

REVIEW

Allergy: the making of a modern plague

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Summary

Allergy is a modern malady. Only one hundred years ago, the term allergy was unknown and diseases subsequently identified as allergic in nature, such as hayfever, asthma and food intolerance, were routinely considered to be rare, non-fatal conditions primarily afflicting only the cultured and civilized classes of Western society. By the end of the twentieth century, however, allergic diseases were increasingly perceived by clinicians, the public and the media as widespread and potentially fatal conditions. In addition, allergies had fostered a distinct clinical specialty, generated new diagnostic and therapeutic strategies, and created a lucrative market-place for international pharmaceutical, cosmetic, food and cleaning industries.

The aims of this historical overview are: firstly, to demonstrate precisely how dramatically allergy has emerged as a global clinical, public health and socio-economic problem during the twentieth century; and secondly, to explore the origins and semantic elasticity of the term allergy since its introduction by Clemens von Pirquet in 1906.

This article suggests that allergy has become the archetypal modern disease of civilization, not only reflecting substantial changes in modern lifestyles but also resonating with broader political and cultural concerns about the environment at the turn of the millennium.

Introduction

‘When will we be able to define the structures that determine, in the secret volume of the body, the course of allergic reactions?’ [1]

In recent decades, scientists, clinicians and epidemiologists have discovered much about the nature of allergic reactions. At the turn of the millennium, we possess

detailed and sophisticated knowledge of the aetiology and pathogenesis of a variety of allergic diseases, the cellular and intercellular mechanisms (such as the roles of T cell subsets and interleukins) involved in allergic reactions, the geographical and historical spread of allergic diseases, the socio-economic impact of allergies, and the genetics of allergy [2]. In addition, pharmaceutical companies have developed a substantial arsenal of therapeutic substances and treatment protocols designed specifically to combat hayfever, control asthma, and relieve skin and food allergies. This rapid expansion of knowledge, improvements in clinical practice, and the increasing production and consumption of anti-allergy medicines together reflect growing medical, public and media preoccupations with what has sometimes been referred to as a ‘plague’ or ‘epidemic’ of allergic diseases afflicting modern civilization [3].

However, in spite of recent developments, allergy remains enigmatic. As Warren Vaughan, one of America’s leading allergists during the middle decades of the twentieth century, suggested many years ago, allergy is a ‘strange malady’, one that even at the start of the twenty-first century still embodies much that is mysterious and puzzling [4,5]. We have no clear understanding of the reasons for the rising incidence and prevalence, and in some instances, mortality of allergic diseases in modern societies, the specific aetiology of many allergic conditions in individual patients often remains elusive, the nature of the interaction between genetic and environmental factors requires greater elaboration, the precise links between somatic and psychological determinants of allergic reactions continue to elude the focus of modern biomedicine, and we remain ignorant of the evolutionary or teleological significance of allergic reactions. Perhaps more strikingly, both the precise scientific definition and the broader cultural meanings of the term itself remain problematic.

In this historical overview, I want to focus on three particularly striking features of the peculiar history of allergy. First, I want to demonstrate precisely how dramatically allergy has emerged as a global clinical,

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public health and socio-economic problem during the twentieth century. Secondly, I want to explore the origins and semantic elasticity of the term 'allergy' since its introduction in 1906. Finally, I want to suggest that allergy has become the archetypal modern disease of civilization, not only reflecting substantial changes in modern lifestyles but also resonating with broader political and cultural concerns about the environment at the turn of the millennium.

The origins of allergy

Although diseases now commonly regarded as allergic, such as hayfever and asthma, had been described and studied for many years before the twentieth century, their aetiology and pathogenesis generally remained obscure. The term 'asthma' had been used loosely to describe difficulties in breathing since antiquity. In general, however, asthma constituted merely a symptom, only inconsistently differentiated from other respiratory conditions, and routinely regarded as the pathological product of a variety of internal disturbances (within the nervous system, for example) and external insults [6]. It was not until the nineteenth century, when novel examination techniques, such as the stethoscope, were developed, that bronchial asthma began to acquire a more particular diagnostic meaning. In a similar fashion, hayfever, first described in 1819 by John Bostock (1773–1846), was for many years regarded as an idiosyncratic response to a wide range of non-specific stimuli [7,8]. Even after Charles Blackley (1820–1900) had successfully demonstrated that pollen, rather than heat, light, various odours or ozone, was the causative agent in 1873, hayfever was considered to be the product of a pollen toxin acting on the nose and eyes, analogous to the action of bacterial toxins in the newly established germ theory of disease [9,10].

