

people. It had struck all these individuals that my father was one of the very few persons they had met who was never heard to criticize others behind their backs or to participate in such character assassination. Of course, he was appropriately critical in professional reviewing, but at a personal and social level, he was truly a model person. He was modest, kind, thoughtful, and considerate to everyone and always visited when anyone he knew was sick. He was always optimistic and equable and extremely brave and stoic when it was necessary. He was respected, loved, and appreciated by all who knew him, worked with him, or were taught by him. His given name was Jacob and the inscription on his tombstone includes the biblical verse "And Jacob was a perfect man," a description that genuinely fits him well.

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REFERENCES

1. Pepys J. Effect of local adrenaline and histamine on tuberculin reactions. *Acta Allergol* 1953;6:265-85.
2. Pepys J. The effect of nitrogen mustard on the tuberculin reaction. *Int Arch Allergy Appl Immunol* 1954;5:233-40.
3. Pepys J. Fixation of tuberculin in the skin of tuberculin sensitive human subjects. *Clin Sci (Lond)* 1955;14:253-65.
4. Pepys J. The relationship of nonspecific and specific factors in the tuberculin reaction: a review. *Am Rev Tuberc* 1955;71:49-73.
5. Pepys J. Relationship of specific and non-specific factors in the tuberculin reaction. *Acta Allergol* 1955;8:157-8.

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Jack Pepys' contributions to the medical literature

In 1977, Professor Jack Pepys presented the J. Burns Amberson Memorial Lecture at the annual meeting of the American Thoracic Society.¹ The Amberson lecturer is described by the American Thoracic Society as "An individual with a career of major lifetime contributions to clinical or basic pulmonary research and/or clinical practice." Professor Jack Pepys met those criteria. PubMed lists 196 publications under his name between 1953 and 1996; on 182 of these articles, he was the primary, senior, or sole author.

Professor Pepys' early contributions, when he was still in South Africa, were in clinical allergy. These were followed by a series of studies on aspects of the tuberculin skin test.² As he remarked in his Amberson lecture, "The presence of very high titers of precipitating antibodies to polysaccharide antigens, for example, of *Mycobacterium tuberculosis* in infected guinea pigs, stimulated my interest in a search in man for precipitins to common environmental allergens. This was greatly facilitated by the introduction of agar-gel precipitation tests." This line of investigation led to the publication, beginning in 1959, of a series of papers in leading medical journals on subjects such as the clinical and immunologic significance of

Aspergillus fumigatus in the sputum,³ and human precipitins against common pathogenic and nonpathogenic fungi.⁴ In 1962, this work led to the description of precipitins against an extract of moldy hay in the sera of patients with farmer's lung disease.⁵ The following year, the investigators identified *Thermopolyspora polyspora* and, to a lesser extent, *Micromonospora vulgaris* as major contributors to the farmer's lung hay allergen.⁶ They demonstrated the presence of precipitins to extracts of the organisms and reproduced the symptoms of farmer's lung disease by inhalation challenges in farmers with a history of farmer's lung disease who had serum precipitins to the organisms. Further epidemiologic studies revealed positive reactions on immunoelectrophoretic testing to farmer's lung hay antigens in 89% of 205 subjects regarded as having farmer's lung disease, and of these, 87% had a positive test result to the antigens derived from *T polyspora*.⁷ Professor Pepys later described studies of precipitin reactions in bird fancier's lung^{8,9} and pituitary snuff reactions.¹⁰

Allergic bronchopulmonary aspergillosis was first described by Hinson et al¹¹ in 1952. In 1959, Pepys et al³ described precipitins against *A fumigatus* in these patients. He later described the characteristics of patients with this condition as typically presenting with transitory pulmonary shadows on chest radiographs, eosinophilia of blood and sputum, type I and type III reactions to skin testing with *A fumigatus*, precipitin to *Aspergillus* in 92% of patients' sputum, plugs containing fungal mycelia in 56%, and sputum culture positive for *Aspergillus* in 58%.¹² He also described proximal bronchiectasis and fibrosis, mainly of the upper lobes in chronic cases. When he launched the journal *Clinical Allergy* in 1971, he reported on the clinical and immunologic characteristics of 111 patients fulfilling these criteria identified among 143 patients with pulmonary eosinophilia seen at the Brompton Hospital in the previous 2 years.¹²

