Demonstration of diphtheria toxin and its pathogenicity by Pierre Roux and Alexandre Yersin at the Institut Pasteur in 1888 provided a starting point for the development of serum therapy. Two years later at Koch’s Institute in Berlin, Emil von Behring and Shibasburo Kitasato produced specific immunizing antitoxin. Although an immediately apparent major contribution to the rapidly developing discipline of bacteriology and infectious diseases, this new knowledge would also prove to be a milestone in the emergence of the field of hypersensitivity.

Meanwhile, revelations of toxin-antitoxin phenomena reactivated scientific interest in the long-held, ill-defined concept of poisons as causes of disease. Paul Ehrlich’s 1891 report of raising antiserum to the toxalbumins ricin and abrin isolated from castor bean and jequirity bean, respectively, added reason to speculate that plant-produced endotoxins and exotoxins in addition to those of bacterial sources might play possible roles in the cause of human disorders. One specific instance was that of Blackley’s 1873 demonstration of the association of grass pollens with symptoms of seasonal hay fever, but whatever the pathogenetic relationship, it remained unexplored for the next 30 years.

In the first approach to the evaluation of that aspect of grass pollen, William Dunbar in 1903 in Hamburg (1) identified the albumin fraction of the isolated proteid component as the active principle, (2) implicated the immunologic factor of complement deviation in the sera of subjects with hay fever, and (3) determined individual susceptibility to pollen by grading conjunctival reactions to dose-related ocular challenges. Interpreting that hay fever and hay asthma were caused by pollen toxin in susceptible individuals, Dunbar sought to duplicate the therapeutic success of passive immunization in diphtheria, applying its principle to the treatment of hay fever. Putative antiserum pharmacologically marketed as “Pollantin” was administered by means of nasal and ocular instillation, bronchial inhalation, and subcutaneous injection. The latter given in combination with pollen proteid, a method designed to immunize with mixtures of antitoxic and toxin, preceded by 12 years Behring’s introduction of the same principle with diphtheria toxin-antitoxin. Other than objections to occasionally experienced reactions to the foreign species sera, both “Pollantin” and a competing preparation, “Graminol,” introduced by Wolfgang Weichardt of Erlangen, found popular acceptance. Until ultimately apparent that neither “Pollantin” nor “Graminol” had any real value, claims and evaluations were based on advantages in serum sources: “Pollantin” was derived from specifically immunized horses and rabbits, and “Graminol” was derived from nontreated herbivorous animals presumed to be naturally immunized by feeding on pollinating grasses.

The possibility that a true pollen toxin might not be the primary causative factor or pathopharmacologic mediator was never questioned. Nevertheless, despite its nonrewarding outcome, the experience had an unforeseen useful consequence. The introduction and widening use of “Pollantin” in clinical medicine in England brought Dunbar and his junior associate, Carl Prausnitz, into contact and appreciation of shared interests with Britain’s foremost vaccinologist, Sir Almroth Wright, Director of the Inoculation Department at London’s St Mary’s Hospital. Among areas that Dunbar’s work had opened up for further exploration was active immunization by means of subcutaneous injection of pollen proteid (“toxin”) alone for patients with hay fever sensitive to the added foreign species animal sera. That project was put aside when Dunbar, himself a patient with hay fever, manifested a violent systemic reaction on receiving from Prausnitz the first trial dose of injected grass pollen extract.

In the ascendancy of his medical career, Wright had served as professor of pathology at the Army medical school in the Royal Victoria Hospital at Netley, where he conducted original bacteriologic studies on Malta Fever (brucellosis) and developed a vaccine against typhoid fever. His antityphoid immunizing agent proved to be a seminal contribution when found to be efficacious in trials of mass inoculation in British soldiers in India and in South Africa during the Boer War. After leaving his association with military medicine and being appointed professor of pathology at St Mary’s in 1892, he developed a self-sustaining (enclave-like) department independent of hospital functions. His pioneering work in immunization was furthered by recruitment of a motivated staff whose participation in bench research was enabled by their generating self-support through private medical practices.
With expansion of the scope of Wright’s initiatives, the St Mary’s–based laboratory evolved into a recognized research institute. It provided the setting for interactions of staff and trainees with visitors of international distinction and expertise in bacteriology and immunology, such as Robert Koch, Emil von Behring, Paul Ehrlich, and Elie Metchnikoff. It offered opportunities to English-speaking physicians for postgraduate study comparable with that available at European centers in Austria, Germany, and France. A group who, after returning from Wright’s mentorship in London to the United States and Canada, kept in contact with the thought of forming a “society of vaccine therapists” and in 1913 founded the American Association of Immunologists.11

