

The ALLERGY ARCHIVES

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Pioneers and Milestones

Noon and Freeman on prophylactic inoculation against hay fever

*The physician of tomorrow may yet become an immunisator.*¹
—Sir Almroth Wright (1861-1947)

Demonstration of diphtheria toxin and its pathogenicity by Pierre Roux and Alexandre Yersin at the Institut Pasteur in 1888² 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.³ 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 antisera to the toxalbumins ricin and abrin⁴ 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,⁵ 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 Hamburg⁶ (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 pharmaceutically marketed as "Pollantin" was administered by means of nasal and ocular instillation, bronchial inhalation, and subcutaneous injection.⁷ The latter given in combination with pollen proteid, a method designed to immunize with mixtures of antitoxin and toxin, preceded by 12 years Behring's introduction of the same principle with diphtheria toxin-antitoxin.⁸ Other than objections to occasionally experienced reactions to the foreign species sera, both "Pollantin" and a competing preparation, "Graminol,"⁹ introduced by Wolfgang Weichardt of Erlangen,¹⁰ 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.

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FIG 1. Leonard Noon in his laboratory at St Mary's Hospital Medical School, 1911. (Courtesy of National Library of Medicine)

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 allergenic properties of pollen and its role in hypersensitivity mechanisms, Noon and Freeman's initial reports of therapeutic benefit^{12,13} 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



FIG 2. John Freeman. (Courtesy of St Mary's Hospital)

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.

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NOTES

1. Colebrook L. Almroth Wright: provocative doctor and thinker. London: Heinemann; 1854. p. 61.
2. Roux PPE, Yersin AEJ. Contribution à l'étude de la diphtérie. *Ann Inst Pasteur* 1888;2:629-61.
3. Behring EA, Kitasato S. Über das Zustandekommen der Diphtherie-Immunität und der Tetanus Immunität bei Thieren. *Dtsch Med Wochenschr* 1890;16:1113-4.
4. Ehrlich P. VI. Experimentelle Untersuchungen über Immunität. *Dtsch Med Wochenschr* 1891;32:976-7.
5. Blackley CH. Experimental researches on the causes and nature of catarrhus aestivas (hay fever or hay-asthma). London: Balliere, Tindall and Cox; 1873.
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.
7. A series of reports in 1903 issues of German journals summarized in Dunbar WP. The present state of our knowledge of hay fever. *J Hygiene* 1913;13:145-8.
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 toxin preparation—Smith's suggestion in 1909 for utilization of T-AT for human use (Kolmer JA, Tuft L. Clinical immunology, biotherapy 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.)
9. Weichardt-Erlangen W. Zur Serumbehandlung des Heufiebers. *Berl Klin Wochenschr* 1906;43:1184-6.
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.
11. Saunders JF, Cruse JM, Cohen SG, Lewis RE Jr. The AAI, 1913 to 1998, in the first century of immunology. *J Immunol* 1988;141(suppl):S37-54.
12. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1:1572-3.
13. Freeman J. Further observations on the treatment of hay fever by hypodermic injections of pollen vaccine. *Lancet* 1911;2:814-7.
14. Cohen SG. Firsts in allergy, Boston remembered. *N Engl Reg Allergy Proc* 1983;4:316-8.
15. Ibid. p. 329-31.
16. Cohen SG. Cooke and Vander Veer on heredity and sensitization. *J Allergy Clin Immunol* 2002;110:674-7.

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