In the early years of the twentieth century, medical approaches to hayfever, asthma, certain skin conditions and food reactions underwent a profound transformation. In 1906, Clemens von Pirquet (1874–1929), an Austrian paediatrician (Fig. 1), introduced the term 'allergy' to describe any state of altered immunological reactivity, whether giving rise to immunity or hypersensitivity:

'What we need is a new generalised term, which prejudices nothing but expresses the change in condition which an animal experiences after contact with any organic poison, be it animate or inanimate. . . For this general concept of *changed reactivity*, I propose the term *Allergy*. . . The term Immunity must be restricted to those processes in which the introduction of the foreign substance into the organism causes no clinically evident reaction, where, therefore, complete insensitivity exists.' [11]



Clemens von Pirquet (1874–1929).

The main aim of von Pirquet's sophisticated philosophical approach was to provide a rational semantic framework within which to analyse and classify various immunological phenomena, including immunity against pathogens, serum sickness, anaphylaxis and other hypersensitivity reactions that had been first described at the turn of the century [12,13]. Von Pirquet's work drew upon, and indeed substantially contributed to, research in the nascent field of immunology and growing scientific interest in exploring the phenomenon of biological specificity [14–16]. However, it is important to recognize that, apart from the link between vaccination and serum sickness first explored in depth by von Pirquet and Bela Schick (1877–1967), the study of immunological or allergic reactivity initially attracted little clinical attention, remaining an esoteric research area within experimental physiology [17]. Even the early recognition that hayfever and asthma shared pathological features both with each other and with the phenomenon of experimental anaphylaxis in animals did little to stimulate clinical curiosity, since both diseases were regularly regarded at that time as relatively rare and

certainly non-fatal conditions [18,19]. Although the incidence of hayfever was clearly rising, it was essentially understood to be an uncommon and mild affliction limited largely to the educated or civilized classes and races [9,20]. Similarly, for many medical authors, asthma constituted only a minimal threat to health and longevity.

Compared with the more pressing public health, socio-economic and political problems associated with mortality from infectious diseases, concerns about the fitness of fighting populations, and the high infant and maternal mortality levels experienced by most European countries at the start of the twentieth century, allergic diseases such as asthma and hayfever remained peripheral. Nevertheless the detailed work of von Pirquet and others in elucidating the immunological mechanisms involved in asthma, hayfever, and food allergies in particular provided the seed from which clinical allergy began to blossom on both sides of the Atlantic in the early decades of the twentieth century.

Clinical practice and the definition of allergy

Growing clinical interest in immunologically mediated diseases both in America and Britain was stimulated not only by the work of von Pirquet and his contemporaries but also by the recognition that the incidence of hayfever was rising and by the elaboration of novel therapeutic techniques, notably allergen immunotherapy or desensitization first devised by John Freeman (1877–1962) and Leonard Noon (1877–1913) in 1911 [21,22]. However, it is noticeable that as the study of allergic diseases became a legitimate focus for both laboratory researchers and clinicians, the meaning of the word began to change. Increasingly, the term 'allergy' was no longer used to denote any form of altered immunological reactivity, as originally proposed by von Pirquet, but was applied instead only to those immune reactions that resulted in tissue damage, otherwise referred to as hypersensitivity.

In North America, the first societies for clinicians and scientists specializing in the study and treatment of allergic diseases were established in the 1920s. The first meeting of the Western Society for the Study of Hay Fever, Asthma and Allergic Diseases was convened in San Francisco in June 1923. Two years later, the Society for the Study of Asthma and Allied Conditions held its first annual meeting in Washington. In December 1943, the two societies merged to form the American Academy of Allergy [23]. From the start, both societies focused on promoting and disseminating research into hypersensitivity. Indeed, according to an editorial comment in the opening issue of the *Journal of Allergy* (first published by the Society for the Study of Asthma in 1929), the aim of the journal was to provide 'a medium for the presentation of papers concerning the clinical aspects of specific hypersensitiveness

in human beings' [24]. The editors' use of the term allergy in this way was supported elsewhere. In 1933, Arnold Rice Rich (1893–1968), renowned for his work on immunity and hypersensitivity related to tuberculosis, distanced himself from the original broad definition of allergy:

