

Ann Janet Woolcock 1937–2001

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Ann Woolcock graduated in medicine from the University of Adelaide and pursued postgraduate studies in respiratory medicine with Professor John Read at the University of Sydney. Her MD thesis, awarded in 1967, was on the mechanical behaviour of the lungs in asthma. From 1966 to 1968 she worked with Professor Peter Macklem at McGill University in Canada, then returned to the University of Sydney to continue researching asthma. Her work in asthma and epidemiology showed that asthma was caused by allergens but that there is a genetic component. Her clinical research was a major contribution to better outcomes in asthma, in particular, the demonstration and practical measurement of airway hyperresponsiveness and her subsequent research that examined its contribution to asthma severity and the ways in which treatments were able to reduce it. In 1989 she wrote, with others, the world's first national guidelines for asthma management, the Australian Asthma Management Plan. In 1984, she was appointed to a personal chair of Respiratory Medicine at the University of Sydney. She founded the Institute of Respiratory Medicine in 1985, based at Sydney's Royal Prince Alfred Hospital. After her death, the Institute was renamed the Woolcock Institute of Medical Research in her honour.

Childhood

Ann Woolcock was born on 11 December 1937 in Adelaide. Her family lived in Reynella, South Australia, then a small country town in the midst of vineyards. Her parents ran the general store from where her mother developed a sideline selling women's clothing that her taste and acumen turned into a highly successful business. Ann's own sense of fashion and her emphasis on always being well dressed can be traced to her mother's influence. Throughout her life, Ann felt that she, and all women, should dress 'up' to the occasion and be stylish, rather than play down their appearance with casual clothes. In particular, she wanted to avoid the 'dowdy academic' stereotype. According to her husband, Ruthven Blackburn, it mattered to Ann that she was always well dressed: 'In outpatients, of course, she wore the classic white coat but when she appeared on a platform or anywhere, Ann was always concerned that she should be well dressed, not fancy dressed but well dressed.' She would send for clothes from her mother's shop in Adelaide; later, her brother Robert would help her choose what would suit.

Ann Woolcock was the eldest of four children born to Angus Norval Woolcock and Dulcie Annie (née Woodroffe). Her sister Sue Basten



remembered that 'Ann was always in charge and we all looked up to her. We knew she knew what to do and we all (Sue and her two brothers) did as she told.' According to Sue, their mother was 'a bit scatty'. A very good businesswoman and very artistic—'she taught us all to appreciate classical music, for example'—but there would be nothing for dinner. She would have lovely flowers

on the table but Ann would do the cooking, not just for the family but on special occasions too. 'She would only have been about twelve and she cooked this beautiful meal because someone was coming to dinner. She was very, very capable right from the beginning.'

According to Sue, Ann loved to organize everything: 'When the family went on holiday, she would have lists with everything ticked off. I think she had more fun doing the lists and packing us all up than going on the holiday.' Asked whether she was bossy, Sue replied 'Absolutely'. However, her siblings took that as a given: 'You just dealt with the "Do this, do that".' Like their parents, Ann had no tact: 'She'd just say whatever came into her head, like, "That dress looks shocking on you, take it off", or "Your hair's not right".' Looking back, Sue wonders why she didn't take offence: 'Perhaps because she wouldn't be saying it to put you down. It was because it was a correct fact. I just knew she'd be right so I'd better do it. And my parents too. She'd boss them around and they'd do it. I used to think it was very funny.'

Education

Ann Woolcock was educated first at the Reynella Public School and then at an Anglican school at Unley in Adelaide called Walford House (later Walford Church of England Girls' Grammar). She and her sister would catch the morning bus together: 'Ann would be practising the piano to the last second and we'd be screaming at her, "The bus is coming" and be racing out the door because the bus stop was outside our house but she would use every second, as she did for the rest of her life.'

At Walford, Ann stood out. 'She was brilliant', said Sue Basten: 'I'm not studious like Ann. She wanted to get a hundred per cent. I was only interested in eighty per cent if I could have another two sets of tennis. Ann didn't want to play sport. She would just study. She wanted to really understand everything she was doing so she could do it to perfection – all the time. She was very clever, but she also worked hard.' The sisters were close and Sue had no memory of feeling jealous. She puts this down to their difference in character and interests: 'I could do my thing and she treated me as an equal always. I wasn't 'That stupid little sister'. But she looked

after me. When I started school, she would keep an eye on me. She was a very loving, caring person.'

