secretion with clinical symptoms in atopics where they fond that positive serum RAST was always present in all subjects with positive skin tests and there was a good correlation between high levels of circulating specific IgE in the serum and nasal secretion and the presence of clinical symptoms. On the other hand RAST of nasal secretion was negative in most symptom free subjects and so, as a diagnostic test, nasal RAST is considered more significant than serum RAST.

Methods of determination of IgE

Different methods for determination of IgE are present, some of the commonly used in vitro tests are :

i) Single radial immunodiffusion method, **Mancini et al., (1965)** : It is one of the simplest and earliest methods used for quantitative determination of immunoglobulins. For IgE the sensitivity of this test is accurate to approximately 200-300 mg/ml (i.e. about 480-720 IU/ml).

ii) Modified radial immunodiffusion method (using radioactively labelled antibody) **Rowe, (1969)** : e.g radioimmunosorbent test (RIST), paper RIST (PRIST) and radioallergosorbent test (RAST) **Mygind, (1978)**. These methods depend mainly on the principal of radioimmunoassay inhibition techniques.

iii) Enzyme-linked immunosorbent assay (ELISA) : **Rubenstein et al., (1972)** described two types of enzyme-immuno assays, homogeneous and heterogeneous. In the homogeneous type a hapten is linked to an enzyme in such a manner that the enzyme activity is altered when the hapten combines with the antibody leaving the enzyme-labelled hapten free to degrade the substrate and this degradation would be read in a spectrophotmeter. The heterogeneous type combines the advantage of immunofluoresence and radioimmuno assay and overcomes many of their disadvantages. It depends on the assumption that either an antigen or antibody can be linked to an enzyme whilst retaining both immunological and enzymatic activity in the resultant conjugate, Nakane and **Pierce, (1967)**. The next stage in the development of enzyme-immunoassays was the linkage of a soluble antigen or antibody to an insoluble solid phase in a way in which the reactivity of the immunological component was retained. This was the basis for the technique known as ELISA described by **Engval et al., (1971)**.

4) Skin tests *:* Skin testing performed by the prick, scratch or intradermal method is widely used in the identification of the specific antigens in cases of bronchial asthma and allergic rhinitis **Feinberg, 1936**. The purpose of these tests is to detect if the patient is producing reagins and if so, against which allergens and to what extent, **Weir, 1979**. The principle of any method of skin testing is to inject an appropriate amount of allergenic material usually in the form of saline extract beneath the stratum corneum epidermis where it comes into contact with specific IgE antibody bound to the most cells. The immediate wheel and erythema response that develops within minutes of the introduction of the allergen into the skin is essentially the result of IgE mediated histamine release from mast cells in the dermis and is considered to be the same occurrence in case of the mucous membrane of the nose on exposure to the specific allergen **Freedman, (1976)**.

According to **Missal, (1974)**, skin tests are considered safe and reliable in most patients especially if correlated with other finding. From the therapeutic point of view, skin tests are important in assessing the degree of sensitivity of the patient and consequently to determine the type and strength of the extract to be used in treatment, **Sanders, (1971)**.

5) Nasal challenge (Provocation) tests:

I-Principal : the principal of these tests is to administer the suspected allergens in a concentration as little as possible directly to nose in order to assess the sensitivity of the subject to these test substances, **Mygind, 1978; Davies et al., 1985; Weeke, Davies and Okuda, 1985**.

II-Significance : **Mygind et al., (1987)**, stated that the last decade has witnessed a considerable increase in the interest in performing nasal provocation test (NPT), not only for diagnostic purposes but also in order to promote the study of pathophysiology and pharmacology of nasal disorders. They also reported that there are now several methods devised, each with its inherent merits and problems and so, before selecting the method for challenge, it is of utmost importance to decide the purpose of the challenge first as it differs radically from simple clinical challenge where only a qualitative answer is wanted to that challenge performed to study pathophysiological event.

Mygind, (1978) and Weeke et al., (1985), stated that, NPT may provide valuable diagnostic evidence of sensitivity in cases where there is some doubt over the result of skin or blood test of allergen sensitivity. They also added that NPT can be useful to confirm that a positive skin or serum IgE test is clinically relevant as a control in immunotherapy and when bronchial challenge of asthmatic patient is contraindicated. It has been claimed that allergy can be localized exclusively to the nose and be demonstrated by NPT but not by skin tests, **Huggins and Brostoff, (1975)**.

Mygind and lowenstein, (1982), however stated that, nasal challenge in patients with negative skin tests has no place in clinical practice, except perhaps for occupational allergy. **Reinert, (1981)**, had performed a study on allergic subjects to assess when a positive NPT is clinically relevant and he found that, for certain allergens there exist threshold concentrations which should not be exceeded, however, where there is no threshold dose, as e.g with mites NPT is no more informative than the skin test.

