DISCUSSION

Allergic disorders put an ever existing challenge, if their prevalence, impact on the life and occupation of patient, their long exhausting course and continued need of drugs are considered. Patients who have seasonal allergic rhinitis or asthma, name the season as that of discomfort and abstinence from work. Condition becomes more miserable when drug treatment does not suffice or patient finds it difficult to live on drugs.

The determination that a clinical syndrome may have an allergic etiology is important, because specific prophylactic and therapeutic interventions can be used once an allergic cause has been identified. For curative treatment is is essential that allergens responsible for the symptoms be accurately identified. There are different ways to arrive at a diagnosis. Case history remains extremely important in all allergological investigations. Skin test procedures can be employed to identify responsible allergens. The size of skin reaction, the dose of allergen required to produce a given skin reaction size, and number of positive skin tests, all provide a clue regarding the etiology and severity of disease.

Clinically, immediate hypersensitivity skin test has been demonstrated to have predictive diagnostic value. Subjects with a history of an allergic syndrome
occurring on exposure to allergen and with skin test reactivity at low doses of that allergen are at a very high risk of experiencing a recurrence of the allergic syndrome when they are re-exposed to that allergen (Norman, 1973 and Hunt et al, 1978). The degree and number of positive skin tests to a battery of allergens have also been demonstrated to be positively associated with the reported prevalence of allergic diseases in the population (Burrows et al, 1976 and Haas tele et al, 1980). Furthermore, asymptomatic subjects, who are skin test positive, are at a higher risk of developing an allergic syndrome (Chambers, 1958 and Hagy, 1976).

Allergy skin testing is, therefore, a useful objective clinical method for evaluating the prevalence of immediate hypersensitivity to selected allergens. In addition, allergy skin tests are ideally suited for population surveys because multiple tests can be performed within a short period of time.

Age had been an important indicator of reactivity in all multivariate analyses. Hendrick et al (1975) and Barbee (1981) have reported that there is a decrease in skin reactivity with advancing age. Peak skin test reactivity had been seen in age group of 20-40 years. Diminished and organ responsiveness in infants and elderly individuals to inflammatory mediators appears to be one contributory mechanism (Van Asperen et al, 1984 and
Gilchrest et al, 1982). There is an age associated loss of vascular bed (50% reduction of mast cells and 35% reduction of venular cross section) also there is a decrease in histamine release with age. A decrease in skin response to mast cells degranulating agents has been reported in infants (Menardo et al, 1985). According to other workers, differences in allergen exposure with age, immunologic responsiveness, or tissue differences are responsible for the age related differences in SPT results (Gergen et al, 1986). Results of our study do coincide with these observations. The IgE increase during these years of age and proliferative capacity of clonable T and B cells during 25-35 years which decline in later years of life (Kay, 1979) may provide a further explanation to this age related change.

Many studies have been conducted to find out the relation of sex and SPT reactivity. In our study no clear cut trend could be made out. Out of 8 patients who showed reactivity against pollen allergens, 5 were males and three were females, while in those who showed sensitivity against dust components, 5 were males and 8 were females. Amongst patients showing sensitivity to dust mite allergen, four were males and three were females.

Male predominance in allergen skin test reactivity could be expected due to higher levels of IgE in men as compared to women (Freidnoff et al, 1984).

Lindblad et al (1961) and Haahtele et al (1979) have also reported more reactivity among males. Pollen
reactivity and dust mite reactivity in present study showed similar trend.

In present study out of 41 patients who showed reactivity against one or more allergen, 26 were resident of urban area while 15 belonged to rural locality. Residency in urban area was an indicator for increased reactivity in all multivariate analyses (Peter Gergen, 1986). Linna (1974) also found in his study that skin reactivity was more in urban dwellers. Smith et al (1982) have reported the same or lower incidence of reactivity in rural population.

The reason for this could be urban clustering of families with positive allergic history or cultural differences in the urban and rural groups. It may be related to pollutants in the urban environment. This is also evident in increasing incidence of allergic diseases with rapid urbanization.

Other variables that may affect SPT reactivity are poverty, education and income. Barbee et al (1976) found increasing reactivity with increasing income. Linna (1974) found more reactivity among educated group.

In present study these variables have affected the results in similar way.

In present study all the tests had been conducted in the morning and before noon. It is often questioned that does circadian variation affect SPT result. Pakit Vichyanond et al (1989) have shown that there is no
significant morning, evening variation in SPT results. Earlier Reinberg et al (1965) and Lee et al (1977) have put similar opinion after their studies. So, it does not affect the result, whether, the SPT is performed in the morning or evening.

