

THE ATOPIC DANCE

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SUMMARY

The atopic march refers to the disorders that commonly occur together and track with age in a characteristic order, starting with atopic dermatitis often associated with food allergy, then inhalant allergy contributing to the development of asthma and then rhinitis. The implication of this model of the allergic march is that there is a linear progression from one manifestation to another, and a further assumption that there is a single predominant mechanism (of 'atopy' which may be defined as the susceptibility to becoming allergic) behind all the manifestations. New insights from the advent of molecular medicine indicate that many allergic diseases are better seen as syndromes comprising multiple phenotypes, with different gene/environment interactions and consequent endotypes. In addition, there are multiple contributing aetiologies to each 'syndrome' and complicated interactions between them are better visualised as causal networks, rather than as linear cause and effect. These factors and the variability of progression from one form of atopy to another are at odds with the concept of the 'atopic march'. We, therefore, suggest that the 'Atopic March' is an outdated concept which might be better considered as an 'Atopic Tango'.

'Atopy' was a term initially used to describe a group of conditions commonly associated with allergic responses and often running in families, namely, asthma, rhinitis and eczema. Now it is usually considered to be a predisposed susceptibility to developing IgE-mediated immune responses. The 'atopic march', sometime called the 'allergic march', refers to the natural history or supposedly typical progression of allergic diseases that often begin early in life. These include atopic dermatitis (eczema), food allergy, allergic rhinitis (hay fever) and asthma (see Figure 1). These conditions may occur on their own, but sometimes occur together and track with age in a characteristic order, starting with atopic dermatitis and food allergy, then asthma and finally rhinitis.¹

The implication of this model of the allergic march is that there is a linear progression from one manifestation to another, and a further assumption is that there is a single predominant mechanism (of 'atopy') behind all the manifestations.

Even accepting a linear process there are inaccuracies in the conventional presentation of progression. It is usually assumed that food allergy is a causative precursor of eczema. However, it is now clear that the commonest primary abnormality in eczema is a genetic defect in skin-

barrier function. This not only produces susceptibility to dry skin, keratosis pilaris and psoriasis but also to eczema. The same skin defect allows penetration of food and inhalant allergens thereby leading to allergic sensitisation. The subsequent progression to inhalant allergy, asthma and rhinitis is far more likely to follow a sequence from allergen exposure to sensitisation and initially rhinitis well before the onset of asthma. This has been well characterised in relation to the evolution of occupational allergen-induced airway disease (see Figure 2). There is good evidence that this sequence is also common in naturally occurring asthma.²

However, the assumption of linearity is also incorrect. In fact, the allergic 'diseases' are not a single disease with a united cause, pathophysiological mechanisms, progression or management! The allergic diseases are better seen as syndromes comprising multiple phenotypes, with multiple endotypes underpinning these phenotypes.

A syndrome may be defined as 'a set of medical symptoms and signs that consistently occur together or a condition characterized by a set of associated symptoms'. The word 'phenotype' originates in genetics discourse and is defined as 'the set of observable characteristics of an individual resulting from the interaction of its genotype with the

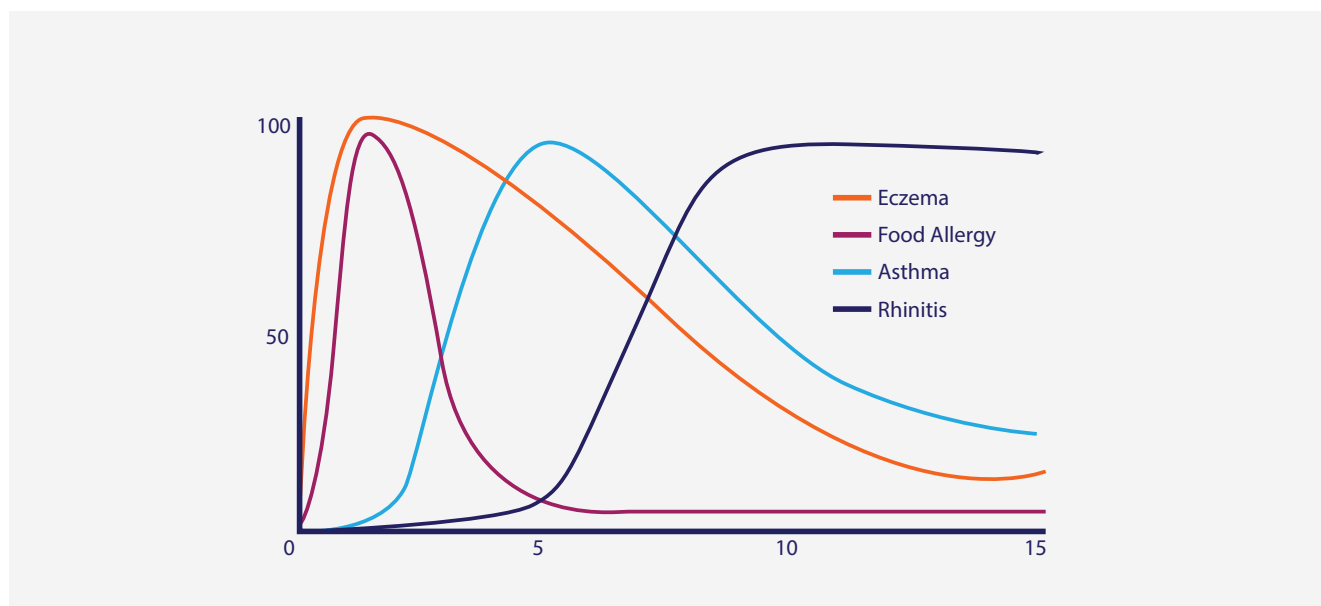


Figure 1: Diagrammatic representation of the 'atopic march' from birth to adolescence