III-Standardization : There is no generally accepted procedure of nasal challenge and before any progression in this field, *the following variables need to be standardized* :

1) Challenge agent :

Several different substances have been used for the study of the pathophysiololgical mechanisms in the nose. Allergens have been used in original forms such as pollen grains **Connell, 1968** and allergen extract **Pipkorn, 1982**. Several different putative inflammatory mediators **Disgaard et al., (1984)**, neuromediators, **Malm et al. (1985)**, irritants, **Maclean et al., (1979)** and physical stimuli, **Togias et al., (1985)**, have also been tried. **Some of these agents are listed in the following :**

The agent	Types
Allergens	Pollens, House dust, Mite, Anti-IgE
Putative mediators	Histamine, sertonine, leukotriens, prostaglandines, PAF
Neuromediators	Metacholine, SP
Physical stimuli	Temperature
Irritants	Cigarette, Ammonium

(A) Allergens : several types of allergens have been employed for the purpose of challenge. The ones most commonly used are pollen allergens such as grains and its extracts. Work with allergen extracts for nasal challenge encounters the same problems as other uses of these substances. The major problems are the purity, standardization **Aas et al., (1978)**, and stability of the extracts. Therefore, only fresh allergen extract should be used. Stock solutions should be kept refrigerated and fresh dilutions made frequently.

(B) Putative mediators : in order to try to evaluate the effect of different mediators on nasal allergy, they have been adminsterated in different challenge models, but at present, there is no relevant knowledge about the levels of these mediators at their sites of action. Histamine has been used for challenge procedure, **Tonnesen et al., 1985** and it can induce all symptoms relevant to allergic rhinitis. Several other putative mediators such as, platelet-activating factor (PAF) **Pipkorn et al., (1984)**; serotonin **Tonnesen et al., (1985)** and leukotriens and prostaglandins **Jackson, (1970)**, have also been used for nasal challenge.

(C) Neuromediators : e.g methacholine which has been used for challenge purposes. According to **Malm et al. (1985)**, although methacholine challenge in the lower air ways have become a standard procedure when diagnosing hyperreactivity, a similar approach regarding the upper airways has not so far produced a comparable results.

(D) Irritants : Several irritants, such as ammonium and cigarette smoke have been used to induce non specific irritation in the nose. One of the problems with this approach is the quantification of the stimulus. Although exposure time may be a useful parameter, the intensity should be quantified **Malm et al., (1979)**.

(E) Physical stimuli : temperature changes have been used as an inducer of changes in the nasal vasculature. Any temperature changes affecting one part of the body or the whole body, such as sauna or cold room exposure **Olsson et al., (1985)**, have been shown to produce changes of the vasculature of the nose. The response is demonstrated in terms of symptoms and mediator generation following breathing cool air through the nose, **Togias et al., (1985)**.

2) Delivery system : it includes :

A-Dry system : depends on the application of substances, such as whole pollen grains in the form of dry powder delivered over a long time period, the aim being to simulate the natural exposure. **Connell, (1968)**.

Another approach has involved the use of nebulizer and a capsule containing the pollen grains, **Nailerio et al., (1983)**. The distribution of the challenge substance in the nasal cavity should be known.

B-Solution system : Several devices have been made in order to introduce solutions of the challenge agents into the nose, such as dripping, nebulizers, small Carlsberg pipettes or mechanical pump sprays. The latter device is fairly easy to use and has been shown

to produce a wide spread distribution of dilution to the nasal cavity **Mygind et al., (1978).**

C-Vaporized system : gases such as ammonia, as well as , cold air may be distributed through any system that delivers gases to the airways. The point which must be considered with regard the system that is used in the reproducibility of the actual challenge dose given and where it is in fact deposited. **Pipkorn et al., (1987).**

3) Phases of the allergic process following NPT : **Naclerio, (1988),** stated that there are three phases of the allergic process following NPT. These are

A-Early-phase reaction : when someone allergic to pollen is challenged with it , the allergy is almost immediately manifested clinically by increased resistance in the nasal airway, mucous secretion and sneezing. This is called the early phase of the allergic process. These responses are the result of the release of mediators into the nose at the time of antigen challenge. Some of the mediators of this immediate response, such as histamine are performed in the mast cell granules; others including leukotriens and prostaglandins are newly synthesized in response to the cross-linking of the antigen to the IgE. The production of the mediators is dependent on the dose of pollens.

B-Late phase reaction : The second phase of the allergic process is called the late phase. In one study, subject with allergy were initially challenged by allergens, the symptoms recurred after a quiescent period and without further antigen challenge about 3-10 hours after the first challenge. This late response probably reflects an

inflammation occurring after the antigen exposure and may correspond to the inflammation seen during the clinical disease.