After finishing school, Ann enrolled in Science at the University of Adelaide, but switched to Medicine the following year. A language was required to matriculate for Medicine so she sat a supplementary examination in French in order to qualify. She played down the significance of the switch with self-deprecating humour: 'I investigated transferring to medicine, partly because I was having a really, really good time as an undergraduate (especially away from home) and I thought that six years of medicine would be much better than three years of science.'

From the age of fifteen, science and mathematics had dominated Ann's studies. Despite being educated at a girls' school, which in those days usually concentrated on the humanities, she had the benefit of excellent teachers in physics, chemistry and mathematics that stood her in good stead in the medical course where she gained many credits and distinctions during her six years. According to her sister, however, Ann never felt that her success was predictable: 'I can remember her final exam. She was exclaiming, 'It's impossible, it's impossible, I can't do it. You can't learn it all.' This is how she'd go on. We never believed her because we knew she'd be all right. She was a bit of a drama queen. Not a show-off. She would just get very keyed-up. And then she'd come among the top few.'

Early Career

In 1961, Ann graduated MB BS with a Fifth Distinction in Final Year. She spent the following twelve months as an intern at Royal Adelaide Hospital before moving to Broken Hill in out-back New South Wales for her second year out. She thought the Broken Hill and District Hospital would be a good place in which to learn and it was: 'I certainly learnt how to do everything, very quickly, from autopsies to cardioversions to diagnosis, through to delivering babies.' Her year in the Silver City fuelled an interest in geology that she pursued with characteristic dedication. The result was an extensive mineral collection, all perfectly preserved and labelled. Geology became a lifelong interest. In the months before her death, her reading included *The Field Guide to Rocks and Minerals*.

Recognizing that she could not spend the rest of her life in Broken Hill, Ann wrote to professors of medicine in Melbourne, Sydney and Brisbane asking if they knew of a job available in medical research. The only reply she received was from Professor Ruthven Blackburn from the University of Sydney, who sent her a list of possible jobs. In 1962, after an interview with John Read, Professor of Respiratory Medicine at the University of Sydney, she was appointed to set up a lung function laboratory at the Page Chest Pavilion at Royal Prince Alfred Hospital (RPAH). In the midst of this process, Read suggested that she do some research in asthma because the New South Wales Asthma Foundation was being established. Later in 1963, when the Foundation raised the immense sum of a quarter of a million pounds for asthma research, Ann was among the first to receive one of its scholarships. She spent the next three years researching the mechanics of the lung for her MD and delivered a thesis that Professor Read described as ‘one of the finest he had read’. Her work into the hyperinflation (trapping of air in the lungs) that occurs during an asthma attack with decrease in lung elastic recoil and, following appropriate therapy, its return to normal, was ground-breaking (Smith 2003, p. 101) (1–5, 9).

In 1966, Ann received a Travelling Research Fellowship from the Asthma Foundation and went to McGill University in Canada, to work as part of Professor Peter Macklem’s team. During her time there she published significant papers about the large and the small airways, the mechanical behaviour of the lungs and collateral ventilation other aspects of the lungs (8, 10, 11, 12, 14, 18). She also developed a test of the resistance in the airways. Called the ‘frequency dependence of compliance’, it was an uncomfortable test for the patient and is no longer used much (13). At the time, however, it became a standard test. It also spurred people to think about how to measure the small airways.

Ann’s time in Montreal was notable for personal reasons also. In 1968, she married Ruthven Blackburn in a private ceremony at Peter Macklem’s home. Her family was delighted with the marriage. Ruthven had meticulously gained her father’s consent beforehand and Sue Basten and their younger brother Robert travelled to Canada for the ceremony. ‘We were all pleased,’ said Sue Basten, ‘It was very hard in those days for a

clever woman to marry: no one wanted a smart, clever wife... She needed someone who had already achieved... so he wouldn’t be jealous of her and could encourage her to do her bit. And he loved her.’ Ann and Ruthven had two sons, Simon born in 1969 and Angus in 1973. Later in life, Ann paid tribute to Ruthven’s influence: ‘Very early on, when we were first married, he said ‘If you want to be an academic, you could be and you should be.’ He pushed me, saying that I should never say no until I had reached enough maturity and established myself that I could say no. So I said yes to everything. He helped me a lot. If I wasn’t home for dinner or the children needed help, he was very supportive. There was never a problem.’