In 1969, Pepys et al¹³ reported the results of studies of 3 workers in the detergent industry who were shown to have asthma caused by sensitization to the enzymes of *Bacillus subtilis* contained in the washing products. The methods of evaluation included skin testing and an inhalation challenge that demonstrated both early and late asthmatic reactions. The previous year, Pepys et al¹⁴ had reported that sodium cromoglycate blocked both the early and late asthmatic responses to inhalation of *Aspergillus* and serum of pigeons and parakeets in sensitized patients. Cromoglycate again blocked the responses to *Bacillus subtilis* enzymes. Over the ensuing years, Pepys conducted a series of investigations in patients with asthmatic reactions to occupational exposures. In these challenges, which were conducted in a small room at the Brompton Hospital, he generated exposures to increasing concentrations of the relevant occupation allergens by simulating the exposure that occurred in the workplace. He described varying



FIG 1. Pepys' method of simulated occupational testing for chemical agents. Patient poured a mixture of agent and lactose from pan to pan creating a dust for inhalation. Reprinted with permission from Pepys J, Pickering CA, Loudon HW. Asthma due to inhaled chemical agents: piperazine dihydrochloride. *Clin Allergy* 1972;2:189-96.¹⁸

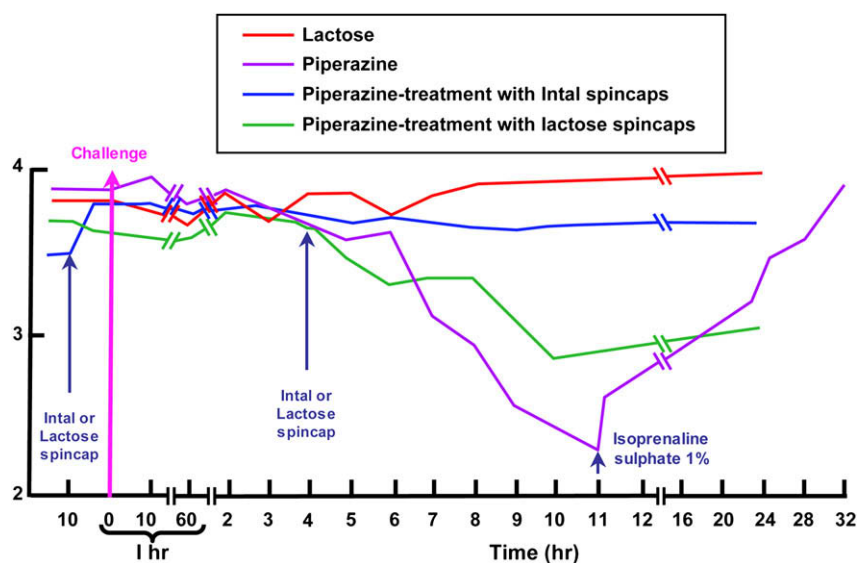


FIG 2. Results of inhalation challenge with piperazine/lactose mixture showing an isolated late asthmatic reaction and blocking of the reaction by Intal (disodium cromoglycate). Reprinted with permission from Pepys J, Pickering CA, Loudon HW. Asthma due to inhaled chemical agents: piperazine dihydrochloride. *Clin Allergy* 1972;2:189-96.¹⁸

time courses of reactions to these inhalation challenges including immediate, isolated nonimmediate, dual immediate and late, and recurrent nocturnal asthma,³ and often as well the protective effects of disodium cromoglycate and/or beclomethasone on these reactions.¹⁵ Among the occupational causes of asthma that he documented using this approach, some were administered as aerosols such as the enzymes of *B subtilis*,¹³ the urinary proteins of rats and mice,¹⁶ and water from a contaminated factory humidifier.¹⁷

Most often, the suspected agent was mixed in increasing amounts with lactose, which the patient poured back and forth from one tray to another (Figs 1 and 2). This approach was used for piperazine hydrochloride¹⁸; wood dusts¹⁹; complex salts of platinum²⁰; products of antibiotic manufacturing such as ampicillin, benzyl penicillin, 6-amino penicillin acid and related substances,²¹ spiramycin,²² tetracycline,²³ and intermediate products of sulbutamol²⁴; wheat flour for baker's asthma²⁵; and insect products such as carmine²⁶ and locusts from a breeding facility.²⁷ When the occupational exposure resulted from fumes, these were generated for the challenges, as with aminoethyl ethanolamine in aluminum soldering,²⁸ colophony (pine resin) soldering flux,²⁹ and electronic soldering³⁰; epoxy resins containing phthalic acid anhydride, trimellitic acid anhydride, and triethylene tetramine³¹; toluene diisocyanate as a component of varnishes³²; and fumes from persulfate salts and henna used in hairdressing.³³