C-Rechallenge phase : The nasal mucosa is hypersensitive to a rechallenge with the antigen 12 to 24 hours after the initial challenge. The nose also becomes more sensitive to non-specific challenges, as with histamine. The explanation for this is not clear, but could be due to an increase in the non-specific hypersensitivity or the migration of additional target cells, such as basophils into the nasal mucosa. Also, as the mucosal barrier is damaged by inflammation it becomes weaker permitting more antigen to penetrate into the nasal mucosa; this in turn exposes additional cells to the stimulus.

IV-Response measurment : **Pipkorn et al, (1987)**, stated that the nose has a limited range of expression. There can be changes in the nasal patency, induction of secretions (volume and composition) and sneezing. In a clinical studies, these can be detected in a simple way by observation and rhinoscopy. For more complicated research procedures, a more sophisticated approach is necessary. Several methods have been devised which enable us to monitor each component of the reaction separately. The presently available methods are :

1-Symptom scores : symptom scores have been extensively applied in clinical studies of rhinitis therapy. Changes in the nasal symptoms as recorded with symptom scores obtained in a group of untreated hay fever patients correspond well with changes in the number of pollen grains appearing in the air **Horak et al., (1979)**.

For clinical studies, symptom scores recording is a reasonable instrument provided that a rather large number of patients can be studied. Similar symptom scores have also been used in the evaluation of

symptoms obtained at nasal challenge, but they should be complemented by at least one objective measurment, **Mygind and Pipkorn, (1981)**.

2-Vascular reactions : from the functional point of view, the vascular supply of the nasal cavity can be divided into resistance vessels, exchange vessels and capacitance vessels. It seems as if these different components have a different reactivity to stimuli and are independently regulated, **Olsson et al., (1985)**. It is now possible to monitor the changes in two of the vascular components separately in a challenge procedure.

3-Secretions : one of the main symptoms at different challenge procedure, is the production of nasal secretion. Several sources of the fluids are possible; tears fluid, anterior serous glands, small seromucinous glands, goblet cells and transudation.

Differences in the composition of the secretions derived from different sources will influence the final nasal secretion e.g if a challenge is performed with an agent that mostly induces secretions via reflex mechanism, the compositions of the secretion will differs from that which ensues after applying an agent which produces direct effect on the vessels inducing vascular leakage **Mygind and Pipkorn, (1981)**.

Collection of nasal secretion : In general there are four methods for collection of nasal secretion :

a-Nasal washes method. **Rossen et al., (1985)**.

b-Modified nasal washes method **Mobday et al., (1971)**

c-Filter paper method : introduced by **Lorin et al., (1972)** and modified by **Mygind et al., (1975)** then by **Mygind and Thomson (1976)**

d-Collection during allergic rhinitis stage **Okuda, (1975)** or after instillation of 18% saline **Merritte, (1975)**

Processing of the specimen : this depends upon the type of secretion collected and the purpose of the study. The process comprises many steps e.g storage at least at 20 C°, ultracentrifugation or filteration for removal of cellular debris mucous and micro organisms, homogenization, dialysis and lyophilizatoin, **Mygind, (1978)**.

V- Drawbacks of nasal challenge tests : The major shortcomings of NPT are its lack of use-fullness if the nasal mucosa is already congested, the subjective nature of the criteria for positive results and the need to postpone fourthere testing with additional allergens for 24 h. if positive reaction occurs, **Freedman, (1976)**.

The tests have also the disadvantages that, they always carry the risk of anaphylaxis, the results may vary from time to time and it may give false positive or negative results. **Weir, (1979) and Mygind, (1979)**.

Topical Corticosteroids and Nasal Allergy

The principal for use of topical glucocorticoid in cases of allergic rhinitis is that, as long as we do not have glucocorticoid with specificity for glucocorticoid receptors of those cells that participate in allergy and inflammatory reactions, but not for other cells, the topical use of steroids offers a possibility of enhancing the local anti-inflammatory activity and minimizing systemic activity. Thus, local application results in a high concentration at the target site, but this is then diluted following absorption and distribution allover the body **Pipkorn, (1985)**.

The ideal glucocorticoid for topical use should be active locally but inactive systemically. Theoretically, this might be achieved by a compound that is either is not absorbed or which is rapidly inactivated after absorption. This inactivation might be achieved by a first-pass metabolism in the liver, or some other mechanism which generates metabolite that are less active than the parent compound, or are inactive.