The inclusion of positive control (Histamine) in SPT is recommended for optimal evaluation of allergen hyper sensitivity (Nelson, 1983 and Malling, 1984). Some investigators advocate semiquantitative grading of skin test reactions to allergens based on a percent size of a positive control reaction (Aas, 1980). We in present study used histamine as positive control but Casale et al (1984) propose to us codeine, which triggers mast cell release via specific cellular receptor while histamine is an end organ mediator.

It has been demonstrated that histamine reactivity is lower in infants and in old persons. Skassa Brociek (1985) has proposed that reactivity to histamine increases up till adulthood, decreases after 50 years and there is plateau after 60 years. As size of SPT reaction to histamine varies with age, therefore, the interpretation of skin tests should not only take into account the wheel size but rather a ratio between histamine induced and allergen induced wheals.

Wheal size produced with histamine in present study was 6 mm to 10 mm. Four patients did not show reaction to histamine, two of them were more than 50 years
of age while one patient was of 44 years of age. The remaining one was 26 years old female. Perhaps they did not comply to stopping all medication (including antihista-
minics) prior to test or the age criteria proposed earlier could be the possible cause of poor reactivity.

Richard Horsinger (1972) pointed towards corre-
lation of allergic asthma and peripheral eosinophil count. Tandon and Saha (1987) found that in their study only 55% of SPT positive patients had raised eosinophil count. In present study patients having high eosinophil count were 18 out of 41 positive results.

Despite the development of various in vitro methods, skin testing with potent allergen preparation and positive and negative control substances, remains the most revealing procedure in diagnosing specific allergic factors associated with allergic diseases. When merits of SPT and KAST (Radio-allergosorbent test) are compared. It has been found that:

1. Both tests detect IgE antibodies accurately and reproducibly.
2. Both the tests reveal information of a semiquantitative nature, but SPT is more sensitive.
3. Results of both tests correlate equally well with allergic symptoms.
4. Both tests can be used as grounds for instituting immunotherapy.
5. Skin tests appears to be superior in diagnosis of life threatening anaphylactic state in which maximum sensitivity is important.

6. The results of SPT are more immediately available (within $\frac{1}{2}$ an hour) in comparison to 2-3 days required for RAST results. However, presence of dermatographia, widespread skin diseases and patients apprehension of pricks may be regarded as states of non-applicability of SPT.

Rosario scolozzi et al (1987) compared SPT with multiple chemiluminescent assay (MAST-CLA) and they propose that no technique is as sensitive as skin tests for allergen specific diagnosis of inhalant allergic disease.

Finnerty et al (1989) have also weighted SPT and MAST and they found both the procedures equally effective.

Prick et al (1989) in their study on asthmatic children allergic to inhalants, compared SPT with other in vitro techniques and they also found SPT more effective.

SPT can act as predictive indicator. Chambers (1958) and Hajy et al (1976) have proposed that asymptomatic subjects, who are SPT positive to certain allergen are at higher risk of developing an allergic syndrome.

Skin prick test has also been compared with direct provocation tests. Warner (1976) and Panli (1977) found strong correlation between SPT and bronchial
challenge test, but the latter test does not mimic a realistic exposure to house dust. In bronchial challenge test, results are assigned according to symptom-score, and positivity is ascertained on the bases of total score.

Clinical bronchial score:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Cough</td>
<td>1</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>2</td>
</tr>
<tr>
<td>Tightness</td>
<td>1</td>
</tr>
<tr>
<td>Wheezing</td>
<td>4</td>
</tr>
</tbody>
</table>

Raihi (1990)

This technique does not quantify the amount of material required to prove bronchial reaction.

Cockroft et al (1979) and Spector et al (1979) could not demonstrate any correlation between cutaneous and bronchial responsiveness.

Peter small (1989) studied the correlation between SPT and nasal provocation test. He concluded that properly performed SPT predicts nasal reactivity to the same allergen, that is nasal provocation adds least to the information yielded by SPT. Direct IgE measurement and SPT result correlation has also been studied. Bernard Berman et al (1986) could not find any statistically significant differences when they compared SPT results and direct IgE measurement in the light of clinical picture.

According to William Knicker (1989), more sensitive test (SPT) lend more opportunity for false
positive interpretations while less sensitive test (RAST) provide more chances of false negative interpretation.

**COMPARISON OF SKIN TESTING WITH IN VITRO TECHNIQUES:**

<table>
<thead>
<tr>
<th></th>
<th>Skin testing</th>
<th>In vitro techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td>15 min + 4/6 hrs.</td>
<td>5 hours to 2-3 days</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>Allergen dependent</td>
<td>Allergen dependent</td>
</tr>
<tr>
<td></td>
<td>skin site dependent</td>
<td>IgE dependent.</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>Varies (≤0.01 IU/ml)</td>
<td>0.01 IU/ml.</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td>Systemic reactions false</td>
<td>false positive</td>
</tr>
</tbody>
</table>

In this way excluding few short comings, SPT is a convenient and useful technique in the confirmation of allergic etiology of disease.

