Time, Distance and Allergy

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Allergy, among all the medical specialties, seems to be the one most inextricably associated with time-dependent processes,[1,2] Indeed, the term "allergy" itself, which consists of the prefix *allo-* (meaning altered, different) and the suffix - *ergy* (from the word ergon - as in energy - that means work, activity) is the exact opposite of homeostasis, which denotes a condition that stays *(stasis)* the same *(homeo-).* The inaugural issue of the new periodical, *The Asian Pacific Journal of Allergy and Immunology,* provides an opportunity to review the concept of time, i.e. the chronobiology of allergy[1] in relation to the equally important relationship of allergic manifestations to geographic location, and to the distances traveled both by patients looking for relief and by doctors searching knowledge and experience. It is truly an honour and a privilege to write a review article for the new journal. Among its internationally prominent editors there is a colleague for whom my close personal friendship and professional respect remain unaltered, despite the time and the distance that separate us since the years we spent together in Colorado.

DISTANCE AND LOCATION

For awhile, it was believed that one could "move away" from the causes of allergic symptoms, especially those of rhinitis - for instance to purported "hay fever heavens"[3] and of extrinsic asthma. Besides the reported "climatic cures", removal from a pathogenic psychological environment, with maneuvers such as the so-called "parentectomy"[4,5] was considered therapeutically efficacious, particularly for children with chronic severe "intractable" asthma. In fact, extended but relatively uncontrolled observations in a specialized centre for asthma, seemed to support the proposition that the greater the distance travelled away from the aetiologic precipitants, the higher the proportion and degree of improvement,[6] For instance, for more than a decade, the large number of children with asthma coming to the institution then known as the "Jewish National Home for Asthmatic Children" in Denver from the states of New York, Massachusetts and Florida and, even more so, several that came from Israel, improved much more or remitted completely, in comparison to patients with the same medical condition originally residing in the Rocky Mountain Region or the surrounding states of the U.S.A.

The passage of time, however, and a careful analysis of clinical data have failed to confirm these initial impressions and the few published reports that claimed a direct relationship between distance traversed and symptomatic amelioration of respiratory allergy. Patients who had gone back home to Israel, New York or Florida and, due to severe relapses of asthma, returned to Denver, generally failed to respond the second time to the same environmental change. In the ensuing years (1965-72), also children arrived to the Denver centre from South American countries such as Brazil, Ecuador and Peru and these, despite the distance separating their homes from Denver and the striking climatic differences, showed no impressive changes in their allergic conditions. The possibility that crossing time zones, such as in going from East to West, rather than covering many degrees of latitude, from South to North, was the critical factor in determining improvement could not be proven or disproven in these cases.

An entirely different population of allergic and asthmatic patients was studied in the past decade in a private consultation practice also located in Denver.[7] Many patients, mostly young adults, were seen during this period of time who came from overseas and had as much or more difficulty in Colorado than they had in the countries of their birth. These included the Arab countries of the Middle East, Greece, Italy, Algeria and other Mediterranean countries and also, on the opposite side of the globe, the Islands of the Pacific Ocean, Australia and New Zealand. It was particularly interesting to note that a number of students from the Arabian plateau found relief for their severe allergic rhinitis when they resided either on the Atlantic or the Pacific coast of the U.S.A. but experienced severe recurrences of nasal symptoms when they spent the summer in Colorado. The oppo-

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site has been observed in some patients who grew up in a tropical climate such as Hawaii and had severe asthma there, as children. A move to the Rocky Mountain region caused the problem to disappear for years but relocation, years later to another tropical region, as in Puerto Rico, were associated with marked and persistent recurrences of respiratory allergy and asthma (unpublished observations). Evidently, an increasing number of individuals now seem to carry the allergic "capacity to react" with them regardless of the distance they travel. Their symptoms are manifested or actually become worse when the aerobiologic conditions that are conducive to the development of respiratory allergy are present. Thus, the problem of location and movement across great distances is, for an allergic individual, practically identical with the question of aerobiology and the type and degree of exposure to specific airborne allergens.

TIME AND PHASE-RELATIONSHIPS

Very different is the question concerning *time*, which is not only the chronological fourth dimension but also the factor that determines the temporary relationship of events known to precipitate or to ameliorate clinical allergic manifestations. The most elementary and easily recognized allergic biological phenomena related to *real* time are the variable processes of immunologic sensitization and the ensuing cause-and-effect sequence that precipitates a reaction. However, it is well-recognized that neither sensitization nor clinical reactivity are very predictable in that not even genetically similar organisms respond identically to a specific allergen and that persons with the same kind and degree of allergic hypersensitivity can react with entirely different clinical manifestations, such as rhinitis, asthma, eczema, urticaria, etc. To understand and explain these apparent clinical immunologic inconsistencies, *chronobiology*, which is the science of time-related biological phenomena, can contribute by borrowing the methodology from other fields such as history (in which also the number of interacting variables is almost infinite) and to investigate "not an entity, but a relation."[2] In other words, instead of looking for a specific abnormal immunoglobulin, a malfunctioning cyclic AMP, an unbalanced release of histamine, leukotrienes and other mediators, an impaired beta-adrenergic activity, etc., the clinical investigator in the field of asthma ought to integrate all these factors and concentrate on their reciprocal interactions.