In 1971, Ann Woolcock began the clinical training required for membership of the Royal Australasian College of Physicians (RACP). The examination was conducted by Drs John Chalmers and Tony Rebeck, who did teaching rounds for people training as registrars in which Ann, who was pregnant, took part. Stephen Leeder, later Dean of the Department of Medicine at the University of Sydney, was also part of the group. He recalled: ‘They were pretty brutal sessions, actually. If you didn’t know your stuff you got walloped.’ The sight of Ann Woolcock being ‘walloped’ would have amused the many researchers who were subsequently trained by her, all of whom at times endured her regular Friday sessions to report about their projects when being ‘walloped’ was a real prospect.

Preparation

On her return from Canada, Ann was still funded as a Senior Research Fellow by the Asthma Foundation of New South Wales. This was followed by the Basser Research Fellowship of the Royal Australasian College of Physicians, in the Department of Medicine at the University of Sydney. She continued research under John Read as well as paying visits to New Guinea for epidemiological projects but, in her view, she did not really have a job: ‘I did research but to earn money I went out and did clinical work at Concord Repatriation General Hospital, at Royal North Shore and also RPAH.’ She ran outpatients’ clinics at RPAH and at Concord. At Concord, she met Norbert Berend and greeted his decision to undertake an MD with her

usual infectious enthusiasm for research. For his thesis, jointly supervised by Ann, he performed detailed measurement of pathological changes in the airways and parenchyma of resected lungs of smokers with lung cancer (37, 47–48, 52–53).

On another front, Ann was actively involved with the New South Wales Asthma Foundation in educating community groups about asthma, or at the swimming pool on Saturday mornings, young children in tow, in conducting lung function tests at the side of the pool. Along with Dr Julian Lee, she was a member of the Foundation's Research Advisory Committee and she joined the Board in 1973. In late 1972, under the auspices of the Foundation, the first National Study Workshop drew together asthma researchers from around the country. Attendees included Kevin Turner from Western Australia who spoke about his investigation of allergies in the Busselton district that was to become a long-term point of reference for epidemiologists. Edmund Tai who, with Ann, was one of the first research fellows to be funded by the New South Wales Foundation, attended from Melbourne. He found the opportunity to hear about work being done across the continent 'informative and rewarding'. The first workshop had been predominantly organized by Ann. Thereafter, she and Eddie Tai organized it jointly on an annual basis (Smith 2003, pp. 157–158).

According to Sue Basten, Ann enjoyed motherhood. Her varied activities between 1969 and 1973 fitted well, as Ann explained: 'Not having a fixed job, I didn't have much teaching. Mainly I was looking after my two children. Then I became the Clinical Supervisor at Concord, looking after the students in the clinical school, which was fun and it did involve a fair bit of teaching and so my head was down. Basically though, I wasn't too worried about anything else except doing research.' In fact, she multi-tasked as she did all her life. As demands on her time increased, she would take her baby to meetings and clinics and breastfeed him regardless of any consternation this caused. In an emergency, or if one of the children became ill, Sue Basten's home was the first port of call. And the habits of her childhood were again to the fore as Sue described: 'Ann would be up early and she'd be at work at seven. She always worked terribly long hours, but she managed exceptionally well. She'd

have the shopping organised and the children organised and us (Sue's family) organised.'

These activities, however, were all preparatory. Ann was trying to make up her mind which direction to take. Circumstances created an opening when John Read died. In 1973, she was appointed Senior Lecturer in the Department of Medicine at the University of Sydney. She would become Associate Professor in 1976, followed in 1977 by appointment as Head of Thoracic Medicine at RPAH (Mellor 2008). In 1974, she told one of her students, 'I'm going to concentrate on asthma. Forget everything else. Be single-minded.' In the next twenty-five years, her strategic skills in advancing asthma research across many fronts would become apparent.

University of Sydney

Ann Woolcock began recruiting postgraduate students. One of the earliest was Iven Young who first met Ann in 1972, in a corridor. There was no time wasted on polite introductions: 'She almost accosted me.' A barrage of questions followed: 'What are you doing? You need to do research.' At that stage he was not sure what he wanted to do and she encouraged him to get into gas exchange physiology, especially as this was a gap in departmental expertise following John Read's death. Some months later, when Iven decided he would do PhD research into pulmonary gas exchange, he became a Research Fellow with Ann as his supervisor (46, 51). Following postdoctoral work in California, he returned to Sydney in 1991 to continue as a physician at RPAH. In 1993, he succeeded Ann as Head of Department when she turned her attention to the development of the Institute of Respiratory Medicine.

