CHAPTER FIVE

Germs, Vaccines, and the Rise of Allergy

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> The state of allergy is bounded on the north by the internist, on the east by the dermatologist, on the south by the rhinologist, and on the west by the pediatrician. In fact, this state has been carved out of the territory originally within the confines of the surrounding states and its borders are still ill defined. A great deal of argument, sometimes acrimonious, is going on continually as to the claims of territory by the surrounding states and even the right to separate statehood is opposed by some of the more pugnacious neighbors …[1]
>
> – J. Harvey Black, President, American Association for the Study of Allergy, 1935.

An Austrian physician, Clemens von Pirquet, coined the term 'allergy' in 1906 to describe all of these forms of 'altered reactivity', ranging from what we think of now as allergic diseases (asthma, hay fever, hives) to various idiosyncratic responses individuals had after vaccinations, and, finally, the natural immunity following many infectious diseases.[2] In the first decades of the twentieth century, the nascent allergy community used the terms 'allergy' and 'reaction' to describe any immune response to a substance to which an individual had previously been exposed, encompassing most of what we now think of as clinical immunology.

This paper situates the nascent medical specialty of clinical allergy in Europe and North America, describes its approaches to the diseases of asthma and hay fever, and points to ways in which their theory and practice initially had strong continuities with bacteriology and natural history, in both laboratory techniques and the physiological ideas that inspired them. While immunologic theory and allergy immunotherapy diverged from these origins, practice of allergy in the lab continued to be strongly linked to theories of infection, and in the clinic to medical geographical discussions about climates of health and disease. The practices of allergy immunotherapy developed into a new body of practice and a new set of understandings about the immune system, but the first attempts at analysis of the asthmatic's sputum and development of pollen antitoxins were firmly in the tradition of microbiology, based on understandings of disease which developed from invading organisms and their poisons. The idea that the problem could be the host's immune system arose through the development of allergy vaccines, but was not the vision that initially inspired them.

As part of the growth of interest in the history of immunology, there is now a growing literature on the history of asthma and allergy, and intellectual histories of theories and experiments which advanced modern understandings of the disease have recently been supplemented by broader scientific, social, and environmental histories. Mark

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Jackson's work on the history of allergy in Britain explores the foundations of allergy in immunology and the social place of allergy within the British medical profession and the wider community.[3] Gregg Mitman's environmental history of asthma and allergies in the United States is characterized by his focus on place in case studies of hay fever in the White Mountains, asthma in the Rocky Mountains, and ragweed as an ecological scourge of disturbed environments.[4]

Building on this literature, this paper attempts to create an historical bridge between the laboratory traditions of microbiology and immunology and the medical geographic traditions of climatological medicine as they transformed the understanding and treatment of asthma and hay fever (later called allergic rhinitis) in the decades just before and after 1900. Following up on an earlier study of the construction of allergen-free indoor environments, in which allergists fought germs by adopting modernist architectural trends, the current paper emphasizes the impact of germ theory on asthma and the emergence of theories of allergy and the use of the techniques and ideas of bacteriology in the development of allergy vaccines.[5] While there were multiple candidates for microscopic causes of asthma and hay fever, including bacteria, coils, and crystals found in the sputum, pollen soon emerged as the most important of these tiny threats to the nose, throat, and lungs. As a microscopic cause of asthma and hay fever, pollen linked microscopic methods with older traditions of geographic medicine.

Before the beginning of the twentieth century, symptomatic relief for asthma and hay fever consisted principally of change of climate and a variety of symptom-relieving drugs including caffeine, opiates, cocaine, and tobacco. Between 1900 and 1950 a small group of physicians sought to replace climatic therapy, working to sever the persistent link between disease and place. In particular, through an ambitious and highly contested set of strategies they sought to adapt the allergic or asthmatic individual to any climate he or she chose through modification of the patient's local environment and his or her immune responses. In so doing, they established both a medical specialty (clinical allergy) and a distinct mode of medical practice that included a detailed analysis of the patient's home environment and occupation, skin tests for specific allergens, and a new form of desensitization therapy (through vaccinations). Their methods held out the possibility for a multi-dimensional technical fix to a refractory clinical dilemma.

Immunology also offered a scientific explanation for the clinical problem of idiosyncrasy. Until the late nineteenth century, physicians used the principle of individual idiosyncrasy to explain observations that some patients were sensitive to certain substances, including horses, cats, roses, and hay, which had no effect at all on the vast majority of people.[6] Detailed explanations of idiosyncrasy were produced in fields as diverse as heredity, immunology, neurobiology, and psychology, all of which attempted to explain why individuals exposed to the same disease-causing stimuli sometimes developed immunity and other times illness.

The field of allergy has been rooted in two distinct traditions: the first, a medical geographic approach to observing the topographies of diseases and their local and regional causes, and second, a vision of the human body and its responses to bacteria and other substances arising from the traditions and practices of germ theory. These two sets of ideas merged in the pollen theory of the cause of hay fever and asthma, which used geographic arguments about pollen distribution to explain the efficacy of travel in mitigating symptoms, and analogies between bacteria and pollen to explain

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the mechanisms of disease. In the first section, we explore the place of asthma and hay fever under the emerging germ theory of disease in the final decades of the nineteenth century. Next, we look at the pollen theory of hay fever and asthma and how it links these new unseen agents of disease with the already established climates of health and illness. Germ theory and pollen studies combine in the creation of pollen vaccines, which are no longer seen as straightforward prophylactics against attacking agents such as bacteria, but instead as modifying the body's immune reactions in myriad ways. This transition from vaccine as booster for natural immunity to modifier of the immune response happened gradually in the laboratories where it was first explored. Finally, while the vaccine treatments for asthma and hay fever attempted to free the sufferer from dependence on favored healthy places, they required the physician to learn the seasonality and geography of pollen distribution in order to use the therapy effectively.

Microscopic Causes of Disease

By the mid-nineteenth century, improvements in glass manufacture and precision instrument manufacture transformed microscopes from expensive custom-made instruments to mass-produced tools available to a wide body of researchers, facilitating first microscopic studies of tissue structure and disease, and ultimately the discovery of microscopic causes of disease. The age-old debates about spontaneous generation and Louis Pasteur's work on fermentation led to extensive use of the new microscopes to study microbes in the air and in the water. From the 1860s to the 1890s, investigators, at first in German and French laboratories, discovered microscopic organisms that they linked to many major animal and human diseases – in short order the bacterial causes of anthrax, cholera, diphtheria, and tuberculosis were identified. After a few spectacular successes, the search expanded, and a race began in which thousands of researchers around the world sought explanations under the microscope to account for many poorly understood diseases. The next stage was for a whole generation of scientific and medical workers to learn to see – and to interpret what they would find – under the 'scope. In these newly-revealed worlds, researchers had to relearn the normal anatomy and physiology that they had formerly known at the level of the naked eye. What were normal findings in blood and phlegm? What were uncommon but healthy variants? And finally, what were clear signs of disease?[7]

As many historians have shown, the germ theory of disease altered both medicine and society, changing the ways that people thought about their bodies and the world around them.[8] The existence of germs changed the way people thought about all diseases. The question, 'Could this be caused by an unknown germ?' had to be asked, even if the answer was ultimately, 'no'. Researchers quickly found that bacteria were everywhere, on the skin, in the mouth and nose, as well as on glasses, plates, and myriad everyday objects. The presence of bacteria in and on the bodies of apparently healthy people presented a challenge to linkages between germs and disease which had to be explained – either these people were immune to these bacteria, or these particular bacteria were not ones that caused disease. The challenge faced by these researchers and their contemporaries was in establishing causality. If a microbe was found in the phlegm of a patient with a disease, did that prove that it was the cause? What about the bacteria found in those apparently perfectly healthy? Koch's postulates, promulgated by the leading German bacteriologist,