Obviously, a study of relationships and interactions is a study in *time*. The examples of intermittent seasonal symptomatology and variable diurnal-circadian-environmental physiopathologic activity are common and require no repetition. Less evident and still not fully appreciated are the time-dependent processes in the internal biologic milieu which may only secondarily be modified by external influences.

Biological periodicity Biological phenomena related to allergy can show rhythmic patterns, at times obvious even to an inexperienced observer and at other times requiring highly sophisticated computer analysis for their detection. Depending on the length of the period involved, one can distinguish periodicities of (a) low frequency, with period length from one week to more than one year, an example of the latter being the cases of seasonal pollinosis, (b) medium frequency, that comprise periods from 30 minutes up to 6 days and include the much studied 24-hour, or circadian variations in blood eosinophils, adrenal cortical activity, pulmonary function, etc. and (c) high frequency cycles occurring more often than every 30 minutes and at times only measurable in fractions of a second.[1]

Among the typical examples of low frequency periodicity are the effects of intermittent immunologic exposures, which can result in allergic sensitization, either due to their frequent repetition or to the lack of it. Immunologic tolerance may fail to develop when properly timed or continuous immunogenic stimuli are absent. On the other hand, repeated allergenic stimuli, such as in the inhalation of airborne pollen, can be responsible for the "priming" effect associated with initial or augmented or nasal and bronchial reactivity. There are also statistical data indicating that allergic respiratory problems, particularly asthma, can exhibit distinct peaks of prevalence in severity, most notable in the months of October and November in the Northern Hemisphere which do not necessarily correlate with periodic variations in airborne pollen and mold concentrations. Another type of low frequency cyclical variations in allergic manifestations are those related to the menstrual cycle. Measurements of peak expiratory flow rate, taken routinely three to four times daily by human volunteers – "autorhythmometry" – have shown a measurable drop in ventilatory function premenstrually in adolescent girls. Induced hormonal menstrual changes, associated with the intake of oral contraceptives, may also be paralleled by periodic allergic manifestations. In the field of dermatologic allergy, circamenstrual or "cyclic" urticaria has been reported.[2]

Numerous rhythmic fluctuations related to allergy are known to occur in the medium frequency range and those called circadian (circa, i.e. about 24 hours) have been most thoroughly documented. Even the simple symptom or pruritus can vary over the day-night cycle and has been reported to be worse in the evening. In fact the so-called "itch threshold" can be 100 times lower at midnight than at 14:00 (2 p.m.) in the afternoon. Experimentally induced wheal-and-erythema skin reactions show a similar circadian periodicity. In the

case of nasal "hayfever" symptoms a biphasic circadian curve has been reported.[1] Most prominent among the cyclically recurring problems is that of nocturnal asthma which has been recognized since antiquity. Regular "around-the-clock" measurements of peak expiratory flow rates with a portable Wright PEF meter have shown a peak in the early afternoon among both healthy and asthmatic individuals. Patients subject to recurrent attacks of nocturnal asthma display a marked "dip" in PEF in the early morning, which, if not corrected with medication, may become a signal of progressive ventilatory impairment and of an eventual need for hospital management. Efforts to prevent the reduction in expiratory flow in patients with nocturnal asthma, including sleep deprivation and forced activity, have shown that only in exceptional cases this nocturnal drop in lung function can be diminished or postponed voluntarily.[8] Utilization of more sophisticated pulmonary physiologic measurements, such as sequential recordings of dynamic lung compliance and airways resistance with the body plethysmograph and chronobiologic analysis obtained with the "cosinor" method has detected late morning peaks for the former and mid-afternoon peaks for the latter.[1] These studies also have shown a parasympathetically conditioned nocturnal increase in bronchial tone with the use of the inhaled anticholinergic drug ipratropium bromide. It is noteworthy that patients with large morning/evening differences in peak expiratory flow also show the highest degree of sensitivity to inhaled histamine and greater responses to bronchodilator drugs such as albuterol (salbutamol).

High frequency cycles may represent the most fascinating and promising approach to the study of allergy phenomena but thus far have not been thoroughly documented. Evidence of "microwaves" in ventilatory function have been recently detected in connection with bronchoprovocation challenges and their modification with premedication. High frequency oscillations may be particularly significant in the study of the molecular pathology of allergic diseases.[1]