Within the inoculation department were the appropriate scientific ambiance and physical and intellectual resources for Leonard Noon (Fig 1) and John Freeman (Fig 2) to follow up Dunbar’s abandoned initiative to carry out prophylactic treatment of hay fever by means of immunization against putative grass pollen toxins. After identification of the allergic properties of pollen and its role in hypersensitivity mechanisms, Noon and Freeman’s initial reports of therapeutic benefit12,13 would be regarded as the seminal contribution to what would be known under the varied and changing terms of desensitization, hyposensitization, injection treatment, and immunotherapy.

Out of their initiatives for clinical care and investigation evolved another first—allergy’s first clinic. The institutional endeavor was operational at St Mary’s approximately 4 years before Joseph Goodale undertook systematized studies of patients with hay fever and hypersensitivity within the Throat Clinic at Massachusetts General Hospital (1915),14 6 years before I. Chandler Walker’s solo clinic venture for asthma and hay fever at the Peter Bent Brigham Hospital in Boston (1917),15 and 9 years before Robert Cooke’s multistaff clinic that opened at New York Hospital in 1920.

From longstanding association with our London colleague, A. W. Frankland, and appreciation of his contributions to advancement in the field of allergy, we have been made aware that he entered the medical specialty in 1946 as a member of the staff of the Inoculation Department at St Mary’s Hospital. Relating to the years of his service invariably recalled accounts of relevant interest, especially pertaining to personal and professional interactions and joint participation with those who pioneered the laboratory’s research (ie, Sir Almroth Wright, John Freeman, and Alexander Fleming) and the history of imaginative initiatives and innovative circumstances that made for the genesis and operation of allergy’s first clinic. Consequently, in the belief that Dr Frankland’s remembrances and reflections held advantages for adding an extra to the tenor and content of the Noon and Freeman Allergy Archives feature, we invited his submission of materials to be integrated into our planned biographic sketches. Not only did this assumption prove to be correct, Bill Frankland’s gracious and generous response provided material the intriguing tenor and content of which surpassed our expectations, so much so that to preserve the flavor of originality, authenticity, and personal touch, we favored it standing on its own.

Accordingly, in lieu of our preparing profiles for Allergy Archives in the customary format, we opted to offer the reader a historically relevant retrospective. A collection of selected, verbatim, and unedited excerpts taken from Bill Frankland’s memoir communications follows.

—Editors

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NOTES
6. William Dunbar, a native American, born in St Paul, Minnesota, remained in Germany after studying medicine at Giessen (MD 1892). In 1893, he became Director of the State Hygienic Institute at Hamburg.
8. A method that followed Theobold Smith’s technique for immunization of horses with injected mixtures of diphtheria toxin and antitoxin (T-AT). Its design allowed for gradual in vivo dissociation of antigenic toxin from the administered neutral mixtures. Apart from Dunbar’s modification—substituting a putative pollen poison preparation—Smith’s suggestion in 1909 for utilization of T-AT for human use (Kolmer JA, Tuft L. Clinical immunology, bio-therapy and chemotherapy. Philadelphia: Saunders; 1943. p. 491) was first used with true bacterial exotoxin (diphtheria) by Behring in 1913. (Behring EA. Ueber ein neues Diphtherieschutzmittel. Dtsch med Wochenschr 1913;39:875-6.)
10. Weichardt, after receiving his MD (1900 Breslau), trained as an assistant to Dunbar at the Hamburg Institute of Hygiene before becoming first assistant at the Erlangen University Institute of Hygiene and Bacteriology (1905-1909) and ultimately director of its Bavarian Bacteriological Research Institute.
15. Ibid. p. 320-31.

Inoculation Department, St Mary’s Hospital; Wright-Fleming Institute, St Mary’s Medical School: A Memoir

In Retrospect.1 My interest in allergy and aerobiology began 57 years ago, when in 1946 I began work in the Allergy Department at St Mary’s Hospital, London. Freeman was my chief until I took over as Director of the Allergy Department in 1962. When I retired from St Mary’s, I then worked for the next 20 years at Guy’s.