environment'. Because multiple different phenotypes may be expressed by individuals with a single genotype, the meaning has broadened to refer to the multiple differing visible manifestations of what is often thought of otherwise as a single disease, that is, as a 'posh' word for differing clinical subtypes (or classifications) within a disease syndrome. 'Endotype' is a more robust term, defined as 'a subtype of a condition, which is defined by a distinct functional or patho-biological mechanism'.

The rise of molecular medicine and pathway-targeted therapies has led to an increased focus on pathophysiological mechanisms and a rising awareness that what we commonly refer to as 'diseases' are better visualised as a heterogeneous group of endotypes that look similar on a superficial level, but may evolve and respond very differently to various therapies.³

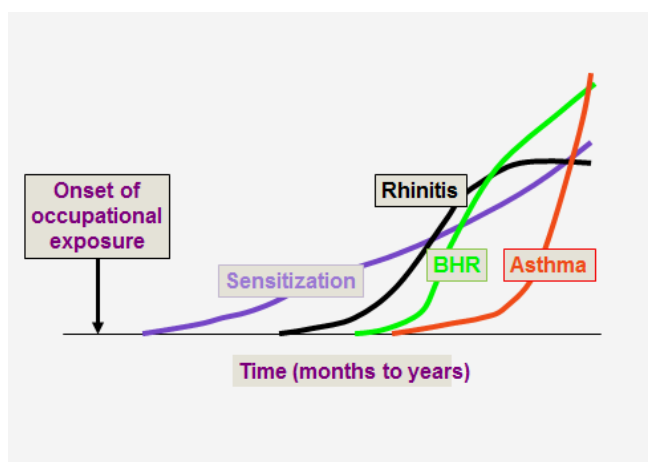


Figure 2: Sequence of events following occupational allergen exposure in susceptible subjects which leads to allergic sensitisation, allergic rhinitis and finally bronchial hyper-responsiveness (BHR) as a precursor to the onset of occupational asthma

The clinical definition of asthma as 'recurrent reversible airways obstruction' embodies a clear syndrome that covers many different sub-types. Older attempts at phenotyping asthma emphasised allergic and non-allergic asthma; however, more recent analyses cluster patients by other features, including age of onset, atopy and severity of airways obstruction, such as early-onset mild allergic asthma, later-onset asthma associated with aspirin intolerance or obesity, and severe non-atopic asthma with frequent exacerbations. Progress in endotyping asthma has been achieved in classifying asthma as predominantly eosinophilic or neutrophilic and in elucidating specific endotypes such as aspirin-exacerbated respiratory disease and allergic bronchopulmonary mycosis.^{4,5} Underlying endotypes are a range of genotypes affecting airway form and function including ORMDL3 and ADAM33. Polymorphisms in these genes are associated with susceptibility to asthma independent of atopy. They increase the risk of infant wheeze and maybe COPD but not necessarily atopic asthma. Separate genotypes, of which there are many, increase risks of allergic sensitisation independent of asthma. The ultimate expression of all these genotypes is affected by environmental modification of gene expression through epigenetic mechanisms (silencing or enhancement of gene expression through changes to chemical moieties attached to DNA sequences or the histone molecules around which DNA is wound), metabolic alterations and effects of the resident microbiome (metagenomics).⁶

This new vision of not only asthma, but also the other allergic conditions, acknowledges the multiple contributing mechanisms to these diseases. Moreover, it is common that as individuals progress, different mechanisms may be operative at different stages of a disease. For example, atopic dermatitis usually commences with a genotype that

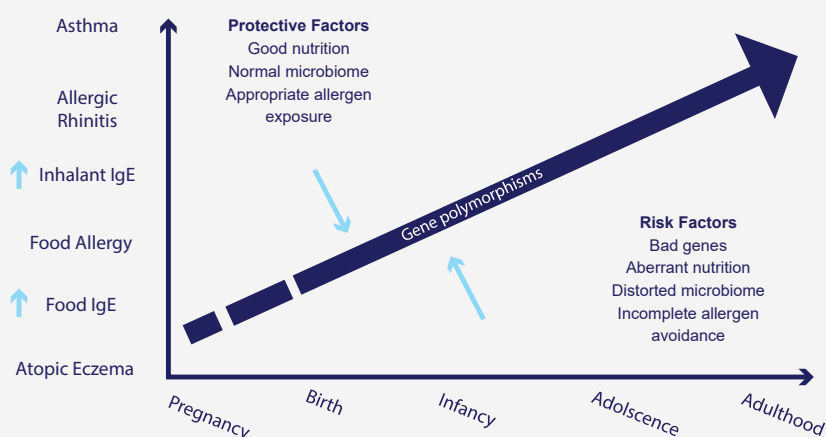


Figure 3: Protective and risk factors contributing to the evolution of allergic diseases across the life course