Molecular chronobiology Developmental changes in immunologic variables, such as the temporary drop in serum IgA in infancy may be an example of time-related immunopathologic changes that may be associated with clinical allergy. A notable example of annual immunologic periodicity are the seasonal fluctuations in serum immunoglobulin E and in specific IgE antibodies that have been consistently observed in patients with pollinosis, allergic rhinitis and extrinsic asthma. There are also daily variations in serum IgG, IgA and IgM, as well as IgE that have been noted to occur during the peak of daily activity and may or may not have practical relevance.[2] Another observation, of possible clinical significance, is the 24-hour rhythm in nasal secretory IgA which appears to peak between midnight and 08:00 a.m. and seems unrelated to other circadian rhythms, such as the plasma cortisol cycle. In many instances, an existing abnormality in biological rhythms among allergic individuals may be found not so much in the activity of the cells and the quantity of the molecules participating in a reaction but in their internal *phase relationships,* that defines which quantitative or qualitative changes come first and which follow. Specifically, the factors that determine whether histamine release will or will not take place from sensitized cells, may be directly the outcome of a relative "desynchronization" of physiologic molecular and enzymatic modulation. When the initial bridging of IgE receptors on the surface of a mast cell takes place, it induces activation of methyl-transferases and also an increase in intracellular cyclic AMP.[1] The critical factor in these cases is the time/phase relationship between this increase in cAMP and methyl-transferase activation (Table 1). While a rise in intracellular cAMP suppresses calcium influx into the cell, phospholipid stimulation at the cell membrane enhances this ionic transfer. It is currently well recognized that modulation of calcium influx determines the phenomenon of mediator release. This release

Table 1 Critical time/phase relationships that affect anaphylactic mediator release.

Primary events:

Antibody (IgE) binding on sensitized cell. Antigen-antibody interaction and/or activation of IgE receptors.

Secondary processes [three alternatives]:

A. Stimulation – increase – of *cyclic AMP,* which suppresses phospholipid methylation, inhibits calcium influx and thus prevents the release of histamine.

B. Activation of *methyltransferases,* which stimulates phospholipid methylation, increase Ca^{++} influx and causes histamine release.

C. Activation of *proteolytic enzymes,* which may influence the reaction course towards either A, or B.

Histamine and other mediator release may or may not take place depending on what happens first: A, B, or C.

***Modified after Ishizaka[1,2]**

and the Ca^{++} as was magnesium transfer across the cell membrane are strongly under the influence of the exact time, in milliseconds, when enzymatic activation takes place, following immunologic or non-immunologic changes in cell-bound immunoglobulin E. Other biochemical events related to allergy, such as the rôle of histamine in controlling its own release and also in suppressing immunoglobulin synthesis through T-lymphocyte stimulation are characteristically time-dependent activities.[1] The relationship between serum levels of endogenous prostaglandin E, specific IgE antibodies and histamine release is also an example of a phase-dependent sequence of events. It may also be postulated that imbalance between prostaglandin E and prostaglandin F2alpha in some cases of asthma, as well as the direction of arachidonic acid metabolism towards the cyclo-oxygenase or lipoxygenase pathways can prove to be dependent on the time and phase relationships of particular molecules.

Time and treatment The correct timing of a therapeutic drug administration is a basic consideration in pharmacokinetics and in clinical medicine. Changes in the susceptibility of a patient to a defined dose of a pharmacologic agent in relation to circadian or other cycles may at times be as high as 50 per cent of the baseline and cannot be ignored. Even more important however than these "chronopharmacologic" considerations is the prompt exercise of correct clinical judgement in treating allergic problems optimally, never giving "too little too late"[9] but also avoiding the opposite mistake of overreaction and overmedication.

A new classical example of proper timing is the treatment of recurring nocturnal asthma with oral or inhaled adrenergic agonists, at bedtime. Although this may be sufficient in the majority of cases, long-acting oral theophyllines and/or corticosteroids may be required additionally. The same of course applies to the control of asthma and related problems that occur in the daytime, whether in relation to activity or to allergenic exposures or both.

The current wide availability of long-acting theophylline preparations has made it possible to control the symptoms of asthma and also, in most cases, to abolish the wide circadian fluctuations in peak expiratory flow that characterize "labile" cases. It is important to recognize that the metabolism of theophylline is not the same in the day and in the night and often a lower dose at bedtime may be sufficient, while repetition of the morning dose at night may be associated with more toxicity.

Some studies have shown also a time related variability in the activity of antihistamines in the treatment of allergy but the most prominent pharmacologic agents related to bodily rhythms are the corticosteroids. In fact, it was the well known circadian rhythm in adrenal cortical function that has led to the initial studies and subsequently to the widespread use of alternate-day systemic steroid therapy for asthma and related allergic problems. The 48-hour span between doses has been noted to control symptoms fairly adequately, while allowing the physiologic cycle in adrenal cortical function to persist undisturbed. Of course, the concern about side effects and maintenance of physiologic periodicity only applies to cases of long-term therapy for chronic or frequently recurring problems. In the case of acute emergencies, such as impending status asthmaticus, anaphylactic shock, generalized urticaria, laryngeal oedema and other acute allergic situations, *timing* rather than time is of critical concern. Delays of even a few minutes in the administration of proper treatment – be it epinephrine, antihistamines, corticosteroids, oxygen, hydration, etc. – can lead to fatalities while, on the opposite side, their timely administration reduces morbidity and mortality and will continue to serve as evidence that experienced clinical judgement is the most critical factor in the proper management of allergic diseases, acute and chronic.

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