Medical help was required for the special extra clinics, which, in the early months of the year, only dealt with patients with seasonal symptoms due to grass pollen. If symptoms occurred at any other time of the year except summer, patients were seen in the ordinary allergy outpatient clinics. The seasonal hay fever patients were normally seen only once a year unless involved in some research project. We used to do very extensive skin prick tests on patients; we had our own laboratory to make up all our extracts and all our vaccines. People with seasonal hay fever—about 80% of them—went on a self-giving course of multiple desensitizing injections to deal with that seasonal hay fever with or without associated asthma. Between one third and one half had an associated pollen asthma.

It may seem hard to believe the number of patients we could deal with in a short time, but I was criticized when the special clinic one Spring had treated over 6000 patients—I was told I had to reduce the numbers because they were overtaking the Hospital! In fact, these clinics were run in a special building at the Wright Fleming Institute. They were self-supporting, and we took no notice of the National Health when it first started, in that patients were asked to contribute if they could afford it. If they couldn’t, no matter.

Leonard Noon, who died in 1913, of course I did not know, but I had a lot to do with his sister Dorothy who was in charge of the Pollen Farm (Pollinarium) when I took over running it. Freeman’s main interest was in summer hay fever because he considered it his moral responsibility to continue Noon’s work. I only just overlapped at the Inoculation Department with Sir Almroth Wright. The “old man” was quite a frightening personality. He sat at the end of the table in the library when we all went for tea at 4 o’clock to sit and listen to his thoughts—often anti-women! On May 8, 1947, I attended his memorial service at Holy Trinity Church, Prince Consort Road, London, conducted by an old Irish friend of his, Canon J. O. Hannay, better known as the author George Birmingham. I can remember what he did not say rather than what he did say about Wright!

The first day I went to work in the Allergy Department in 1946, I had to see how professional I was in making Wright’s famous capillary glass tube to take blood—I never used it!

Although fluent in French, German and Spanish, when he was over 75, Wright taught himself Russian so that he could be up to date with their ideas. Freeman was a great friend of Wright but not of Fleming, who followed Wright as director of the Wright-Fleming Institute. Both Wright and especially Freeman were jealous of the title of director and the Nobel Prize that Fleming achieved.

Alexander Fleming was my boss for 2 years when working in the Allergy Department, and I was eventually persuaded to write a chapter on penicillin allergy in the second edition of a very popular multiauthor book on penicillin of which he was the editor. Although I was very friendly with Fleming, he would never accept that penicillin caused allergic problems because he considered that penicillin reactions were caused not by penicillin but by impurities in the penicillin preparations then available. When I wrote a chapter in his book, my conclusions were that “with increasing use of penicillin, allergic reactions would
become more common.” Fleming made me change this to “the more recent penicillin preparations rarely cause local or general reactions.” Who was I to argue and disagree with the discoverer of penicillin?

I had John Freeman as a chief, but from 1950, I hardly saw him at all, and in retrospect, it is amazing that, as a junior, by doing a double-blind control trial, I really destroyed all his work on giving asthmatics autogenous bacterial vaccines. He never discussed this trial or even the one that I did with seasonal hay fever with Rosa Augustin. I wonder whether he even read it. When everyone in the department was asked to come to a meeting so that I could discuss what I was going to carry out in these trials, he did not turn up. Nearly 2 years later, when I gave the results of the trial, again he did not come to the meeting, but he never came to any of these teatime meetings from the time that Wright died. He was a delightful man to work with in many ways, and the only time I ever heard cross words from him was when I congratulated him on reaching his 80th birthday, and he flew at me in a rage and said, “I know what you want, you want the old b— to retire, and I’m not going to.”

Leonard Noon. Dr Noon and Dr Freeman were at the same school, Charterhouse, and were great friends because they were both very good at shooting. Many years later, the reason that Professor Alexander Fleming, the discoverer of penicillin, was invited to the Inoculation Department of St Mary’s Hospital was not because he was a brilliant bacteriologist but because he was a good shot! St Mary’s had a very good shooting team, and they wanted to increase its strength.

For 34 years, Noon’s father was Mathematics Master at Charterhouse, and his mother was a sister of a famous House Master at the school, which Noon entered in 1891.

Noon went to Cambridge University in 1896 as a science scholar. He obtained a Double First in his exams, so he was a brilliant undergraduate. However, it was not all work at Cambridge because he stroked his college (First Trinity) boat.