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became the gold standard for proof that a microbe was the cause of a disease, including isolation of the suspect microbe, growth in pure culture, then reproduction of the disease by exposing a new person to the bacterium.[9] While suited for these narrow purposes, Koch's principles failed to explain the laboratory anomalies of microbes without disease, disease without microbes, and the coexistence of individual microbes with a host of different diseases. These puzzles fed debates about heredity and predisposition, infection and resistance, and the new science of immunology.[10]

Coils, Crystals and Bacilli

Clinical observations that 'animal emanations' from horses, cats, and other creatures caused asthma in some patients led researchers to search for microscopic elements that these animals released, whether germs or otherwise.[11] The most compelling studies, though, came from the examination of the sputum of asthmatics, which showed bacteria, crystals and spiral forms which appeared to be specific to asthma. Circumstantial evidence also came from the discovery of bacteria related to other respiratory diseases. Diphtheria and its associated toxin became a microbial success story when antitoxin started saving children's lives. And while asthma and consumption were frequently seen as distinct diseases before the tubercle bacillus was discovered in 1882, they had been just as often seen as part of a spectrum of disease, as conditions which could transform into one another, or at least as related diseases of the lungs which could benefit from the same treatments. Both diseases were sometimes thought to be caused by the same diathesis, with weak lungs manifesting as asthma in one family member and tuberculosis in another. Most of all, the laboratory orientation that had placed all diseases under the microscope led researchers to search for causes of asthma in the copious, thick sputum produced by its sufferers.

In 1860, when Henry Hyde Salter published his authoritative monograph on asthma, he reviewed the leading theories on the causes of asthma from the eighteenth and nineteenth centuries.[12] He reviewed theories of nervous spasm or paralysis of the bronchi, irritating mucous which caused cough and wheezing, and toxins in the blood, as well as arguments that asthma is not a specific disease at all. Absent from Salter's discussion, but present in monographs on asthma from the 1870s and 1880s, was a detailed microscopic analysis of the asthmatic sputum. In 1853, Jean-Martin Charcot, best known for his work as a pathologist and his descriptions of neurological diseases, published a paper on hexagonal crystals seen in the blood of a person with leukemia and in the sputum of someone with bronchitis.[13] In 1870 Ernst von Leyden expanded on Charcot's observations, arguing that the crystals caused mechanical irritation to the bronchial lining, directly causing the characteristic asthmatic wheezing and spasm.[14] Heinrich Curschmann disagreed with von Leyden, arguing that it was not the crystals but the thick mucous which he noted sometimes came out in the sputum in thin coils which led to difficulty of breathing in asthma.[15]

Other authors pointed to the frequent findings of bacteria in the sputum as well as in the mouth and nose. These bacteria, however, lacked specificity for asthma, being commonly found in other diseases and in the absence of disease. One group of authors explained, 'The number of streptococci in the nasal secretion of hay fever patients greatly exceeds that in the secretion of normal persons. Often streptococci were present in pure

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cultures in the case of hay fever sufferers', which implied a claim of causation, in that pure cultures were a requirement of Koch's postulates.[16] The authors went on to say that '*while there are not enough data on hand to permit the assignment of an etiological role to the streptococci found in the nasal cavities of hay fever patients,* these observations certainly tend to compromise the pollen theory of hay fever and should stimulate renewed investigations of this interesting malady'.[17]

British physician J.B. Berkart analysed these debates in an 1889 monograph. He advocated the bacterial origins of asthma based on his observations of the inflammatory quality of the mucous during an attack of asthma, and because he felt that a self-reproducing bacterium could explain how asthma could affect the entire body and progressively worsen for days:

> The clinical peculiarities of Bronchial Asthma plainly indicate the nature of their exciting cause. As has above been shown, the pathological process involved is a progressive form of inflammation … The sero-fibrinous exudation becomes more and more fibrinous, where such is wont to occur; and the consequent mechanical interference with the respiratory function now constitutes the most striking of all its symptoms. No mechanical nor chemical irritant – no foreign body, no abnormally high nor abnormally low temperature, no vaso-motor neurosis, nor anything else, that has hitherto been alleged as a provocative of the disease – can possibly give rise to such a series of phenomena. None of them can exert its injurious influence beyond its immediate point of impact … The agent, endowed with such properties, must necessarily be one, that is capable of reproducing itself. Suspicion, therefore, attaches itself to the various microorganisms, which have previously been described … It shall, at once, be conceded that the mere presence of a micro-organism, however constant it may be, proves absolutely nothing as regards its pathogenic nature. Nor would it serve any useful purpose to refer here to the failures, which attended my numerous attempts to satisfy, as far as possible, the postulates of bacteriological science, in order to arrive at some decision on that point.[18]

Berkart's qualifications about the problem of satisfying Koch's postulates in asthma highlight the difficulty of making either a definitive case for a bacterial cause for disease but also the challenge of dismissing such a theory when it was so strongly held. The bacterial candidates for the causation of asthma eventually faded from favor as the pollen theory of asthma and hay fever was widely adopted. Likewise, the Charcot-Leyden crystals and Curschmann spirals took on the status of curiosities rather than causal agents.

William Osler's 1892 textbook of medicine offered a learned observer's compromise on this debate, explaining the appearance and disappearance of Curschmann spirals and Charcot-Leyden crystals as pathologic markers of the length of an asthmatic attack.[19] First, the sputum appeared as Lännec's perles, which could often be unfolded into collections of Curschmann spirals. Then, in two to three days, as the mucous hardened and decomposed in the bronchial tubes, the Charcot-Leyden crystals would form. These findings, while characteristic of the sputum in an attack of asthma, were seen not as the cause of the disease but its consequence.

Bacterial theories about the origins of asthma persisted, with periodic case reports and discussions in the literature, but the dominant explanations at the end of the nineteenth century were of nervous excitement and pollen intoxication. The evidence for bacterial

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explanations was ambiguous, but was best demonstrated by the empiric use of antiseptic inhalers to treat the disease based on the new practice of antisepsis for surgery, which Joseph Lister introduced through his use of carbolic acid in 1869.[20] The treatment was promoted for lung diseases like asthma, bronchitis, and catarrh, as well as influenza and consumption with substances like carbolic acid, phenol, nitric acid, creosote, benzoin, tar extracts, and chlorine inhaled for the purpose of disinfecting the lungs. [21] The use of caustic and acidic inhaled antiseptics to treat asthma continued into the 1920s, long after researchers stopped publishing on possible bacterial causes of asthma, illustrating the distance that often separates medical theory and pharmaceutical practice. But the microbial vision proved important in thinking about pollen, 'animal emanations' and other causes of asthma and hay fever. If these were not infections with living organisms, could they be mediated by some kind of toxin, or did they work in another way?

Pollen, Infusoria and Toxins

Pollen, on the other hand, has had a longer and more successful career as a microscopic cause of asthma and hay fever, as it linked microscopic methods with older traditions of geographic medicine.[22] Pollen explained the seasonality of asthma and hay fever in some patients, the problem of 'rose cold' as well as much of the clinical lore about which places were safe and dangerous for those with asthma and hay fever. The precise mechanism by which pollen produced its symptoms of burning of the eyes, cough, sneezing, congestion, and in some asthma, however, remained uncertain.