Ann's early postgraduate students also included Stephen Leeder (of whom more below), John Armstrong (later Head of Respiratory Medicine at Princess Alexandra Hospital in Brisbane), Bob Edwards (founder of the Lung Foundation), John Mann (senior physician at the developing Liverpool Hospital) and David Allen (senior physician at Royal North Shore Hospital).

Epidemiology

During the 1970s and early 1980s, Ann Woolcock's research focus was epidemiology. Her interest dated back to experience in New Guinea



Figure 1. Ann Woolcock and Ruthven Blackburn performing an electrocardiograph on a villager, Pompomere, Eastern Highlands, Papua New Guinea, c. 1966.

in the 1960s. In 1964, Ruthven Blackburn had begun a long-term project on the epidemiology of liver disease in New Guinea. Noticing the prevalence of coughing among the population, who lived in very smoky huts, he asked his colleague John Read for a respiratory researcher to investigate its cause. This led to Ann's visiting New Guinea in 1965 and again in 1966 before leaving for Montreal later that year (Fig. 1). She and Ruthven Blackburn did further research in New Guinea in 1969–71 (15–16).

Subsequent epidemiological studies were carried out in the next ten to twelve years in Papua New Guinea, particularly at Baiyer River in the Western Highlands (which included also a visit to Madang), in the Kuniawa River District and at Okapa (Eastern Highlands) (61, 67, 69, 71, 77, 87–88, 112). The prevalence of asthma in patients with kuru was a particular focus. For epidemiological research, Ann also visited a village at Kano in Northern Nigeria, Singapore where she investigated the prevalence of asthma

in school children, Kung Kaang in Northern Thailand, and Hanjura near Srinagar in Kashmir which she visited three times in two years. Visits usually lasted seven to ten days and many publications emerged from the work.

The work in Papua New Guinea proved extremely influential, not only for its findings but for the subsequent research it triggered. Ann's team included Wesley Green, a technical officer in the Department of Medicine at the University of Sydney, among others. They found no incidence of asthma but much evidence of widespread chronic obstructive pulmonary disease (COPD) that was severe and caused many early deaths. They found that COPD could arise in non-smokers as well as in those who smoked. Furthermore, environmental factors could create passive smokers. Gender could also be significant with the data showing a slight skew to greater prevalence in women.

Ann recalled that working in Papua New Guinea taught her a lot about epidemiology and

revealed its potential as a tool that could be used to track changes in asthma and detect risk factors: 'We started thinking about setting up some epidemiological studies to get a test of airway hyperresponsiveness which we could do in schools.' She and Ruthven planned a large-scale study of 12,000 Australian schoolchildren that would measure the growth of their lung function and the factors that influenced it. Initially, they obtained funding for a two-year project from the Tobacco Foundation, which was, in those days, a common source of financial support for everything from the performing arts to science.

In 1969, Ann and Ruthven had met Stephen Leeder who was doctor in charge of the Baptist Mission Hospital at Baiyer River. Learning that he had become interested in public health and epidemiology, they invited him to do his PhD with them. His investigation focused on whether smoking in school children affected lung function and established that it did. His doctorate was awarded in 1974 (Leeder 1974) (24, 26–27, 34–35). Subsequently Leeder did important work overseas, establishing the dangers of passive smoking, particularly for young children whose parents smoked.

A research assistant named Jenny Peat, an honours BSc from Britain, had collected lung-function data for the studies that formed Stephen Leeder's thesis. With that task finished, her role expanded to handling the massive data the team had accumulated. Some of the information was stored in early versions of computer databases, a technical innovation that ultimately expanded into a sophisticated network after John Reynolds joined Ann's team in 1988 as IT Manager.

The investigation into school children was not just large in breadth but continued longitudinally as well. Cheryl Salome, who started work as Ann's research assistant in 1974, did many lung-function tests with asthmatic children who came into the laboratory for follow-up.

Many asthma epidemiology projects around Australia were subsequently conceived by Ann and flourished under her leadership. Christine Jenkins described her as 'a driving force' in asthma epidemiology: 'this work brought her great international distinction and respect. It also emphasised the relevance of population health studies to the practice of clinical medicine and she never lost an opportunity to make population health relevant to the individual.'