Noon qualified at St Bartholomew’s in London in 1903. He then obtained a research scholarship in bacteriology at the Lister Institute and also did further research at Cambridge with a John Lucas Walker scholarship. During the winter of 1905-1906, he worked in Paris at the Pasteur Institute in the laboratory of Professor Borrel. When back in London, Freeman persuaded Noon to leave St Bartholomew’s and join him in Almroth Wright’s laboratory in the allergy department. Wright had many different ideas in using vaccines for preventing and treating various infectious diseases. Noon thought he would try with a series of injections of solutions of *Phleum pratense* pollen to see whether he could help patients with summer hay fever.

In Germany, Noon and Freeman had learned that Dunbar had already tried injections for summer hay fever by injecting horse serum into patients. Dunbar theorized that horses could eat grass pollens without any symptoms: they must have formed grass pollen antibodies. These antibodies of the pollen toxin should help hay fever patients. Dunbar seems to have had some success, but also many patients developed serum sickness and, finally, tragedy occurred on injecting a horse-allergic patient. Dunbar himself had seasonal hay fever and, when given not horse serum but a grass pollen extract, had severe anaphylaxis.

So Noon had been persuaded to carry out research on the treatment of seasonal hay fever by Dr Freeman when he first went to St Mary’s in 1906. Both Freeman and Noon had visited Dunbar at Hamburg, who was working on seasonal hay fever and particularly how to extract what was then called “the pollen toxin.” Dunbar also had a complicated method of collecting many pure specimens of different grass pollens. Rather strangely, Dunbar had not seen Charles Blackley’s paper of 1873, which showed very definitely that grass pollen was the cause of seasonal catarrh.

Noon states in his paper that hay fever is caused by a soluble toxin found in the pollens of the grasses. This toxin is innocuous to normal individuals. Noon wrote that the pollen extract was prepared by Dunbar’s method of extraction with distilled water, aided by freezing and thawing several times. The extracts were boiled for 10 minutes after having been sealed in glass tubes. This treatment was not found to decrease the activity at all. He also states in the paper that Timothy grass (*Phleum pratense*) was found to yield the most active extract.

It may seem strange that Noon took the Fellowship of the Royal College of Surgeons and the Cambridge Degree in Surgery at a very early age. It is for this reason that, in the paper in *The Lancet*, he is described as “Mr Noon” and not “Dr Noon.” Why he took these surgical degrees and not a medical degree is not known.

It has been reported that it seems incredible that the extract was boiled for 10 minutes because many allergists have stated that this must have destroyed the activity of the pollen solution.

Rosa Augustin, an immunologist in the Allergy Department at St Mary’s Hospital, was asked by me to repeat what Noon did. Freeman said that Dunbar definitely insisted that the distilled water had to be very fresh. It was found that if the pH was 7.0, 10 minutes’ boiling did not, as Dunbar stated, cause any decrease in activity. If the pH was 6.8 or 7.2, then the activity was very quickly destroyed. Boiling for 20 minutes had the same effect.

Fresh distilled water has a pH of 7.0. It was my casual remark to Augustin that stressed that boiling for 10 minutes did not destroy the activity of the pollen extract so long as the water was freshly distilled.

Noon realized that if a series of injections was going to be given, an increase of each dose would have to be very small, and Freeman said he was told by Noon,
We will create a new unitage. Let’s multiply everything by a million, and then there will be no fractions involved. One unit is one millionth-fold dilution of the pollen in water.” Or, as Noon originally stated, “One unit of pollen toxin can be extracted from the thousandth part of a milligram of Phleum pollen.” He also found that what he called a measurement of the patient’s resistance was the strength of pollen extract necessary to excite a conjunctival reaction. He stated that only 4 units would give a reaction in a very pollen-sensitive patient, but 70 units in the less sensitive, while a normal individual would not react to 20,000 units.

It must be remembered that all Noon’s work on the sensitivity of pollen in humans was not performed by skin tests but by conjunctival testing.