The first studies linking pollen to asthma and hay fever were published in the 1870s, in the midst of the discovery of microbial causes of many diseases.[23] Pollen grains appeared to fit smoothly into this new vision of disease from unseen attackers, leading to an explanation of hay fever and asthma as 'pollen poisoning'. Pollen theory explained both the seasonal and geographic features of hay fever and asthma, and allowed for predictions of when and where patients could expect to be free of symptoms. Pollen maps supported the old wisdom that mountains and seacoasts were best for asthmatics, while reducing that clinical observation to a single numerical pollen count. Questions would follow about why some people were susceptible while the majority of the population was not, about the identity of a particular pollen toxin or group of toxins, and innumerable other details. But in the beginning, pollen counters and pollen maps explained much about patterns of illness, and pollen soon formed the foundation of a new set of methods for testing and treatment based on theories of allergy.

Unlike the Rocky Mountains and Desert Southwest, which became the favored new homes for many asthmatics, the White Mountains of New Hampshire became a treasured retreat during the summer and early fall, a gathering place for those asthmatics and hay fever sufferers wealthy enough to take a vacation, and who could also afford the long and arduous trip by ship, rail and carriage.[24] For a significant number of the Bostonians, New Yorkers, and Philadelphians who annually turned to the small towns of the White Mountains as summer retreats from work and city life, these places also afforded relief from their sneezing, wheezing, and misery at home.[25] The United States Hay Fever Association, founded in Bethlehem, New Hampshire, in 1874, dispensed advice about such areas to its members, who consisted primarily of sufferers of hay fever and 'hay asthma' (for those who had both sneezing and shortness of breath) and

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interested physicians. A kind of self-help organization, the group met to discuss hay fever and share their experiences with treatments. They combined their findings and produced official tables that, like weather reports, offered the reader an idea of the sort of pulmonary responses they could anticipate in their new locale. Their annual *Manual of the US Hay Fever Association* included as a regular feature a list of places members had visited and been 'exempt' from symptoms. The table from 1892 shows that high mountains and seacoasts dominated the list of favored destinations, though the list of places is most notable for their status as tourist destinations (Figure 5.1).

Locality.	Exempt.	Not Exempt.	Partially, or to particular persons
Adirondack Mtn, interior	3		
Ashland, Wis.	2		
Atlantic City,		1	
Atlanticville,		1	
Ausable,	1		
Barton, Vt.	1		
Bayfield, Wis.,	4		
Beach Haven,		1	1
Bennington Centre,		1	
Berlin Falls,			1
Bethel,			2
Bethlehem,	19	2	
Block Island,		1	1
Blue Mountain, Md.,		1	1
Blue Mountain, Adir.,	2		
Blue Ridge Summit,		1	
California, *	2		2
Campobello,	1		
Cape May,		2	1
Catskills,	1	7	1
Charlevoix, †			1
Chautauqua,		1	
Clayton,			1
Colebrook, N. H.	1		
Colorado, *	1	1	1
Cooperstown, N. Y.,			1
Crawford,	1	1	
Cresson,		1	
Cresson Springs,		1	
Delhi,		2	
Denver,		1	
Duluth,	2	2	1
Eaglemere,		1	
Ellenville, N. Y.,		1	
Europe,	11		2
Fire Island,			4
Franconia,	2		
Gilmanton, N. H.,		1	
Glen House,	1		
Glen Summit, Pa.,		1	
Grand Isle, Mex. Gulf,			1
Halifax,	1	1	
Jefferson,	6		
Kaaterskill,	1		
Keene Valley,	1		
Lake Bomesen,		1	
Lake George,	1		
Lake Mohonk,		1	
Lake Placid,	1		
Lake Superior Region,	1		
Lansdowne, Can.,	1		
Leeds, Can.	1		
Litchfield,			1
Littleton,			1
London, Eng.,	1	1	
Los Angeles,		1	
Mackinac, †	1	3	1
Maine Coast, ‡	‡2	1	
Marquette,	2	1	
Minneapolis,		1	
Montpelier,		1	
Montreal,	1	1	
Mountain Lake Park,		1	
Muskoka,	2		
Nantucket,	1	1	
New Jersey Coast,		4	
North Conway,		2	
Oakland, Md.,		2	1
Ocean—to most people,		1	
Ottawa,		1	
Overlook Mtn House,		1	
Pasadena,		1	
Petoskey, †	1	1	1
Pittsfield, Mass ,		1	
Pocono,			1
Pompeii, N. Y.,	1		
Port Arthur,	1		
Prince Edward Island,	2		
Put in Bay,			1
Quebec,	3	1	
Quogue,		1	
Rangeley Lakes,	4		
Richfield Springs,		1	
San Diego,	1	1	
San Francisco,	2		
Saranac Lake,	1		
Santa Barbara,		1	
Saratoga,		2	
Schroon Lake,		3	
Shellburne,			1
Saulte St. Marie,	2		
St. Andrews, N. B.,	4		
St. Paul,		1	
Sugar Hill,	4		
Thousand Islands,		2	
Twin Mountain,	3		
Upper Bartlett,		1	
Watch Hill,		2	
Waterville, Me.,		1	
Wernersville,		1	
White Mountains, ⁂			

* High regions of
† Suffered mildly.
‡ One sailed off it; the other drove along it.
⁂ Generally exempt, with few or partial exceptions.

Figure 5.1 Exempt places from hay fever (1892). Source: Survey of the Membership, *Manual of the United States Hay Fever Association*, 1892.

Many of the visitors to the White Mountains during the autumn hay fever season (late August and early September) had medical or scientific training, and these visitors sought explanations for why they felt well in New Hampshire and ill at home. In keeping with the scientific discoveries of the day, the discussion was dominated by talk of miasmas, spores, animuncules, infusoria, mites and other microscopic culprits which might be carried on the air unseen, and which might die with the autumn frosts – just when symptoms were almost universally relieved each year. As Secretary of the association, Edmund S. Hoyt discussed the causes of hay fever as he understood them, emphasizing both local atmospheric factors and individual idiosyncrasy:

> It is evident that whatever may be the occasion of Hay-Fever in the physical idiosyncracies [*sic*] of the victim, the real causes of it exists in circumstances external to himself, and over which he has, or may have, more or less of control, and that those circumstances are atmospheric, or, in other words, that the atmosphere is the bearer of the specific poison, whatever it be, whether it be *miasmatic, sporadic or animalcular* … it is evident that these atmospheric influences are periodic … it is evident that these atmospheric influences are local in their character, and this is the great comfort which your secretary has to bring you in all your affliction. Time one may not annihilate, even by sleep, but localities may be selected, according to the liking, or, according to the purse. Medicine may accomplish little or nothing, and it is safe to say, notwithstanding the protestations of interested parties, that medicine has yet accomplished little or nothing, yet there is 'balm in Gilead,' and in Gorham, and in Bethlehem, too, and in numberless regions known and perhaps unknown.[26]

Many physicians and scientists in the association published on both their personal experience of hay fever and experiments and observations about the disease. By the end of the 1870s, for example, Dr. Morrill Wyman of Harvard Medical School – whose family had been traveling to the White Mountains for some years – was, like his British counterpart Dr. Charles Blackley of Manchester, England, arguing that pollen was the major exciting cause for asthma and hay fever. Its appearance coincided with intensification of symptoms in the summer and fall, and such a concept fit the most modern theories of the day – finding the causes of disease in microscopic particles. Neurologist George M. Beard called the pollen hypotheses the 'infusorial' theory of hay fever, linking it explicitly with germ-based explanations of disease.[27] Morrill Wyman's experiments in this vein began with the observation that he and his family suffered in Boston in the late summer and fall, and found relief in the White Mountains. Wyman conducted a series of studies of pollen and its relationship to hay fever and asthma, paying special attention to the geographic distribution of pollens. When Wyman published his book on hay fever in 1872, he included several maps of pollen distribution during peak season in the United States, which he had developed from his wide correspondence with physicians and hay fever sufferers. The frontispiece featured his favored White Mountains region (Figure 5.2).[28]