Using SPT, Lyndon mansfield et al (1988) put an idea of local miniscreen for detection of allergic disease which would provide an accurate referal. This miniscreen included SPT and IgE assay.

Rodriguer et al (1988) has documented heterogeneity in skin tests results, when the tests were done by 4 different practices using the same panel of allergens. The difference in performing test, different in the criteria of reading result and difference in the standardization and concentration of allergen extracts lead to heterogeneity in test results.

In our study we performed skin prick test using a lancet with free hand technique. Sandreborg et al
(1987) compared this technique with, that, using a glass syringe attached to a micrometer, but they found no difference in results.

It is being questioned that does it make any difference if different area of human skin is taken (like forearm and back) for SPT. Voorhorst (1973) compared the two and reported that SPT results vary. Stendreborg et al (1987) also did a comparison. But both these studies could not find a common pattern for variation. In present study we prefered forearm to do SPT in order to avoid this discrepancy.

From time to time various studies have been conducted to assess the prevalence of various allergens. This exercise provides etiological precision along with guiding the approach of the management of allergic diseases prevalent in a particular locality. In general the group of allergen which are tested include dusts and dust mites, pollens of various plants and trees, molds, food allergens and industrial products. Physical agents and industrial products are tested for their allergenic implications by patch test.

Like present study many workers have studied the prevalence of various allergens along with associated characteristics. In present study out of 84 patients tested of their allergic disorders, 41 showed positive SPT. Out of these 41, 29 patients have shown positive reaction with dust components and dust mite allergenic extracts.
8 patients have shown positive reaction with pollens while 2 each have shown positive reaction with fungi and food component.

Table 10 shows the distribution of reactivity of 41 patients. Maximum sensitivity has been found against dust and dust mite. Persons who were positive to house dust alone had the peak severity of their symptoms in summers. The hot and dusty climate of Bundelkhand region during summers well complies with the statement.

Maunsell et al (1968) conducted study to evaluate allergic etiology of bronchial asthma. In most of their study group patients, dust and dust mite (Dermatophagoides) were triggering factors of asthma.

Tandon and Saha (1987) analysed the house dust from the houses of 20 bronchial asthma patients suspected to have sensitivity against house dust. They found almost similar levels of infestation by Pteronyssinus and Farinae mites in homes of asthmatics and control, meaning thereby that it is the reactivity of individual to particular allergen which results into clinical syndrome. In this way, only measurement of levels of mite in house dust cannot provide solid grounds for making diagnosis. Dixit and Mehta (1973) had similar opinion.

Tripathi and Parikh (1983) after studying allergens in Bombay had found that maximum number of positive patients were sensitive to one of the component of dust, and D. farinae plays an important role in house dust allergy.
For the growth and persistence of dust mites low temperatures are required, but Tandon and Saha (1987) have conducted their study in Calcutta and Tripathi and Parikh (1983) did their study in Bombay. At both the places, temperature is more than 30°C during most of the months. Second requisite is humidity or more than 50%. In present study five patients were positive to dust mite alone. In all of them peak severity of their symptoms were during November and December.

Two patients had sensitivity against dust mite allergen along with one more allergen. Two possibilities can be put on the basis of above results. Either house dust of these patients or the dust around their residences is infested with dust mites or the growth of dust mites occurs during winters or rains when the conditions are suitable for their growth. Dust samples should be investigated for dust mite and it has been decided to investigate dust samples from appropriate places in and around the residences of these patients.

In international workshop report, Germany, 1987 HR Ranganath from Bangalore had reported a high prevalence of mite allergy among subjects with asthma and a high number of mite in house dust of these patients.

Sometimes patients relate triggering of their symptoms and exposure to house dust, but who are actually sensitive to some other allergen, or their symptoms do not have an allergic base. Murray (1983) found discre-
pency between number of patients giving history of house
dust sensitivity and number of patients coming out
positive on SPT.

Dust components sensitive asthmatic patients
sometimes develop pollen sensitive allergic rhinitis.
Smith (1978) explained this on the bases that asthma and
rhinitis are related to each other. However, study of
Masanau Shibasaki (1990), proposes that these two are
independent of each other and allergic rhinitis developing
in patients of bronchial asthma should be looked upon as
separate entity. According to Ranson (1989), mite antigen
level of 2 ug/g is associated with risk of allergic
sensitization, but according to Wood et al (1987) a level
of 1 ug/g is associated with significant risk.

Many studies have been conducted to find out
the prevalence of various allergen in the environment of
a particular city. Lakhan Pal and Nau (1960) conducted
their study in Almora, Singh et al (1981) in Amritsar
while Tripathi et al (1982) conducted their study in Bombay,
Shivpuri (1980) and Singh Babu (1980) have conducted
similar studies in Delhi.