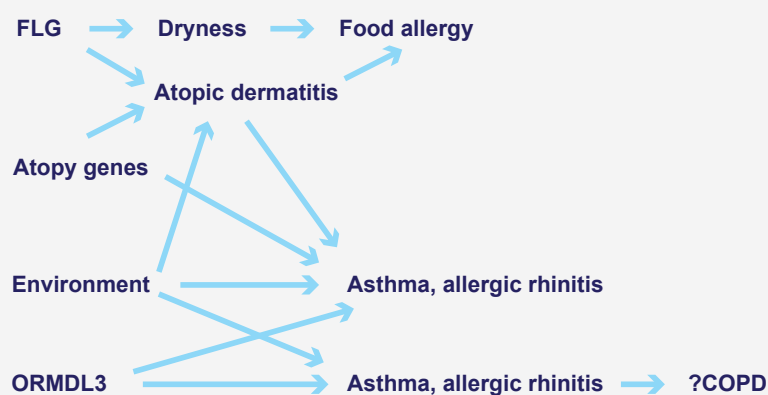


Figure 4: The Atopic Tango: Interaction between genetic, environmental factors and other allergic 'diseases' in allergy

predominantly manifests as a skin-barrier defect, of which polymorphisms in the filaggrin gene is most common, with increased trans-epidermal water loss and drying of the skin. As a secondary effect, multiple sensitisation may occur, including to both aero- and food allergens.⁷ The barrier defect and immune dysregulation contribute to impaired defence against pathogens, alteration of the microbiome and colonisation with pathogenic organisms, particularly *Staphylococcus Aureus*. This, in conjunction with the aberrant immune response may lead to sensitisation against *Staphylococci* or their toxins. In other individuals aberrant immune responses may be directed against fungal organisms such as *Malassezia Furfur*. In many individuals a degree of autoimmunity results with the production of antibodies against self-proteins.⁸

In most (IgE-mediated) allergic disease, sensitisation

occurs, followed by the establishment of the disease, episodes of exacerbation and progression of the pathological processes. However, it is important to consider that different associations, causative factors and mechanisms may be at play for each of these.⁹ The major categories that are operative are one's genetic makeup and environmental influences.¹⁰ Important subgroups within the genetic category include atopy genes, barrier genes and disease-specific genes. Environmental influences may be thought of as either protective (healthy microbiome, single nutrients, food and environmental diversity) or pro-inflammatory (abnormal microbiome, poor nutrition, toxins, advanced glycation end-products and others) (See Figure 3).

Some of the causative factors are very strong and clearly defined for specific endotypes of allergic diseases, yet allergy is quintessentially a multi-factorial disease with complex

causal networks (see Figure 4). There are numerous interactions between these mechanisms resulting in complicated relationships between genes and environment. In addition, sequelae of one mechanism may serve as an exacerbating or causative mechanism for a different manifestation of allergy.

The complex causal networks and lack of uniform progression from one manifestation of allergy to another, are at fundamental odds with the concept of the 'allergic march'. The progression of allergy is not linear and is not due to a single unified pathological mechanism underpinning all the manifestations. The connotations of the word 'march': 'a walk, especially by a group of soldiers all walking with the same movement and speed' or 'a piece of music with a strong, regular beat, written for marching to' is incorrect. The music of the dance of atopy is not a march. It has some features of a waltz in triple time performed by a couple turning rhythmically around each other as they progress around the dance floor.

However, we propose that the most appropriate descriptor is a tango danced by couples and characterised by marked rhythms, varied steps, unusual postures and abrupt pauses.

DECLARATION OF CONFLICT OF INTEREST

In the past two years, M Levin has received departmental support from Cipla, ThermoFisher, Aspen, Nestlé, Astra Zeneca, Astellas, PharmaDynamics, Novartis, MSD, Beiersdorf and Nutricia. The author has spoken for Cipla, Aspen, Astra Zeneca and Sanofi Aventis.

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This article has been peer reviewed.

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NOTICE OF ALLSA ANNUAL GENERAL MEETING

16H30 Saturday 16th September 2017

Boardwalk Hotel, Port Elizabeth

AGENDA

- Welcome**
- Minutes of previous meeting**
- Matters arising**
- Treasurer's report** Sarah Karabus/André van Niekerk
- Secretary's report** Shaunagh Emanuel/Di Hawarden
- Portfolio Reports**
 - Journal Eugene Weinberg/Di Hawarden
 - Research Sharon Kling/Refiloe Masekela
 - Education /Training Mike Levin
 - ALLSA Handbook Ahmed Manjra/Claudia Gray
- Reports by working Groups**
 - Journal Refiloe Masekela
 - Research Lindsay Archibald-Durham
- General**