Airway Hyperresponsiveness (AHR)

Airway hyperresponsiveness is an important feature of asthma, where the airways are exquisitely sensitive to stimuli that cause them to narrow. Bronchial provocation tests, in which asthmatic subjects were exposed to environmental or occupational agents, such as allergens, to provoke airway narrowing, were being used diagnostically to assess AHR by allergists during the 1960s and early 1970s, but these tests were complex and risky and required close supervision of the patient for up to eight hours. In 1975–6 research groups in Canada and the USA published protocols for bronchial provocation tests using drugs such as histamine and methacholine, which did not have the same risks as allergens. They were still too technically complex, however, for use in epidemiology or routine clinic use.

Ann Woolcock was determined to find a simple, portable test to measure AHR, but getting the methods right involved what she described as 'lots of stops and starts'. Her first experiments with methacholine, using a very simplified protocol with hand-held equipment, were undertaken in 1977. For this, she studied a group of soldiers at Holsworthy army base on the outskirts of Sydney, showing that the technique was safe to use in healthy subjects. Further studies, undertaken by Cheryl Salome and Robyn Schoeffel (research assistants) and Kwok Yan (respiratory physician) at RPAH, were designed to refine the test, making sure it was safe for use in asthmatic patients. One of the earliest studies showed that histamine and methacholine produced similar results, and because previous studies suggested that there were differences in the stability of histamine and methacholine in solution (later disproven), histamine with its longer shelf life was selected as the most economical and convenient drug to use in further studies. The paper describing the final protocol was published in 1983 and remains Ann's most highly cited scientific paper (79).

Epidemiology of AHR and Asthma

In 1980, with a working protocol for the bronchial provocation test, Ann and her research assistant Cheryl Sedgwick carried out an initial pilot study on children in the small village of Banyuatis in northern Bali, in Indonesia (70, 83).

The study was a collaboration with Professor P. G. Khonten, a respiratory physician in Jogjakarta. The aim of the pilot study was to standardize the procedures, which included allergen skin-prick tests, which were routinely used in the clinic, as well as questionnaires, basic lung-function tests and the bronchial challenge test, and to test the practicality of this procedure under field conditions. This pilot study paved the way for a much larger study undertaken in 1983 (83).

In 1981, Ann joined the Busselton health survey—the population of Busselton had been surveyed every three years since 1966 by teams from the University of Western Australia—where she undertook the world's first study of the prevalence of AHR in a large random population of adults. The results were published in 1987 (102) and follow-up studies were undertaken in Busselton in 1983, 1987 and 1992 (127, 148–149).

In 1982, the first study of the prevalence of asthma in children was undertaken in New South Wales, in Belmont and Wagga Wagga, studying 2,363 schoolchildren between 1982 and 1984. In Belmont, the field team had support from Stephen Leeder, who was by then Professor of Community Medicine at the University of Newcastle. In Wagga Wagga, field support was provided by the local branch of the New South Wales Asthma Foundation. Jenny Peat continued to manage and analyse the data collected. The use of standardized protocols for all of the studies meant that data could be pooled in the accumulating databases concerning risk factors for asthma (91, 93, 100–101, 103).

These seminal studies provided major breakthroughs in understanding. The working hypothesis for the study was that asthma and AHR would differ in areas where the prevalence of house dust mites differed (high in humid Belmont and low in the dry inland of Wagga Wagga). However, what became evident was that allergic sensitization was the most important risk factor for asthma and AHR in both children and adults. AHR was slightly more prevalent in Wagga Wagga but where people lived, whether inland or on the coast, made only a small contribution to the risk. Where children lived determined what they became allergic to, however, and this varied regionally between mites, pollens or fungi.

Once it became known that Ann and her team had the tools to measure the prevalence of

asthma, there were requests from many communities concerned that local environmental factors could affect asthma. Studies were undertaken in coastal suburbs of Sydney, such as Sans Souci in response to concerns about sewage outfalls, and in Western Sydney in response to concerns about air pollution. In Villawood in 1986 Jenny Peat's study of 417 children demonstrated that being atopic was a major risk in developing twitchy airways. Genetic factors were also significant (108, 119, 136, 137, 160, 162). If a child's parents had asthma, then the risk increased (Smith 2003, p. 236–237).