In parallel with Wyman's observations, British physician Charles Harrison Blackley studied the relationship between pollen counts and symptoms of hay fever and hay asthma with a novel device. He invented a 'pollen counter' which featured a microscopic slide covered with a layer of sticky glycerine and left outside to catch pollen in a birdhouse-like apparatus with a roof but no walls. Rather than geographic variation, Blackley's

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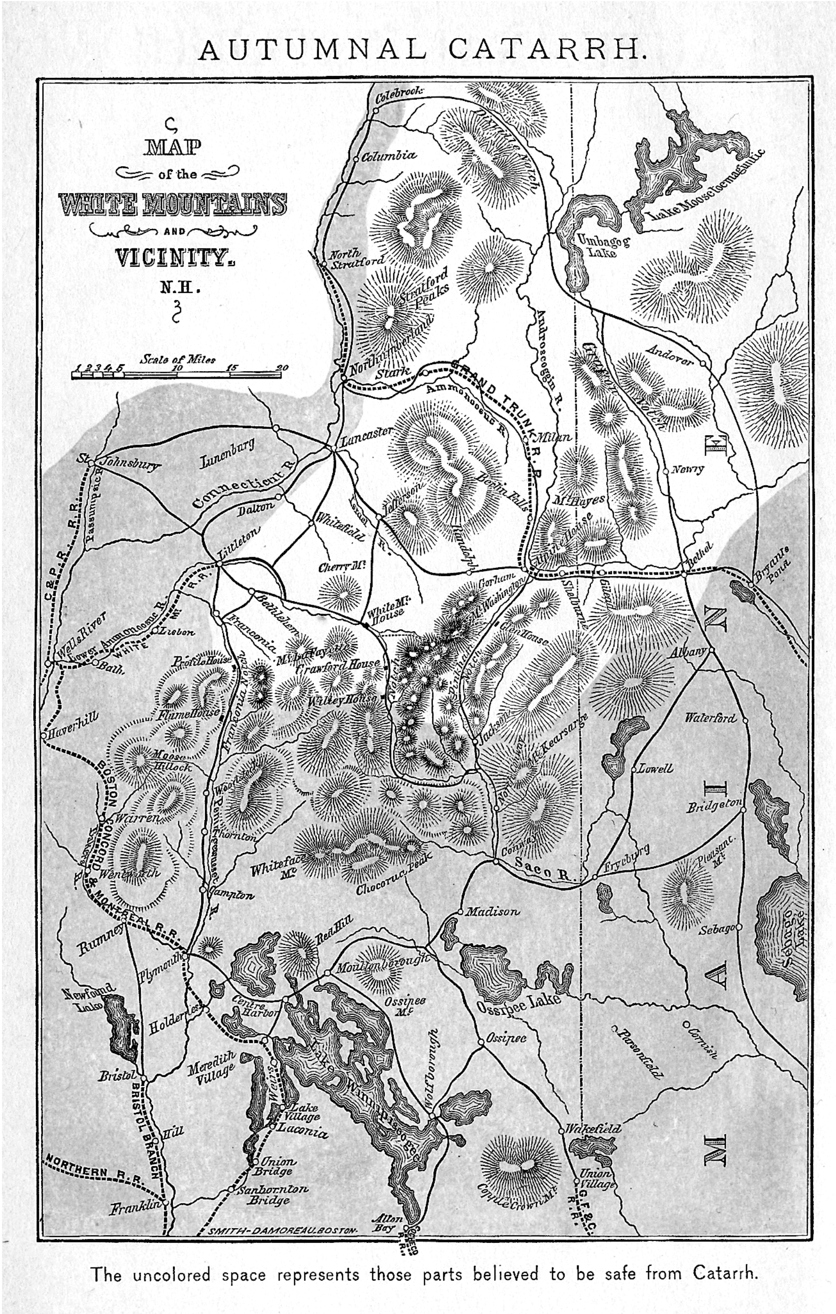

Figure 5.2 Map of the White Mountains and Vicinity. The light area in the middle of the map was considered exempt from pollen. Source: Morrill Wyman, *Autumnal Catarrh (Hay Fever)*, New York: Hurd & Houghton, 1876, frontispiece.

work illustrated seasonal variation, with day-by-day counts from May to August which showed late June peaks 20–50 times his counts from early May or early August.[29] This illustration from his book, *Experimental Researches on the Causes and Nature of Catarrhus Aestivus,* published 1873, shows the pollen counter, and the graph following shows daily pollen counts for the summer of 1866 (Figures 5.3 and 5.4).

Despite the first rush of enthusiasm for pollen counts, Wyman, Blackley and others soon found that individual cases responded differently to the same counts. Individuals

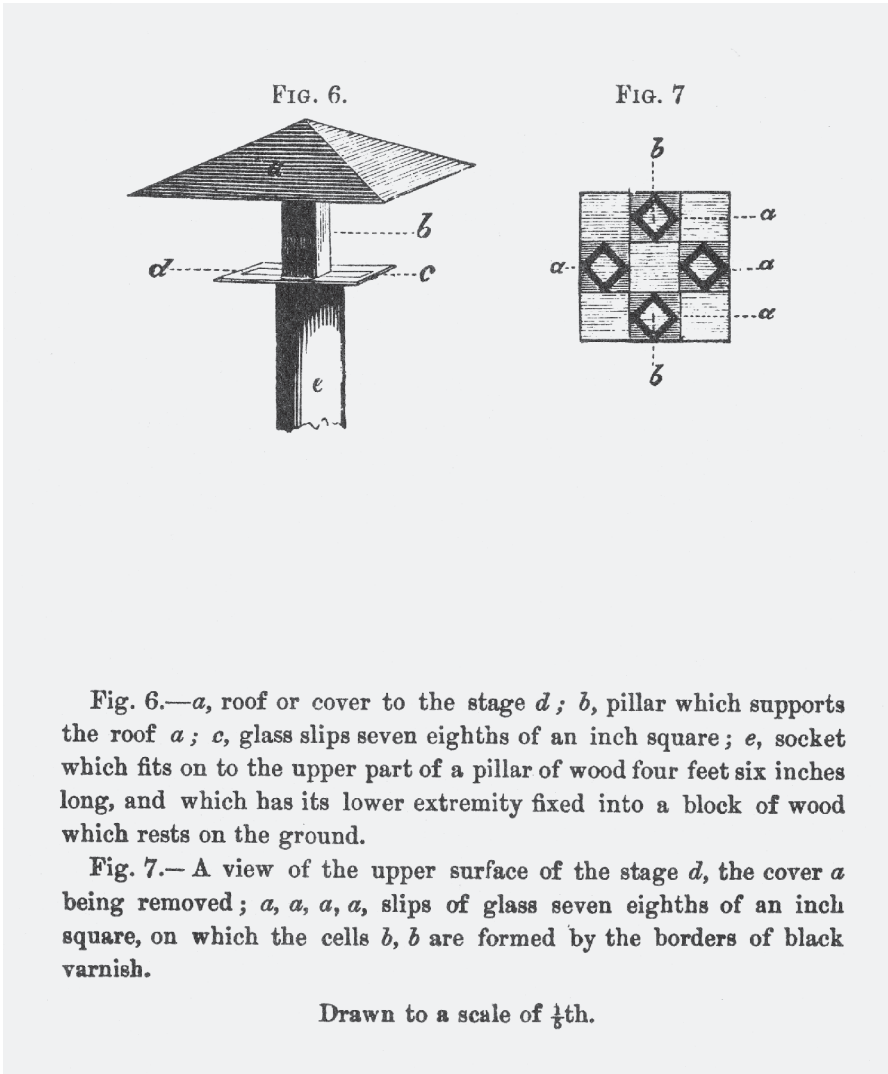

Fig. 6.—*a*, roof or cover to the stage *d*; *b*, pillar which supports the roof *a*; *c*, glass slips seven eighths of an inch square; *e*, socket which fits on to the upper part of a pillar of wood four feet six inches long, and which has its lower extremity fixed into a block of wood which rests on the ground.