Noon was so sure that his method of giving injections of the pollen extract to the pollen-sensitive patient would give good clinical results that the paper he produced in 19113 only showed in early June the results of the lessening sensitivities of the conjunctival testing, and he left it to Freeman later on in the year to describe how clinically effective this treatment was.4

Noon had tuberculosis and was feeling very ill. Almroth Wright, who could not measure Noon’s opsonic index, nevertheless told him that his phagocytes needed stimulating, and he advised Noon to take continuous mild exercise. We know that, at this time, Wright was treating tuberculosis in the ward by a series of injections and also using pneumothorax and complete rest. Wright did admit that his injections required a regulation of dosage which was often a matter of great difficulty and, in some cases, impossible. There is no record that Noon had any injections from Wright, but Wright’s advice of mild exercise seems to have started Noon’s rock climbing with friends in the Peak District, and later he decided to go rock climbing on Mount Snowdon in Wales. There he had a very severe hemoptosis and eventually died in January 1913 aged 35.

At the end of Noon’s paper, he states that, “This work is now in the hands of my colleague, Dr Freeman,” so he knew he was incapable of continuing the work that he had set out to do. Indeed, when working in the laboratory, he began to lose weight and developed a cough with a night temperature so that, when his sputum became positive with tubercule bacilli, he was banished from the laboratory.

Dorothy Noon. When he started working with grass pollen, Leonard Noon quite naturally wanted as much grass pollen collected for carrying out his experimental work, particularly in man. To collect the pollen in the summer, he asked his sister, Dorothy, to collect as much as possible. She collected grass pollen from different grasses, but as Noon states in his paper in 1911,2 he found that Timothy grass (Phleum pratense) was the strongest pollen to use. Dorothy therefore spent most of her time collecting Timothy grass pollen, which has a relatively late and short season of pollination in the UK.

Dorothy devised a method of producing grass pollen on a vast scale at the Pollen Farm, the so-called Pollinarium by Dr Freeman (Fig 3). She also instructed the local villagers to come and hand cut the individual grass stems. She told them exactly when they had to cut the grass-pollinating heads just before they began pollinating. If they were cut too soon, a lot of time was wasted waiting for the pollen to come; if too late, a lot of pollen would be lost. Dorothy was not an easy manager, and of the villagers, she said, “and some are incompetent and I cannot teach them simple things.”

Dorothy Noon was in charge of pollen collecting for the next 40 years after her brother’s death and only stopped doing so when a full-time botanist was employed by the Allergy Department at St Mary’s Hospital.

John Freeman. John Freeman was born in Leeds but went to school in the South of England at Charterhouse. One year later, Noon went to the same school, and because of their proficiency in shooting, they remained friends forevermore, although Noon went to Cambridge and Freeman to Oxford University. He served in the South African War before finishing his clinical studies at St Mary’s Hospital, where he came under the influence of Almroth Wright with the great experiment of injection therapy prophylactically and therapeutically. It was Wright who persuaded the Army medical authorities that typhoid-paratyphoid A and B vaccine was an essential prophylactic in war. Freeman joined Wright in the Bacteriological Department and, by
1907, had done enough research work to write his MD thesis on “Studies on immunization.”

Noon and Freeman spent the winter of 1905-1906 at the Pasteur Institute and later went to Germany to visit Dunbar, who was very involved in trying to treat hay fever with injections. The first successful treatment of hay fever by a series of injections was described in 1911 by Noon, and the clinical effects were described by Freeman.

During the 1914-1918 War, Freeman worked with Wright as a Liaison Officer with Russian Army Medical Service: Wright had already self-taught himself Russian. Later, they both went to Boulogne to study wound sepsis.

Freeman’s third war came in 1939 when, in the Inoculation Department with his wife, Violet, he established the local blood bank. After the war, although on paper he was Director of Clinical Bacteriology, in practice he spent all his time building up the Allergy Department and his extensive private practice.

In 1948, when the National Health Service came out, Freeman said that he would have nothing to do with it because he was not going to take instructions from politicians and the hospital. He had a department that was financially self-sufficient because it sold pollen and vaccines by arrangement with the firm Park Davis. Patients who came to the clinic were inoculated and their own adrenaline knew that they had to immediately give themselves self-administered injections according to build-up and maintenance schedules. These were usually of grass pollen, but sometimes they were injections of animal allergies.

Preseasonal injections of pollens required over 50 injections given either daily or every other day. The high dose aimed at was 1 mL of 100,000 Noon units. Reactions did sometimes occur, but patients with their own adrenaline knew that they had to immediately give themselves an injection of adrenaline for any untoward reaction. He considered that anyone over the age of 15 years should be capable of self-inoculation. Symptomatic treatment of patients with severe symptoms and often an associated pollen asthma was, in Freeman’s day, very ineffective, so perhaps it is not so amazing that so many subjects were willing to self-inoculate.