Throughout his career, Professor Pepys maintained an interest in and contributed to the literature of clinical allergy. His first article, in 1951, was about negative skin tests in allergic rhinitis and nasal polyposis.³⁴ One of his last articles, in 1994, was on skin prick tests in the etiologic diagnosis of reactions to anesthetic and related agents.³⁵ Between these articles, he published articles on skin prick testing technique,³⁶ the spectrum of skin test reactivity in patients with asthma,³⁷ and the reproducibility of skin prick testing.³⁸ He reported studies on the high prevalence of asthma among the population of the Tristan da Cunha islands^{39,40} and was an early contributor to the studies of house dust mite sensitivity.⁴¹⁻⁴³

For 45 years, Professor Jack Pepys made numerous original and significant contributions to the field of allergy/immunology. For these contributions he received many honors from medical organizations. However, perhaps as great a tribute was that from his fellow physicians, who for many years reported in their methods skin prick tests according to the Pepys technique and occupational challenges according to the method of Pepys.

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REFERENCES

- Pepys J. Clinical and therapeutic significance of patterns of allergic reactions of the lungs to extrinsic agents: the 1977 J Burns Amberson lecture. *Am Rev Respir Dis* 1977;116:573-88.
- Pepys J. The relationship of nonspecific and specific factors in the tuberculin reaction: a review. *Am Rev Tuberc* 1955;71:49-73.
- Pepys J, Riddell RW, Citron KM, Clayton YM. Short EL Clinical and immunologic significance of *Aspergillus fumigatus* in the sputum. *Am Rev Respir Dis* 1959;80:167-80.
- Pepys, Riddell RW, Clayton YM. Human precipitins against common pathogenic and non-pathogenic fungi. *Nature* 1959;184(suppl 17): 1328-9.
- Pepys J, Riddell RW, Citron KM, Clayton YM. Precipitins against extracts of hay moulds in the serum of patients with farmer's lung, aspergillosis, asthma and sarcoidosis. *Thorax* 1962;17:366-74.
- Pepys J, Jenkins PA, Festenstein GN, Gregory PH, Lacey ME, Skinner FA. Farmer's lung: Thermophilic actinomycetes as a source of "farmer's lung hay" antigen. *Lancet* 1963;2:607-11.
- Pepys J, Jenkins PA. Precipitin (F.L.H.) test in farmer's lung. *Thorax* 1965;20:21-35.
- Faux JA, Wide L, Hargreave FE, Longbottom JL, Pepys J. Immunological aspects of respiratory allergy in budgerigar (*Melopsittacus undulatus*) fanciers. *Clin Allergy* 1971;1:149-58.
- Faux JA, Wells ID, Pepys J. Specificity of avian serum proteins in tests against the sera of bird fanciers. *Clin Allergy* 1971;1:159-70.
- Pepys J, Jenkins PA, Lachmann PJ, Mahon WE. An iatrogenic autoantibody: immunological responses to "pituitary snuff" in patients with diabetes insipidus. *Clin Exp Immunol* 1966;1:377-89.
- Hinson KFW, Moon AJ, Plummer NS. Broncho-pulmonary aspergillosis. *Thorax* 1952;7:317-33.
- McCarthy DS, Pepys J. Allergic broncho-pulmonary aspergillosis. *Clin Allergy* 1971;1:261-86.
- Pepys J, Longbottom JL, Hargreave FE, Faux J. Allergic reactions of the lungs to enzymes of *Bacillus subtilis*. *Lancet* 1969;1:1181-4.
- Pepys J, Hargreave FE, Chan M, McCarthy DS. Inhibitory effects of disodium cromoglycate on allergen-inhalation tests. *Lancet* 1968;2: 134-7.
- Pepys J, Davies RJ, Breslin AB, Hendrick DJ, Hutchcroft BJ. The effects of inhaled beclomethasone dipropionate (Beclotide) and sodium cromoglycate on asthmatic reactions to provocation tests. *Clin Allergy* 1974;4:13-24.
- Taylor AN, Longbottom JL, Pepys J. respiratory allergy to urine proteins of rats and mice. *Lancet* 1977;2:847-9.
- Taylor AN, Pickering CA, Turner-Warick M, Pepys J. Respiratory allergy to a factory humidifier contaminant presenting as pyrexia of underdetermined origin. *BMJ* 1978;2:94-5.
- Pepys J, Pickering CA, Loudon HW. Asthma due to inhaled chemical agents: piperazine dihydrochloride. *Clin Allergy* 1972;2:189-96.
- Pickering CA, Batten JC, Pepys J. Asthma due to inhaled wood dusts, Western red cedar and Iroko. *Clin Allergy* 1972; 2:213-8.
- Pepys J, Pickering CA, Hughes EG. Asthma due to inhaled chemical agents: complex salts of platinum. *Clin Allergy* 1972;2:391-6.
- Davies RJ, Hendrick DJ, Pepys J. Asthma due to inhaled chemical agents; ampicillin, benzyl penicillin, 6 amino penicillanic acid and related substances. *Clin Allergy* 1974;4:227-47.
- Davies RJ, Pepys J. Asthma due to inhaled chemical agents: the macrolide antibiotic spiramycin. *Clin Allergy* 1975;5:99-107.
- Fawcett JW, Pepys J. Allergy to a tetracycline preparation—a case report. *Clin Allergy* 1976;6:301-4.
- Fawcett JW, Pepys J, Erooga MA. Asthma due to "glycyl compound" powder an intermediate in production of sulbutamol. *Clin Allergy* 1976;6:405-9.
- Hendrick DJ, Davies RJ, Pepys J. Bakers' asthma. *Clin Allergy* 1976;6:241-50.
- Burge PS, O'Brien IM, Harries MG, Pepys J. Occupational asthma due to inhaled carmine. *Clin Allergy* 1979;9:185-9.
- Burge PS, Edge G, O'Brien IM, Harries MG, Hawkins R, Pepys J. Occupational asthma in a research centre breeding locusts. *Clin Allergy* 1980;10:355-63.
- Pepys J, Pickering CA. Asthma due to inhaled chemical fumes—amino-ethyl ethanolamine in aluminum soldering flux. *Clin Allergy* 1972;2:197-204.