The use of topical steroids in treatment of allergic rhinitis has gained widespread use in the past ten years; it was tried soon after the demonstration of the efficacy of systemic steroid. However, there was little or no advantage in the topical route as compared to systemic administration, as there was a depressive effect on the hypothalamo-pituitary-adrenal (HPA) axis; also ocular symptoms were depressed indicating a systemic effect of the drug **Mygind and Weeke,(1985)**.

The choice of the drug : In the early 1960's the more potent dexamethasone was introduced, **Norman et al., (1956)**. Several studies demonstrated its efficacy in the treatment of seasonal and perennial rhinitis, **Groter, (1963)**. however, there was still a considerable effect on the HPA-axis because the absorbed part is not first-pass deactivated in the liver. Thus, the search for other compounds with other pharmacokinetic profiles was encouraged. Dexamethasone has now been replaced by newer compounds, **Michels et al., (1967)**. The first drug that clearly demonstrated a differentiation between systemic and local anti-inflammatory activity was beclomethasone dipropionate (BDP). It was introduced for topical use in the nose by , **Mygind, (1973)**. BDP was followed by the introduction of flunisolide, **Turkeltaub et al., (1976)** and budesonide, **Pipkorn et al., (1980)** with similar pharmacokinetic profiles. As regards the systemic activity, budesonide has less systemic activity than BDP, **Johansson et al., (1982)**. The dose needed to demonstrate systemic activity however, seems to be considerably higher than the recommended dosage for the drugs; this may be of clinical significance if a higher dosage regimen is considered.

Dosage : BDP was introduced for topical use in the lower airways, using a daily dose of 400 mcg, **Brown et al., (1972)**. The same daily dose was subsequently adopted for nasal treatment without any dose-response studies. It might seem unnecessary to use the same daily dose in the nose which has an area of about 15 cm2, as in the lower airways which has an area of about 10 m2. however, the nose is exposed to the same amount as the lower airways, and due to its filter function the nasal mucosa is exposed to more allergens than the mucosa of the lower respiratory tract, **Siegel et al., (1982)**, concluded in a study of patients with seasonal allergic rhinitis that, the efficacy seemed to level off at a daily dose of 300-400 mcg.

So, there are now general recommendation for BDP as well as flunisolide and budesonide of a daily dose 200-400 mcg. **Mygind, (1982)**. This dose should be decreased to the lowest level in cases of perennial rhinitis when the symptoms are controlled. The dose may be increased in cases of seasonal allergic rhinitis under certain circumstances up to 800 mcg or even 1200 mcg per day as for example in days with high pollen counts, **Wohn et al.,(1978)**.

Safety aspects : Concerning local side-effects, two different types have been described : immediate irritation, mostly found in flunisolide-treated patients and haemorrhagic crusting and dryness in the anterior part of the nose, **Mygind, (1982)**. These side-effects are mostly intermittent and not progressive. A dose reduction, use of an ointment or the change to another delivery system will minimize the problem which seldom leads to discontinuation of therapy. In pregnancy, the topical steroid seems to be safe, although animal studies show a possible teratogenic effect, this seems not to be the case in humans, **Greenberge et al., (1983)**, as the absorbed amount of the intranasally adminestrated steroid is very small.

Topical steroids and nasal challenge tests : Clement and Kaufman, (1984), reported that 14 days treatment of patients with perennial rhinitis with BDP in a daily dose of 400 mcg. resulted in a significant increase in tolerance to house mite-house dust and grass pollen allergens during nasal provocation tests.

Naclerio, (1988), stated that, exposure of individuals with allergic rhinitis to antigens, such as pollens can activate the nasal mast cells to initiate the allergic process. During this process, the patients develop

symptoms and mediators are released (including histamine, prostaglandin D_2 and leukotriens L_4) to produce inflammation characteristic of allergic rhinitis. The allergic process can be divided into 3 phases; early phase, occurring within minutes of allergen challenge, late phase, occurring in about half those challenged about three to ten hours later and rechallenge phase occurring 12 to 24 hours after the first exposure. mediators are released in each phase but during the late phase and rechallenge phase, cell including basophils, eosinophils, neutrophils and mononuclear cells enter the nose in large numbers. The basophils can release mediators increasing the allergic response.

Pretreatment of such patients with systemic steroids such as prednisone prevent the late and rechallenge phases of allergic process. However, with the exception of kinin generation, such pretreatment has no effect on the early phase. In contrast, pretreatment with the topical steroid prevents many more aspects of the allergic process; the production of symptoms, the release of mediators in the early phase and the further development of symptoms and mediator release in the late and rechallenge phases

Topical steroids also prevents the influx into the nose of mediator-releasing cells, including basophils. Therefore, physicians should consider pretreating their patients with allergic rhinitis with topical steroid several days the pollen season begins, where the early response to these allergens will be reduced and the inflammation associated with chronic allergic rhinitis will be suppressed.