Fig. 7.— A view of the upper surface of the stage *d*, the cover *a* being removed; *a*, *a*, *a*, *a*, slips of glass seven eighths of an inch square, on which the cells *b*, *b* are formed by the borders of black varnish.

Drawn to a scale of $\frac{1}{8}$th.

Figure 5.3 Pollen counter used by Charles Blackley, with glass slide covered with glue and placed under a roof to collect only airborne particles. Source: Charles H. Blackley, *Experimental Researches on the Causes and Nature of Catarrhus Aestivus*, London: Ballière, Tindall & Cox, 1873, opposite p. 122.

differed in their reactions and showed variations in symptoms when they stayed in the same place. Competing explanations for the disease persisted. Samuel Lockwood, a member of the Association, explained the state of hay fever and hay asthma pathology in 1890:

> I think that writers generally on this disease are too apt to specialize in theory. The very nature of the malady is a temptation in this direction, since it exhibits such a complication of symptoms, and is accredited to so many and diverse causes. One ascribes it mainly to summer heat; another to dust in general; another to pollen in especial; and still another to a peculiar microbe, which he calls diplococcus … I hesitate not to express my belief that Hay-Fever in its advanced stages is the collective effect of all the causes stated.[30]

While crediting pollen with causing much of the suffering of hay fever and 'hay asthma', Lockwood went on to argue that: 'This pollen theory, as a sole, or main cause of Hay-Fever, has been unduly magnified, and should be given up. I am now convinced, however, that of all the atmospheric dust it is the most irritating'.[31]

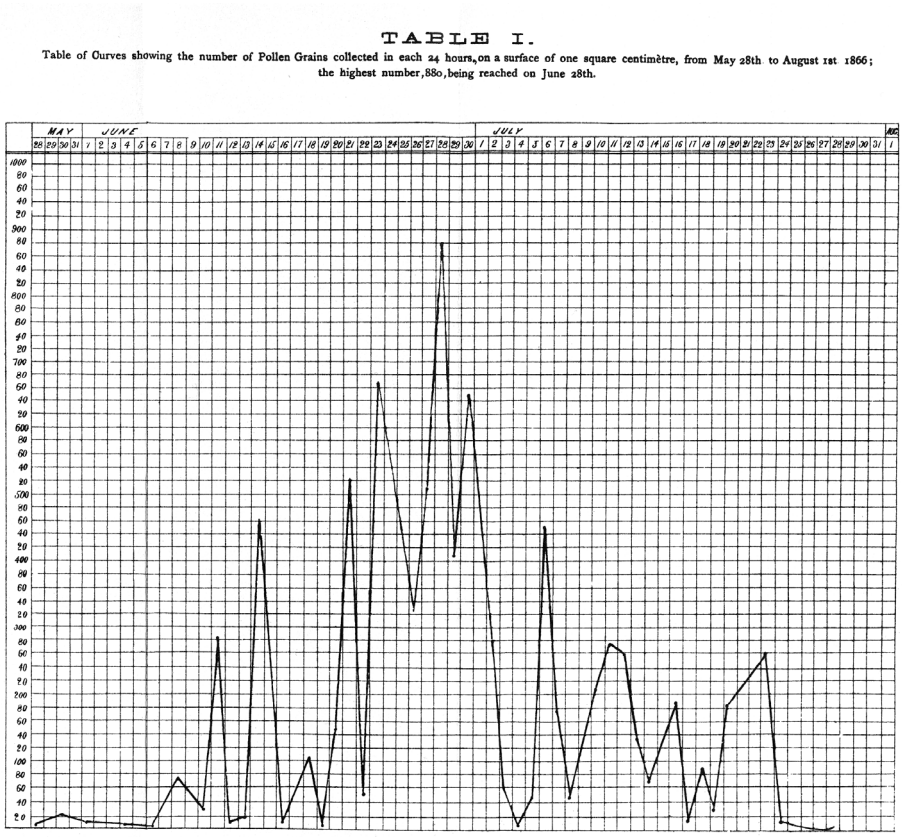

Figure 5.4 Graph of daily pollen counts. Source: Charles H. Blackley, *Experimental Researches on the Causes and Nature of Catarrhus Aestivus*, London: Ballière, Tindall & Cox, 1873, opposite p. 129.

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Beard, also a member of the association, offered an alternative explanation by building on the widespread belief that asthma and hay fever were nervous diseases restricted to the upper classes.[32] He wrote about hay fever as part of a family of enervating diseases of civilization afflicting the new urban American élite. While Beard's work was respected, and hay fever earned a place among the nineteenth-century nervous diseases, this designation did not exclude a role for pollen in causing the disease; it rather specified why certain individuals seemed especially sensitive to it.

By the 1910s, the pollen theory had been widely accepted. The correlation of the temporal and geographic appearance of pollen with wheezing and sneezing made a compelling case, but it was one that had not yet been explained through a pathological mechanism. Such a theory would have to account for not only the connection between pollen and the symptoms of asthma and hay fever, but also the puzzling individual idiosyncrasies in the diseases. Starting in the 1890s, William Philips Dunbar in Germany would begin to explain the links between pollen and asthma and hay fever as a reaction mediated by a specific, soluble pollen toxin, and to develop vaccines for that toxin.

The Rise of Allergen Immunotherapy

The science of immunology that underlies twentieth-century explanations of allergic diseases such as asthma arose from nineteenth-century successes in fighting infectious diseases. The desire to improve existing immunizations and antisera, and to develop new therapeutic agents, led researchers to explore more carefully the mechanisms of immunity from infection, both naturally occurring and vaccine-induced.[33] In the first decade of the twentieth century, disturbing reports that some individuals were becoming ill after receiving potentially life-saving antisera added to the urgent need to understand more about the human immune system. As an accumulating number of clinical accounts demonstrated, foreign serum could produce a slow reaction called 'serum sickness', or an acute and fatal form which Charles R. Richet (1850–1935) dubbed 'anaphylaxis', or a kind of 'anti-protection', to contrast it with the normal 'prophylaxis' from the serum.[34]

This model of anaphylaxis was widely used (and many argued misused) in the first two decades of the twentieth century, applied to everything from gastroenteritis to eugenics, but it had special resonance for those who studied asthma.[35] The commonalities between anaphylaxis and asthma included triggering of an attack by exposure to foreign protein and the resulting shortness of breath and feeling of suffocation, which led to widespread application of the concepts of anaphylaxis to the study of allergy. Dr. S.J. Meltzer, of the Rockefeller Institute for Medical Research, explained: 'The theory is here offered that asthma is an anaphylactic phenomenon; that is, that asthmatics are individuals who are "sensitized" to a specific substance and the attack of asthma sets in whenever they are "intoxicated" by that substance'.[36] Meltzer went on to describe in detail the relationship between nerves and muscle fibers deep in the lung. But his principal point was that asthma was a toxic response like anaphylaxis rather than a nervous reflex, the mechanism behind contemporary theories of nervous asthma. This comparison with anaphylaxis placed asthma squarely within the realm of a new immunology.