Those who came for treatment just before the pollen season started would come into hospital for “rush desensitization.” The word he coined seems to have stuck, not so the “idiotoxin” of pollen or the many complaints that now might be considered to have an allergic and possibly genetic basis, which he described as the “toxic idiopathies.” Later, he thought that “protein idiopathies” was a better term.

Freeman did not know how many years “vaccination against hay fever” should be given. By 1914, there was the suggestion that perhaps 3 years would be enough.
ratory was immediately below Fleming’s laboratory. The mold that contaminated the bacteriological plate was the *Penicillium* mold, which was being grown by the allergy department. Most *Penicillium* molds produced toxins, but luckily for mankind, the *Penicillium* mold–contaminated plate was toxic to bacteria and not to man, so that with the eventual production of penicillin, the antibiotic era had begun. Without the allergy department, this would never have so happened.

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Noon and Freeman: Prophylactic inoculation against hay fever—Part 2

The events leading up to Noon and Freeman and some of the details of their work have already been reviewed by Cohen and Frankland. In addition to the work of Dunbar, a few earlier trials of active immunization in the United States were reported by Curtis in 1900 and Scheppergrell in 1909, with Curtis trying both injections and oral administration and Scheppergrell sniffing dried pollen into the nasal cavity. They both abandoned these studies because of inconclusive results, leaving Noon and Freeman the first to establish active immunization by means of subcutaneous injections of Timothy pollen extract as effective treatment.

Their work appeared in 2 separate brief reports, the first by Noon, who studied the effect of a course of injections of pollen extract in patients with hay fever on their degree of sensitivity, as measured by conjunctival testing. He found a decrease in their sensitivities, which he attributed to active immunization. Immunization and testing were done during the off season, and he awaited the clinical response of these patients during the upcoming pollen season. The project was then turned over to Freeman, whose report followed 3 months later. Patients received their injections preseasonally and coseasonally, with the dose progressively increasing every week or 10 days, usually finishing with the fifth or sixth dose. Doses were determined, at least in part, on the basis of the degree of sensitivity to conjunctival tests done at the time of inoculation and also frequently between doses. A table listed the dates of the beginning and end of treatment, the first and last dose given, the results as reported by the patient (“patient’s opinion”), and the results as evaluated by Freeman (“writer’s opinion”).

The patients’ opinions were direct quotes of their own evaluations. The writer’s opinion was listed as “eminently satisfactory,” “moderately satisfactory,” “satisfactory,” “fairly satisfactory,” “disappointing,” “failure,” and “inconclusive.” There was no quantification such as a symptom score or evaluation of objective findings, so that it is difficult for the reader to extract concrete data from the results. An example of “eminently satisfactory” as described by a patient was as follows: “extremely bad with hay fever for last four years. Inoculated persistently during the off season; stopped treatment in May. Tested well but absolutely immune.” An example of satisfactory was as follows: “has been practically free from hay fever this season, but has felt on the verge of it once or twice. Went in hay fields, motored, etc., which was impossible formerly.” An example of fairly satisfactory was as follows: “although I came to you having hay fever rather severely, the hay fever inoculations did me an immense amount of good. . . .” The only one listed as failure was as follows: “did not improve after several inoculations . . . decided to postpone the treatment for prophylaxis in the winter.”

Freeman concluded that there was “a distinct amelioration of symptoms with fewer, milder, and more short-lived attacks, with less constitutional symptoms and less asthma,” stating that “the list is not a collection of flattering unsolicited testimonials, but gives an account of every case which had any systemic treatment, excluding only one or two people who were seen once and then lost sight of.” However, the patients’ opinions could not have been entirely avoided, and most of them coincided with his evaluations.

Freeman pointed out possible sources of error in evaluating results. These included natural bias of the physician, bias of the patient, and outside circumstances, including luck, such as a mild season. Having pointed out these sources of error, however, he dismissed them for some of the very reasons that have led clinicians through later years to recognize the need for properly controlled studies. For example, he com-
mented that the patients in his study had undergone previous “cures” that had been unsuccessful and that they were in general highly intelligent and critical, “acquainted by their position of employment to give discriminating judgments.” He did not comment on the possibility of physician bias.