John Santilli (1988) did his study using SPT
with mold extracts and he obtained many positive results.
He proposed that panel of allergens to which patients are
subjected while performing SPT should also contain mold
extract allergens.
When observant patients can provide fairly exact dates of onset and offset of seasonal symptoms, correlation with allergen known to occur in that pollinating season in patient's environment, can provide important diagnostic information.

RATIONAL OF IMMUNOTHERAPY

When incremental doses of a specific allergen extract, known to produce allergic symptoms in an individual are administered over a certain period of time. Patients tolerance to that allergen increases on natural exposure and patient's symptoms are significantly diminished or ameliorated. Various studies support the efficacy of immunotherapy: Horman (1974), Van Metre et al (1980) Normal and Lichtenstein (1978). Studies of these workers support the efficacy of immunotherapy. Some other studies provide an objective measurement of improvement following immunotherapy. Aas (1971) has shown decreased bronchial sensitivity to dust extract in persons who had immunotherapy against dust allergen. Warner et al (1978) conducted a double blind study and reported that 50% of patients receiving immunotherapy had resolution of late phase of bronchial reactivity on bronchial challenge.

Bousquet et al (1985) demonstrated that skin prick test reactivity also decreased in patients who received effective immunotherapy.

Along with clinical improvement, efficacy of
immunotherapy is judged by immunological and mediator response.

Both WHO and FDA have attempted to standardize immunotherapeutic (in context of allergic diseases) preparations so that they can be safely used and results of two different studies can be compared.

Immunotherapy is generally recommended in cases where avoidance is not feasible and in cases where drug therapy becomes palliative. Immunotherapy is allergen specific and dose dependent. High dose therapy is superior to low dose therapy. Patients undergoing immunotherapy subsequently develop antibodies (Blocking antibodies) that are capable of blocking passive transfer reaction.

Allergic extracts which are deployed in hyposensitization are either aqueous extracts, depot extracts or modified extracts.

Both local and systemic reactions may occur with immunotherapy. A recrudescence of symptoms may occur on discontinuation of therapy (Creticos et al, 1987). Though hyposensitization is quite safe but severe life threatening anaphylaxis may be observed but very rarely and this may be followed more rarely by death (Schaeffer and Sisk, 1984). Excluding the unexplained cause, error or dose selection could be possible cause of this. Patient should be kept under supervision for about 2 hours after therapy.
Reactions occurring early in the course of therapy are because immunotherapy stimulates IgE production but no IgG protection. According to one CSM report (1986), 30% patients may experience minor reactions. 6 of our patients complaint of nausea, dizziness but drop in blood pressure was recorded in only one patient.

In the employment of immunotherapy following methods have been proposed:

A. Preseasonal method.
B. Co-seasonal method.
C. Perennial method.

Preseasonal method is employed for seasonal allergens especially pollens, the treatment is started in such a way that maintenance dose is reached before the start of season.

In co-seasonal method, injections are given throughout the season in which patients have complaints.

In perennial method, after a top dose in the preseasonal method is attained, it becomes possible to continue treatment by administering a dose just below that of top tolerable dose every 3 or 4 weeks, top well tolerated dose is continued at 2 to 3 weeks interval throughout the year.

Dose schedule used in present study is given in annexure - III.
The immunological bases of improvement provided by immunotherapy are:

1. There occurs a rise in serum IgG antibodies.
2. There occurs a blunting of the usual seasonal rise in IgE antibodies followed by a slow decline in the peak level of a specific IgE antibodies during immunotherapy.
3. There is elevation of blocking IgA and IgG antibodies in nasal secretions.
4. There is a decrease in basophil histamine releasibility when cells are incubated with allergen.
5. There is a reduction in vitro lymphocyte responsiveness to specific allergens.
6. There is a generation of specific suppressor T cells.
7. There is blunting of the late skin and brochial responses.

IgG antibodies which are produced following immunotherapy have high affinity for allergens but form nonspecific immune complexes that do not fix complement, and there occurs no immune complex mediated diseases.

A favourable clinical response to immunotherapy is found in the ratio IgG/IgE, that is protective immunologic responses mediated by IgG antibodies balancing out the allergic immunologic responses mediated by IgE antibodies. Studies have suggested that immunotherapy
that does not induce IgG antibody response, is not associated with measurable clinical response. Sometimes when immunotherapy is done with unstandardized allergen extract with low potency, results are not satisfactory.

Failure of immunotherapy may occur due to improper assessment of culprit allergen which may be due to use of conservative cut off point to define SPT positivity.

If the patient is sensitive to allergen other than used in certain study. Test may not detect the causative allergen.