Though vaccinations, allergies, and serum sickness seemed initially to constitute divergent processes, early immunologists recognized that in each case a previous exposure to a substance could change an individual's response to that substance when

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they encountered it again. Individual variation in responses to the environment could be accounted for in immunological terms, based in a combination of hereditary predisposition and life experience. Contemporary theories of protein sensitization set two prerequisites to an asthmatic reaction to a specific substance such as a pollen: first, it had to be in a susceptible individual (a condition that seemed to travel in families), and secondly, the allergic response followed an earlier exposure.[37] When von Pirquet coined the term 'allergy' in 1906 he used it to describe all of these forms of 'altered reactivity', ranging from what we think of now as allergic diseases (asthma, hay fever, hives) to responses to vaccinations, and, finally, the natural immunity following many infectious diseases.[38] This usage of the term 'allergy' to describe all immune responses, protective or deleterious, was not widely accepted, with most practitioners instead using it synonymously with hypersensitivity reactions, though the use of the term was certainly in flux for some time (and arguably still is).[39]

Visions of the immune system as a cause of disease were only beginning to emerge when the first serious attempts were made to modify response to pollen in hay fever and asthma.[40] So while the terms and concepts of allergy and anaphylaxis would come to define allergy immunotherapy, initial attempts at vaccination were based, instead, on theories of hay fever and asthma as infectious diseases, either resulting from direct infection or a toxin akin to diphtheria.[41] Both the vaccines against hay fever created by H. Holbrook Curtis, a New York physician, and the 'Pollantin' antitoxin developed by Dunbar, for example, were derived from the previous generation's work linking pollen to asthma and hay fever.[42]

Pollen Toxins, Antitoxins, and Vaccines

By the 1910s, these trends had become organized around three research groups centered around Dunbar in Germany, Almroth Wright in Britain, and Robert Anderson Cooke in the United States. These emerging allergists offered courses of 'desensitizing' immunizations along with other approaches, to try to accommodate their patients to climates and occupations that they could not avoid through relocation or retraining.

Dunbar (1863–1922) was an American physician from St Paul, Minnesota, who, in the last decades of the nineteenth century, followed the path of many ambitious young scientists. He traveled to Germany to learn the new microtechniques, eventually earning his medical qualification at Giessen in 1892 before becoming swept up in a devastating cholera epidemic in Hamburg during which he was credited with improving the detection of cholera in the water supply and thereby helping to eradicate the disease.[43] He spent the rest of his career in Germany, eventually rising to the position of Director of the State Hygienic Institute in Hamburg. Best known for his work on sanitation, he had a side interest in hay fever, which sharpened every spring when his own symptoms worsened.[44] Dunbar laid out his vaccine treatment of hay fever and asthma as the only alternative to physical methods of avoidance such as masks or relocation:

> Since the discovery of the etiology of hay-fever it has been evident that there are only three ways by which the disease can be successfully treated. The first is to search for localities free from the specific agent; the second to employ apparatus to protect the eyes,

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> nose and mouth of patients from contact with such agents; the third to immunize the patient actively against pollen toxin or to use a specific antidote.[45]

The ways in which Dunbar's expectations were shaped by his work on bacteria, and on the receptor-specificity theories of Paul Ehrlich, are apparent in his own description of his work: 'I advanced the theory that hay-fever is a disease caused by vegetable poisons contained in the pollen of certain plants. These substances were connected with the proteid of the pollen grain and of a highly specific character'.[46] He went on to say that 'for hay-fever patients the proteid of active pollen is a toxin comparable to abrin, ricin, diphtheria toxin, etc'.[47] While the clinical manifestations of hay fever were not as dire as those of the other deadly and recently-discovered toxins he listed, Dunbar argued that his procedures for chemical isolation of the active extract of pollen were consistent with fractionating a toxin from a bacterium, a toxin which would, in time, be further characterized.

Dunbar's arguments about the specificity of his solutions were somewhat inconsistent. He argued that there were distinct reactions to grasses, North American ragweed, and cat saliva, and that a person sensitive to one may be impervious to the others, but also argued that most would respond to a generic 'Pollantin' as the common factor in each might be an identical toxin. He described a case of a woman whose sensitivity to her cat responded to treatment by the pollen antitoxin. He explained this curious situation by arguing that the sensitivities to cat and pollen were of a kind: 'The case appears particularly important to me because such idiosyncrasies to my mind are very nearly related to hay-fever, for otherwise it would be impossible to influence them favorably by pollen antitoxin'.[48]

As with many researchers, he performed a large series of experiments on himself and his assistants, with the hay fever sufferers in his lab serving as subjects and those without the condition as controls. Following the techniques of bacteriology, Dunbar's group worked to obtain pure supplies of pollen, and prepared multiple extracts to determine the active element, testing these solutions on the conjunctiva (in the eyes) of the hay fever sufferers who worked in his lab. Once the active extracts were isolated, they were injected into horses and rabbits to produce Pollantin, the manufacture of which they contracted out to Schimmel & Company in Miltitz, a local chemical, drug, and perfume manufacturer. Patients could choose from an antitoxin for injection, a powder form which could be applied to the mucous membranes, an ointment, and pastilles. Though most preparations were made from horse serum, Pollantin R, the rabbit serum, was available for those who had reactions to horse serum.

A competing remedy, Graminol, was introduced by Wolfgang Weichardt of Erlangen, who had served as one of Dunbar's assistants. Graminol was derived from the serum of ruminants, presumed to be naturally exposed to pollinating grasses by their grazing, rather than through a process of injecting purified pollens and later isolating a specific antiserum. The precise constituents of the formula were, however, secret, and Dunbar in discounting this 'nonspecific' serum (as opposed to his laboratory prepared antisera) argued first that there was little chance that exposure via the digestive tract would produce natural immunity because of breakdown of proteins, and, second, that the true active ingredient in Graminol was adrenaline.[49]

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As Dunbar's group continued their work on pollen and Pollantin, they were disturbed by increasing reports of reactions to horse serum preparations, both in their patients and in those receiving antitoxins for diphtheria and tetanus. The substitution of rabbit serum did not solve the problem, however. In fact, an even larger percentage of their hay fever patients appeared to develop sensitivity to the rabbit serum form of Pollantin than to the horse once they started using it. Dunbar presented his dilemma as follows:

> The occurrence of horse serum anaphylaxis in hay-fever patients using pollantin has led me to pursue my investigations on this subject since 1905. All endeavours to prevent it have been in vain. On the other hand I found that it only occurred in a comparatively small percentage of cases, and that it then is regularly an indication of a decline in the hay-fever predisposition … Nevertheless this condition was not desirable, especially since the alternative use of antitoxin from the rabbit was also soon followed by anaphylaxis. Such experiences convinced me of the desirability of recommencing experiments on *active immunization*.[50]

Dunbar's group was not the only one pursuing immunization strategies for hay fever and asthma, with the early efforts of Curtis supplanted by systematic efforts in Britain and the United States by some of the leading immunologists of the early twentieth century.[51] The precise meaning of 'antisera' and 'vaccine' was still in flux, and the scientists themselves were still trying to understand the mechanisms for their largely empiric treatments. Antiserum was generally used after exposure to a bacterium, and had as its goal treatment, such as with diphtheria antitoxin used to fight outbreaks. Vaccines were initially preventive, as with the use of the Vaccinia virus to prevent smallpox. But in the early twentieth century, as the science of immunology was developing rapidly, the boundaries of vaccine therapy were open, with preventive strategies well-established, but with many researchers working to show the value of deliberate manipulation of the immune system with vaccines at every stage of illness. It was no accident that allergy desensitization should emerge in the Department of Inoculation run by Sir Almroth Wright.