'Regardless of what Pirquet's concept of the term allergy may have been, although there is no strict uniformity in the usage of the word at present, nevertheless allergy to-day in the minds of most medical men is synonymous with acquired hypersensitiveness, as any examination of the many papers published every year on the subject will at once disclose; and it is in this sense only that I shall use the term in the present paper.' [25]

By the 1930s therefore it would appear that the term 'allergy' had become a convenient and euphonious shorthand for a variety of related immuno-pathological phenomena, generally referred to as supersensitivity or hypersensitivity, but also frequently embracing the concepts of anaphylaxis and atopy (a term introduced by Arthur Coca and Robert Cooke in 1923) [26]. However, as the titles of both American societies and of the papers published in early issues of the *Journal of Allergy* demonstrate, in practice the interest of clinical allergists in the States was generally focused even more specifically on a set of conditions with similar pathologies mediated primarily by a specific type of antibody, referred to as reagin (designated IgE in 1967), and by the release of certain chemical mediators: in the clinic, American allergists dealt largely with hayfever, asthma, urticaria, bee stings and food reactions.

In Britain, the development of clinical allergy was more gradual and more piecemeal. For much of the early twentieth century, one of the prime sites for the study and treatment of allergic diseases in England was the Inoculation Department (and later the Allergy Clinic within that department) at St Mary's Hospital in London, where a number of leading British allergists (such as John Freeman and A. W. Frankland) trained and worked. Other allergy clinics were established elsewhere throughout the country, sometimes with the support of the Asthma Research Council, which had been founded in London in 1927. However, there was no formal organization for specialists in immunological diseases until the British Association of Allergists was established in 1948. This organization became the British Allergy Society in 1964 and finally the British Society for Allergy and Clinical Immunology in 1973, shortly before which it had begun publishing the leading British journal in the field, *Clinical Allergy*.

Although the precise chronology of development in Britain differed from that in the States, the focus of British clinicians in practice closely mirrored that of their North

American counterparts. By far the majority of patients tested and treated in allergy clinics during the middle decades of the twentieth century, when clinical allergy was blossoming, were referred to allergists for advice on the diagnosis and management of hayfever, asthma, idiosyncratic reactions to food and some skin conditions. For British specialists, the meaning of the term 'allergy' had therefore similarly been narrowed from von Pirquet's broad conception to a much more limited notion of a specific type of hypersensitivity.

Significantly, this trend to restrict the use of the term in the clinical setting has been accentuated in recent years. In their textbook of immunology published in 1997, for example, Mark Peakman and Diego Vergani noted that:

'Allergy. . . is a term much abused. For our own purposes it can be defined as a state of heightened reactivity of the immune system to foreign substances. For the sake of clarity, we will also confine the use of the term "allergic" to those reactions that are initiated when mast-cell bound IgE interacts with its target antigen, known as an allergen.' [27]

In a recent supplement of *Nature* devoted to allergy and asthma, William Cookson similarly pointed out that, for pragmatic purposes, the terms 'allergy' and 'atopy' had become synonymous:

'Common usage has meant that the original broad meaning of allergy is lost, and the terms "allergy" and "atopy" are often used interchangeably, which has been the practice in this supplement.' [28]

However, from a historical perspective, it is striking that while many clinicians and scientists were attempting to define 'allergy' in more precise scientific terms, the word was also being increasingly used in a range of imprecise and unsubstantiated ways and being applied indiscriminately to symptoms and diseases often with no apparent immunological basis. Thus, early issues of the *Journal of Allergy* included papers on migraine, headaches, epilepsy and a miscellany of conditions sometimes subsumed under the heading 'minor allergy'. More recently, it has become commonplace for a variety of complementary practitioners and their patients in particular to identify a range of non-specific symptoms (such as headaches, abdominal pains, fatigue, fibromyalgia, hyperactivity, loss of appetite and so on) as allergic in origin [29].