29. Fawcett JW, Taylor AJ, Pepys J. Asthma due to inhaled chemical agents-fumes from "Multicore" soldering flux and colophony resin. *Clin Allergy* 1976;6:577-85.
30. Burge PS, Harries MG, O'Brien L, Pepys J. Bronchial provocation studies in workers exposed to the fumes of electronic soldering fluxes. *Clin Allergy* 1980;10:137-49.
31. Fawcett JSW, Taylor AJ, Pepys J. Asthma due to inhaled chemical agents-epoxy resin systems containing phthalic acid anhydride, trimellitic acid anhydride and triethylene tetramine. *Clin Allergy* 1977;7:1-14.
32. Pepys J, Pickering CA, Breslin AB, Terry DJ. Asthma due to inhaled chemical agents, tolylene di-isocyanate. *Clin Allergy* 1972; 2:225-36.
33. Pepys J, Hutchcroft BJ, Breslin AB. Asthma due to inhaled chemical agents—persulphate salts and henna in hairdressers. *Clin Allergy* 1976;6:399-404.
34. Pepys J, Duveen GW. Negative skin tests in allergic rhinitis and nasal polyposis. *Int Arch Allergy Appl Immunol* 1951;2:147-60.
35. Pepys J, Pepys EO, Baldo BA, Whitwam JG. Anaphylactic/anaphylactoid reactions to anesthetic and associated agents: skin prick tests in aetiological diagnosis. *Anesthesia* 1994;49:470-5.

36. Pepys J. Skin tests for immediate, type I, allergic reactions. *Proc R Soc Med* 1972;65:271-2.
37. Hendrick DJ, Davies RJ, D'Souza MF, Pepys J. An analysis of skin prick test reactions in 656 asthmatic patients. *Thorax* 1975;30:2-8.
38. Clarke CW, Mitchell J, Nunn AJ, Pepys J. Reproducibility of prick skin tests to five allergens. *Clin Allergy* 1982;12:1-8.
39. Citron KM, Pepys J. An investigation of asthma among the Tristan da Cunha islanders. *Br J Dis Chest* 1964;58:119-23.
40. Mantle J, Pepys J. Asthma amongst Tristan da Cunha islanders. *Clin Allergy* 1974;4:161-70.
41. Pepys J, Chan M, Hargreave FE. Mites and house-dust allergy. *Lancet* 1968;1:11270-2.
42. Holford-Strevens V, Wide L, Milne JF, Pepys J. Allergens and antigens of *Dermatophagoides farinae*. *Clin Exp Immunol* 1970;6: 49-59.
43. D'Souza MF, Pepys J, Wells ID, Tai E, Palmer F, Overell BG, et al. Hyposensitization with *Dermatophagoides pteronyssinus* in house dust allergy: a controlled study of clinical and immunological effects. *Clin Allergy* 1973;3:177-93.