Sir Almroth Wright (1861–1947) was the leading proponent of vaccine therapy in Britain in the early twentieth century.[52] Wright established the Inoculation Department at St Mary's Hospital in London soon after his appointment in 1902 to the pathology staff. His department was concerned with the therapeutic possibilities of vaccination against infectious diseases, and Wright was a leader in promoting the potential of vaccines to prevent and treat infections.[53] Wright developed a relationship with the Parke Davis Company, who had the right to produce and market vaccines developed at St Mary's and split the profits with the Department to support its research and clinical activities. By 1907, Wright had been joined by John Freeman and Leonard Noon, young physicians who had studied together at the Pasteur Institute in Paris. While most of the work of Wright's laboratory was directed to fighting pneumonia, boils, and other bacterial diseases, Noon and Freeman developed a program in hay fever vaccines which both would continue for the rest of their careers.

After working on several other projects, Noon and Freeman began experimenting in 1908 with vaccines for hay fever. In his first publication on the topic, Noon immediately adopted Dunbar's pollen toxin theory: 'Hay fever is a form of recurrent catarrh affecting certain individuals during the months of May, June, and July. It is caused by a soluble

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toxin found in the pollen of grasses. The patients present the idiosyncrasy of being sensitive to this toxin, which is innocuous to normal individuals'.[54] But in opposition to Dunbar's extensive work on antisera, both Noon and Freeman were committed to direct immunization with pollens – so-called 'active immunization' – both because it avoided the problems Dunbar had encountered with serum reactions, and because they reasoned that if the patient's own immune system produced a protective response, it might be lifelong (in contrast to the temporary protection offered by antisera). As Noon explained, 'The local application of a specific serum, such as pollantin, offers a reasonable method of treatment, but one which is difficult and laborious, and which is not calculated to bring about a permanent cure'.[55]

Their initial clinical trials demonstrated both qualitative and quantitative success: 'The result of these experiments so far is to show that the sensibility of hay fever patients may be decreased, by properly directed dosage, at least a hundredfold'.[56] But they continued to depend upon careful calibration of the pollen dosage to the individual patient's state of reactivity. After Noon's premature death from tuberculosis in 1913, Freeman carried on their work on hay fever inoculation, reporting in 1914 on their first three years of clinical experience:

> The 84 cases have between them experienced 113 hay fever seasons after – or under – treatment. The results of these summers are as follows:
>
> In 34 seasons (30.1 per cent.) the hay fever was completely cured or was so slight as to be insignificant.
>
> In 39 seasons (34.5 per cent.) the hay fever was greatly diminished.
>
> In 27 seasons (23.9 per cent.) the hay fever was admittedly diminished, but only to a slight extent.
>
> In 13 seasons (11.5 per cent.) the hay fever was no better, and of these, two cases reported that they were worse.[57]

Freeman continued his work on hay fever until his death in 1962. In keeping with the atmosphere of Wright's Inoculation Department, and perhaps inspired by the financial imperatives to produce the profitable 'Pollacine' series of vaccines, Freeman concentrated on the practical issues of extracting pollen, formulating vaccines, and techniques and schedules of administration. He left scientific matters such as the mechanism of allergy immunotherapy to others.[58] By 1915 several other researchers had published their work on hay fever vaccines, but that of Robert Anderson Cooke (1880–1960), Arthur F. Coca (1875–1959) and their colleagues in New York stood out for their careful laboratory methods, commitment to standard procedures, and extensive research into the mechanisms of human sensitization and the precise immunological responses patients had to treatment.[59] Cooke and Coca became known for their rigorous laboratory-based investigations, which yielded improved practical tests such as skin tests for sensitization to replace the ocular tests used by Dunbar and Freeman and a means of standardizing strengths of pollen extracts.[60] Skin tests for allergenic sensitivities, for example, had the advantage of allowing testing for many different allergens at once.

In the 1920s and 1930s, Cooke and his team, using techniques such as transfusion and serum injections from inoculated hay fever patients to those who had not undergone desensitization treatments, postulated the existence of a 'blocking antibody'

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which interfered with the interaction between the pollen grain or other allergen and the sensitized cells of the patient:

> Using ragweed hay fever as the representative of a certain type of allergy we have made studies to determine if possible the mechanism of the protection afforded by specific injections thus far established only by clinical observation.
> 1. Blood transfusions and serum injections from clinically immune, treated patients stopped the clinical reaction in untreated patients, thus indicating a transferable immunity.
> 2. The amount of skin sensitizing antibody in the serum was found to be practically unchanged by specific injections.
> 3. Injection of allergen-antibody mixtures into normal skin showed an immediate (1 hour) reaction when sites were made if serum of untreated cases (Serum A) was used but none or slight reaction if serum of treated cases (Serum P) was used.
> 4. When sites made with allergen-antibody mixtures were tested after 48 hours, reactions were absent with Serum A mixtures if enough allergen had been used, but were positive with mixtures of Serum P even though a much stronger allergen was contained in the mixture.
> 5 The primary inhibition of reactions with mixtures including Serum P was not due to antihistamine effect nor to binding of skin sensitizing antibody nor to binding or lysis of allergen.
> 6. The inhibiting antibody appears to be specific.
> 7. These serological studies supported by transfusion experiments have been interpreted by us as showing the development under treatment of a peculiar blocking or inhibiting type of immune antibody that prevented the action of allergen on the sensitizing antibody and hence showed in the type of human allergy under consideration (hay fever) the coexistence of sensitization and immunity.[61]

While early confirmations such as that by Francis Rackemann's team at Harvard helped the 'blocking antibody' theory gain currency, continuing studies of the mechanisms of allergen immunotherapy would reveal additional immunologic mechanisms.[62] From a purely clinical perspective, responses to allergy shots varied substantially from one patient to the next, just as the symptoms of allergic diseases themselves had. As an early twentieth-century researcher complained: 'nothing is more difficult to explain than why any particular method of treatment should cure one case and have no effect on another which is apparently exactly similar. The recognized practices of bacteriology show strange misfits when applied to asthma'.[63] This individual variation confounded both standardization of procedures – which were often customized to the patient – and evaluation of the therapeutic value of allergen immunotherapy. In the 1940s and 1950s, A.W. Frankland and Rosa Augustin, both members of Wright's institute and both well aware of the new standards for blinded, placebo-controlled clinical trials, set out to study the benefits of allergen immunotherapy.[64] During the summer of 1953, they received support from the Asthma Research Council to study 200 patients who were sensitive only to grass pollen and had never received injections for hay-fever. Half received one of two active vaccines and the other half received one of two inactive controls. Seventy-nine per cent of the hay-fever patients reported good or excellent results following pollen vaccines, while thirty-three per cent of those receiving control vaccines reported good or excellent results, both evaluated by daily symptom diaries as well as the patient's overall

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impression of the success of treatment at the end of the summer.[65] Likewise, Francis C. Lowell and William Franklin at the Massachusetts General Hospital studied ragweed pollen injections over the summers of 1959 to 1963. They also found improvements in those receiving ragweed extracts over controls, but their papers are more notable than the British group's for their frustration with daily and weekly variations within as well as between groups – ultimately they found a modest, but real effect in favor of pollen injections.[66]

Allergy in Practice

After these initial developments, the practice of allergy immunotherapy still required substantial standardization of techniques and reagents. Even after Parke Davis in Britain and Lederle Laboratories in the United States began commercial production of pollen vaccines, there were problems in supply, variations in concentration, and limits to the number of different extracts available, which was a particular problem because of different regional ecologies of hay fever plants. Sometimes, practitioners had to collect and purify their own antigen preparations for diagnostic and therapeutic use. In some cases, a particular item was not commercially available; in others, the dosage had to be modified according to the sensitivity of the individual patient, since even early attempts to create standard solutions by weight, protein content, or nitrogen content did not correlate with allergenic strength. This proved an ongoing problem, and many methods