This vague and elastic use of the term did not pass unnoticed, or indeed unchallenged, by allergists and immunologists. In 1950, in the foreword to his influential but rather idiosyncratic book, *Hay-fever: A Key to the Allergic Disorders*, John Freeman expressed his dissatisfaction with the term allergy:

'I am not proud of using the phrase 'Allergic Disorders', even when decorated with inverted commas, because the word allergy is in such a linguistic mess. . . a year ago at a meeting in Oxford to discuss the proposed 'Association of British Allergists', I heard enthusiastic but indiscriminating medical men boasting that 'allergy covers nearly all medicine'; so I started to weed the word allergy out again as too dangerous for general use. . . I believe the word 'allergy' obscures more than it illumines in medicine.' [30]

While Freeman proposed the term 'toxic idiopathy' instead of 'allergic disease', and 'idiotoxic' rather than 'allergic' (pointing out that 'idiotoxic' could at least 'only mean what I mean it to mean'), other commentators preferred to distance themselves completely from the vagaries of contemporary usage and argued for a return to the conceptual clarity originally provided by von Pirquet. Thus, in the first edition of their monumental *Clinical Aspects of Immunology*, first published in 1963, P. G. H. Gell and R. R. A. Coombs began their innovative classification of hypersensitivity with the following plea:

'In the minds of many practising physicians, the term 'allergy' though a useful and indeed a fashionable one, implies no precise concept; it is used as a rough and ready label for all conditions in which the active reaction of a patient's own tissues, rather than a disordered physiological process like cancer or diabetes, or the direct damage by an invading organism determines the manifest lesions of the disease, or at least a large part of them. . . To evade this source of confusion, and to set out the newer knowledge to the greatest advantage, it is essential to build on a sound semantic foundation. It is our feeling that this is most easily achieved by going back to the original concept of von Pirquet. . . Thus the term 'allergy' should be taken to mean the specifically altered state of a host following exposure to an allergen. This altered biological state or allergy has in itself no implied connotation as regards the production of either clinical hypersensitivity or clinical immunity.' [31]

Gell and Coombs' considered approach proved to be in vain. As allergists and immunologists attempted to define allergy more precisely (whether in terms of IgE-mediated diseases or in terms of more general altered biological reactivity), the term 'allergy' was being invested by the public and media with a widening range of metaphorical meanings. In the late twentieth century, in addition to being allergic to all manner of environmental stimuli, people could be allergic to work, allergic to Mondays, or allergic to their mothers-in-law. In 1997, Jacques Delors, former President of the European Commission, reportedly accused

German politicians 'of having an allergy towards southern European states such as Spain and Italy' [32]. By the turn of the millennium, in spite of dramatic developments in clinical understanding of the aetiology, pathogenesis and indeed treatment of allergy and allergic diseases, allergists had nominally lost control of their subject.

Allergy in the new millennium

In 1995, Jeff Noon published a highly acclaimed science fiction, or cyberpunk, novel entitled *Pollen*. Set in a futuristic Manchester during the first nine days of May, and motivated both by Noon's personal experience of hayfever and by his knowledge of the AIDS epidemic that was escalating during the early 1980s, the backdrop for the action in *Pollen* comprises the gradual invasion of reality by a murderous strain of pollen leaking through from the dream world [33]. Although the novel is clearly shaped primarily by Noon's expansive imagination, it strikingly reflects the ubiquity and depths of modern fears about the proliferation of allergic disorders. Unlike the situation at the start of the twentieth century, when allergy constituted little more than an intellectual puzzle for a select band of European clinicians and experimental physiologists, by the start of the new millennium allergic diseases had emerged as a major global clinical, public health and socio-economic problem, and as a perpetual source of public, political and media interest.

The spectacular contrast between allergy at the start and end of the twentieth century is evident at a number of levels. In the first instance, it is clear that the incidence and prevalence of allergic diseases have risen dramatically during the course of the century. By the 1990s, approximately 20% of the British population apparently suffered from some form of allergic (that is, atopic IgE-mediated) disease, one in seven children suffered from asthma, and one in 10 children had allergic eczema. Such figures were substantially higher than those recorded only 30 years earlier. At the same time, it would appear that since the Second World War allergic reactions have not only become more diverse (with a rapid increase in the range of potential allergens) but also more dangerous: more frequent deaths from asthma, bee stings, and nut allergies, for example, have prompted major revisions in the delivery of health services, stimulated the establishment of educational charities (such as the Anaphylaxis Campaign), and regularly attracted media attention.