In an exhaustive history of hay fever and the development of its treatment, Thommen cites no less than 15 workers in Europe and the United States who published, over the ensuing 5 years, studies with pollen extract therapy, including such pioneers in allergy as Alexander, Koessler, and Cooke and Vander Veer. All reported satisfactory results, with one interesting exception. Ellern showed favorable results in most of the 13 cases he treated but believed them inconclusive because symptoms of many of the other untreated patients were less severe during that year of 1912, possibly an example of the “luck” mentioned by Freeman.

Active immunization soon became an accepted standard treatment of hay fever, especially in patients whose symptoms were severe and unrelied by medication, limited in the early years to epinephrine, atropine, iodide, acetylsalicylate, anesthetic ether, morphone, and cocaine, the latter in very severe cases; ephedrine was not available until 1924, and even this was often inadequate and overstimulating.

Immunization schedules were preseasonal at first, followed by a variety of schedules, including year-round treatment, which came to be the gold standard again which others were judged. Allergens, first limited to pollens, came to include dust, molds, and animal materials after their causation became suspected. It was soon learned that specificity, which is characteristic of immunologic reactions, applied to pollens, and that although many were related antigenically, there were distinct differences between, for example, trees, grasses, and weeds. It was also important to know about the geographic distribution of pollens. In 1929, Durham reported on data from a number of cities in various parts of the United States in a collaborative study involving a large number of allergists, who reported on both the distribution and the concentration of pollens in cities from coast to coast in the United States. Because of this enormous contribution by Durham to the field of allergy, The American Academy of Allergy established a Distinguished Service Award, of which he was the first recipient in 1963.

In 1931, a joint committee of survey and standardization was established by the American Association for the Study of Allergy and the Society for the Study of Asthma and Allied Conditions, the parent organizations that later joined to become The American Academy of Allergy. They were unable to define standards for methods and materials and noted a lack of correlation between skin test results and allergic manifestations in many of the patients.

Over subsequent years, much research was carried out, including the discovery and elucidation of so-called “reagin,” a heat-labile, passively transferrable antibody that was believed responsible for the positive skin test responses in allergic patients, and a heat-stable antibody, called “blocking antibody,” which was induced by immunotherapy. This was believed for a while to explain its mechanism of action, but this theory has not stood the test of time. Indeed, through the years, the precise mechanism of action of immunotherapy has remained unclear, as reflected by its various names through the years: immunotherapy, desensitization therapy, and hyposensitization. Lowell once stated at a meeting of the American Academy of Allergy in the 1960s that until we understand the mechanism, it will be better to call it injection therapy (which he used as the title of his classic paper in 1964) a suggestion which correlates with Noon and Freeman, who called it “inoculation.”

Noon and Freeman’s work gave impetus over the next 5 decades to the establishment of the specialty of allergy in the United States and Europe, as well as in their own country. In the United States, through the efforts of Allergy Societies, the allergy subboards in Internal Medicine and Pediatrics were established in 1941 and 1945, respectively, combining to form the American Board of Allergy and Immunology in 1971. The first training program in allergy was started at the New York Hospital’s Allergy Clinic founded in 1920, to be followed by programs all over the country.

All of this occurred without properly controlled studies. One exception was a report by A. W. Frankland and R. Augustin, who performed a controlled study on the treatment of hay fever and asthma comparing crude pollen extract with isolated main protein component. They compared a defatted extract of Timothy/Cocksfoot pollen (then called “pollacine”), a purified pollen protein, an ultrafiltrate (which had been shown to contain little or no antigenic activity), and phenolized saline as a placebo control. Both active materials were strikingly more effective than the ultrafiltrate or the placebo. Perhaps because the only mention of “control” was in the title, which indicated a comparison between 2 active materials rather than with placebo, this article did not receive the attention it deserved. In any case, for unknown reasons, the anecdotal era continued until Lowell and Franklin changed our thinking, thus making theirs a classical article.

In 1965, they carried out their innovative double-blind study, effectively ending the anecdotal empiric era and heralding the scientific approach to studies on the effectiveness of immunotherapy for hay fever. The Lowell and Franklin article will be reported next in our “Allergy Archive” series, where the evolution of controlled clinical studies will be discussed.

None of the above is intended to reflect negatively on this seminal work of Noon, Freeman, and the
other innovative clinical researchers who contributed monumentally to the current state of immunotherapy. Noon and Freeman were the prime movers, and their article was a true classic.

Pigmies [sic] placed on the shoulders of giants see more than the giants themselves.
—Lucan (39-65)
The Civil War, Book 2, 10

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