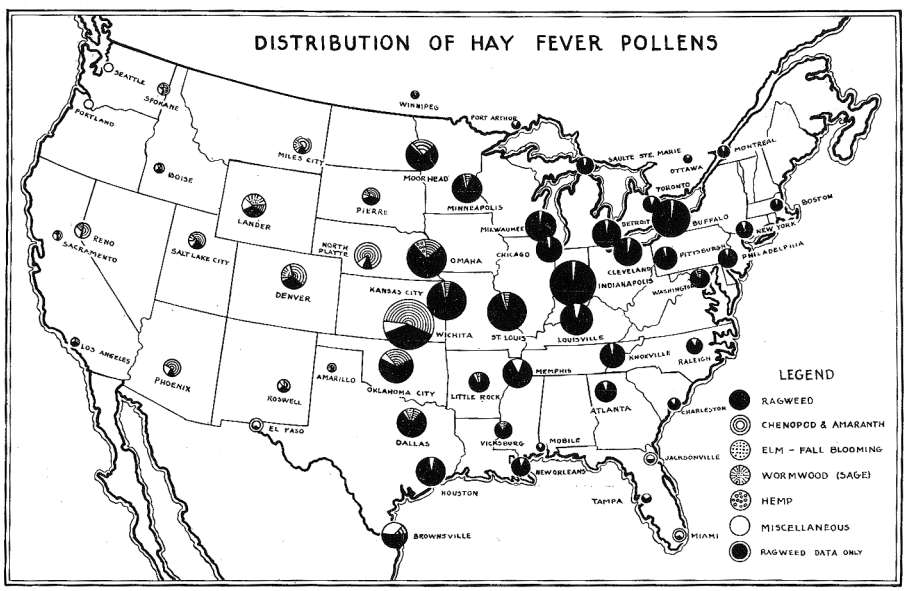

Figure 5.5 Map produced by O.C. Durham (Abbott Laboratories) demonstrates both overall pollen counts and the species of plants representing most airborne pollen. Source: O.C. Durham, 'The Pollen Content of the Air in North America', *Journal of Allergy*, **6**, 1935, pp. 128–49 at p. 129. With permission from the American Association of Allergy, Asthma & Immunology.

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were developed to create and measure the clinically-relevant strength of pollen and other allergen desensitizing vaccines. Over the years, working groups and professional societies of allergy have taken this project to facilitate both intellectual dialogue and therapeutic safety and effectiveness.[67]

An irony of allergy practice in the early twentieth century was that the allergists' determination to free patients from the constraints of geography required that these physicians themselves obtained a detailed local knowledge of the plants in the region where they practiced. This was essential both so that they would know what their patients might be sensitive to, and to enable them to prepare allergen extracts. Even after commercial companies began producing vaccines for allergy, the allergist still had to know his local ecology, the distribution of allergy-inducing plants in his local region, and be able to produce his own extracts when commercial vaccines were not available for local hay fever plants.[68] In order to improve understanding of the epidemiology of allergic diseases and to guide clinical practice, pollen surveys were conducted across the country, some by clinics, others by public health authorities, and others by botanists employed by the companies selling pollen extracts (Figure 5.5).[69] Botanist Oren C. Durham, for example, started collecting pollens in 1916 for his brother-in-law R. Claude Lowdermilk, who published one of the earliest studies of pollen vaccines. Durham then started working for William Duke, an early president of the American Association for the Study of Allergy, and finally did extensive work with Abbott Laboratories in the production of many pollen vaccines.[70] Botanist Roger Wodehouse started his work on pollen grains when he was a graduate student in plant physiology at Harvard and began to collect material for Dr Joseph Goodale's allergy patients at Massachusetts General Hospital. Wodehouse helped produce vaccines at the Arlington Chemical Company while working on his doctorate at Columbia, and then directed work on pollen vaccines at Lederle Laboratories with Coca.[71]As Mitman has shown, partnerships between allergists, botanists, and pharmaceutical companies were critical to the establishment of vaccine treatment of allergy, but the pharmaceutical companies' plans to create a single, universal pollen vaccine for all patients and all regions of the country ultimately proved futile.[72]

In 1923 and 1924, two allergy societies were founded in the United States: a western group founded in San Francisco as the Western Society for the Study of Hay Fever, Asthma and Allergic Diseases (later renamed the Association for the Study of Allergy) and an eastern group based in New York founded the Society for the Study of Asthma and Allied Conditions.[73] These new specialty organizations shared technical knowledge about the manufacture and use of the new allergy vaccines as well as the survey data about the distribution of pollinating plants. They also worked together first to plan hospitals and clinics, then to work to establish the field of allergic diseases within academic medicine.[74] They merged in 1943 to form the national allergy society for the United States and formed a specialty board for recognizing and certifying allergists under the American Board of Medical Specialties.

Immunotherapy Challenged

After 1945, the new specialists in allergy would find themselves in scientific and territorial disputes with chest physicians over asthma, with dermatologists over urticaria

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and eczema, and with gastroenterologists over food allergy.[75] After 1950, as tuberculosis declined in prevalence, allergists and chest physicians in the United States would argue over almost every aspect of the treatment of patients with asthma.[76] The safety and efficacy of the allergists' immunotherapy became one of the most bitterly contested points.[77] Allergist Philip Norman, summarizing nearly a century of data on allergen immunotherapy, presented the following puzzle about its interpretation:

> Despite continued use by specialists in allergy and immunology worldwide, immunotherapy for asthma is a perennial target for criticism by nonallergists who also care for patients with asthma. Immunotherapy for hay fever, on the other hand, generates little controversy, even though the immunologic pathogenesis of hay fever is essentially identical. The reasons for this difference are not apparent from the evidence collected. Similar numbers of studies of hay fever and asthma may be found, and both find similar clinical improvement and immunologic changes.[78]

Norman was too polite to name the 'nonallergists' in question as the chest physicians who competed with allergists for the opportunity to care for asthma patients but not for those with hay fever. While allergy had become an established outpatient specialty in the United States with thousands of practitioners, in the British hospital specialist system, allergists were a small group, and the clinical practice of allergy immunization often fell to interested general practitioners. As Jackson has demonstrated, when questions arose there about allergy immunotherapy's efficacy and safety, it had only a small community of defenders to fall back on.[79] Asthma immunotherapy was much better established in the United States than in Britain, with thousands of fellowship-trained allergists. There has been a decline in the past 25 years, however, because newer non-sedating antihistamines, safer selective bronchodilators, and inhaled steroids have come to be seen as safer, simpler, and less expensive than weekly injection regimens, making it seem more convenient for patients and more cost-effective for health insurers.

Conclusions

In the early twentieth century, allergists created a dual-pronged strategy of allergy desensitization shots and manipulation of the indoor environment as a conscious alternative to climatic treatment and available pharmaceuticals. The practice of allergy and the immunologic theories that underlay it had their origins in the germ theory of disease and in the subsequent development of new theories of immunity. These beginnings shaped early theories of hay fever and asthma as diseases of infusoria, initially imagined as specific but unknown germs. It was only later that allergy came to be understood as a disease of the body's pathological response to ubiquitous stimuli such as pollens and animal danders. Even after the theories of allergy diverged from their origins in microbiology, the microscopic nature of the threat and the community of researchers continued to extend microbiological thinking into the theory and practice of allergy, borrowing both techniques of immunization and strategies of cleansing the patient's environment. While improved drugs became available in parallel with the development of allergen immunotherapy and avoidance strategies, theophylline, ephedrine, and cortisone had serious limitations both in effectiveness and safety, and were better treatments for severe manifestations of asthma than the more common symptoms of

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sneezing, congestion, and itchy eyes. The everyday symptoms of allergy and asthma remained the province of the allergist and his complex schemes of allergen avoidance and immunization through the second half of the twentieth century.

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