As a result of rising morbidity and mortality, allergies have emerged as a major public health and socio-economic problem in both developed and developing countries. In the early 1980s, the financial cost of allergic diseases in the United States (in terms of physician time, hospitalization and medication, but excluding time off work) was

estimated at \$1.5 billion. By the mid-1990s, that figure had risen to \$10 billion [34]. Currently, the estimated cost to the National Health Service of treating 3.4 million asthmatics in Britain is £23 million. Although more studies are needed to evaluate the impact of allergic diseases elsewhere in the world, it would appear that allergies are also increasing in developing countries. One response to these epidemiological and economic transitions has been the establishment of national and international committees, congresses and symposia (such as those of the World Health Organization and the European Academy of Allergy and Clinical Immunology) committed to researching and combating the plague of modern allergic diseases.

As allergies emerged as an important focus for clinicians, epidemiologists and health care systems in the modern world, they also generated an expanding market for the industrial sector. Although some pharmaceutical companies (notably Parke Davis and Co.) had been subsidizing the development of new treatments for hayfever since the early twentieth century, after the Second World War the production of drugs for treating asthma and allergies both consumed and generated massive financial resources. Similarly, in recent years, allergic reactions have attracted investment from the cosmetic and cleaning industries and encouraged the elaboration of more careful standards of production and labelling in the food and retail industries. At the turn of the millennium, allergy means money.

Conclusion

Almost exactly 200 years ago, Thomas Beddoes, a physician from Bristol, lamented the impact of civilization on health by pointing out that: 'Our chronic diseases are of our own creating.' [35] At one level, Beddoes was merely reiterating a traditional, indeed ancient, belief in the close empirical relationship between lifestyle and environment on the one hand, and health and disease on the other. At the same time, Beddoes' words also reflect an awareness that certain diseases have attracted medical and public attention at certain times not only as a result of their prevalence or severity but also as a consequence of their social, political and cultural utility. When Beddoes was writing, gout and nervous diseases stimulated particular interest not merely because of an apparent increase in the numbers of cases but, more pertinently, because the perceived class distribution of both conditions served to reinforce class boundaries that were being threatened by the emergence of an affluent industrialized, capitalist, consumer society. In the eighteenth century, gout became a badge of honour, indicative of social status and good breeding, serving to separate the real aristocracy from the nouveau riche, or old money from new [36].

The proliferation of allergic diseases in the modern

world can similarly be seen as the product of both an economy and a culture. At one level, the current epidemic of allergic diseases is clearly linked to modern civilization. The birth of the consumer society in the Western world during the eighteenth and nineteenth centuries, and its global dissemination during the twentieth century, brought with it substantial changes in both indoor and outdoor environments and in our lifestyles. Changing levels and patterns of industrial and traffic-related pollution, shifts in diet, the introduction of double glazing, carpets and central heating, changing family size, increasing time spent indoors on computers or watching television, and modern standards of hygiene and medical care (such as immunizations and antibiotic use) have all been implicated in the eruption of allergies in modern times.

Yet, while allergic diseases appear to have been generated largely by a changing environment, the roots of current preoccupations with allergy can also be traced to the particular political and cultural context of modern society. In the late nineteenth century, hayfever (like gout before it) was regarded as indicative of social, racial and intellectual superiority, supposedly setting the British apart from their European competitors [20]. More recently, allergy has served a different political purpose. Since the publication of Rachel Carson's *Silent Spring* in 1963, the environmental movement has been warning the Western world of the dangers of unfettered production and consumption of natural resources [37]. The emergence of allergy as a direct consequence of the civilizing process has been used to strengthen environmentalist opposition to modernity, to reinforce doubts about the benefits of progress, and to underwrite radical critiques of modern orthodox medicine.

It is ironic that at precisely the moment when allergy has become a major global political and socio-economic concern, clinical allergy in Britain at least has undergone a retrenchment of services. The reasons for what could be regarded as a crisis in clinical allergy at the turn of the millennium are complex and are linked partly to stringent, and controversial, controls imposed on the practice of immunotherapy following the intervention of the Committee on Safety of Medicines in 1986 [22]. The crisis may also be a product of the manner in which allergists have to some extent been forced to relinquish control of both the definition and indeed the treatment of allergy to a variety of alternative and competing practitioners and commentators. In responding to this crisis, the challenge facing clinical allergists of the future will not simply be to define more rigorously 'the structures that determine... the course of allergic reactions' [1], but to recognize, engage with, and shape the immense political, socio-economic and cultural investment in the notion of allergy in the modern world.

Acknowledgements

I am grateful to the Wellcome Trust for funding the research on which this article is based.

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