Risk-factor studies focused on areas or populations where there was some variation in the prevalence of the disease, to try to identify the factors that might promote high or low prevalence:

- Seven regions of New South Wales, to compare prevalence of AHR and symptoms in regions where hospital admissions for asthma varied widely (151, 161, 171, 185);
- Aboriginal populations in far north Queensland and central Australia with differences in lifestyles, allergen exposure and genetic background (196, 209);
- longitudinal studies in Belmont—the original cohort of children was restudied every two years until age 18, then every five years, to understand the effects of age and lung growth on risks for asthma and AHR (193, 239, 249);
- South Fore region of PNG, where there was an extraordinary 'epidemic' of severe asthma that was associated with severe allergic sensitization to house dust mites (88, 112);
- A laboratory study of adult asthmatics to determine the effects of indoor air pollution by oxides of nitrogen from gas heaters. This study was a collaboration with CSIRO (195).

Intervention Studies

Ann Woolcock was keen for Australians to be at the forefront of investigations into the role of mite and allergens as the cause of asthma. She was aware of Euan Tovey's significant research in England using a newly developed assay for mite allergens that had revealed that the major source of the main house dust allergen in house dust mite was their faeces and that these faeces become airborne like pollen and are widely distributed within houses. In 1982 Tovey had been

involved with Professor Tom Platts-Mills in a landmark study that showed that some asthmatics dramatically improved if they were isolated in an allergen-free environment (Tovey, 1981a, 1981b). In 1989, Euan Tovey joined the Institute of Respiratory Medicine. He recalled Ann at their first meeting as ‘friendly, challenging, direct, smiling, sharp . . . and interested to have me. Her broader interests were from nurturing Cheryl [Salome] and Guy [Marks] and Jenny Peat as epidemiologists. My allergen work was compatible to those interests.’ An early task was collaborating with Ann in preparing an ultimately successful grant application. He was struck by how committed she was with staff and their grant writing: ‘She gave everyone her time, polishing language and refining ideas.’

The accumulating evidence of the importance of allergic sensitization, particularly in temperate climate zones to house dust mites (HDM), begged the question of whether reducing exposure could reduce the severity of asthma or even prevent it (138, 145). Euan Tovey set up the allergen side of Ann’s intervention studies, devising methodology for collecting, measuring and assessing them. To facilitate the collection of small samples, he created tiny vacuum-cleaner bags that allowed a field team to measure all the factors about the prevalence and characteristics of allergy and asthma as well as to measure the quantities of allergen exposure that might be responsible (161).

During the early 1980s, Wesley Green, working for Ann, had developed a spray based on tannic acid that could denature the house dust mite allergen so that it no longer triggered an allergic response (116). In 1989 a clinical trial of the spray with asthmatic patients formed part of Guy Marks’ doctorate, which was supervised by Ann Woolcock (170). A second and major part of Marks’ project was the development and testing of a quality-of-life questionnaire that could be used as an outcome in clinical trials (146, 158).

By 1990, Ann Woolcock was convinced that allergy was the greatest risk factor for asthma. Speaking at a conference of the American Thoracic Society in 1990, she told her audience of pulmonologists that she believed asthma was caused by allergens. Her willingness to take a stance on this longstanding controversy played a significant role in shifting people’s thinking (Smith 2003, p. 232).

In the early 1990s, Ann became interested in the role of diet in asthma. She was senior investigator on studies by Linda Hodge and Jenny Peat respectively. The latter’s analysis during her doctorate (1991–4) of the accumulating database for risk factors had thrown up a surprising indication that regular consumption of fish was associated with a reduced risk of asthma (151). In 1993, Linda Hodge, who was a dietitian at RPAH, carried out a detailed dietary analysis of 800 children in the Sydney area for her Master of Science in Medicine. She confirmed that consumption of oily fish was associated with reduced risk of asthma (192, 216).

Interest in both diet and allergen exposure culminated in the establishment of the Childhood Asthma Prevention Study (CAPS) in 1997, the idea for which had been brainstormed at a meeting that included Ann Woolcock, Stephen Leeder, Jenny Peat, Craig Mellis, Euan Tovey and Guy Marks. This was a major study involving a birth cohort of 616 children in the first five years of life and aimed to test, separately, the preventive effect of fish-oil supplementation and house dust mite avoidance in a randomized, placebo-controlled study (Marks *et al.* 2006). Essentially CAPS found no benefit (slightly more eczema in the intervention group), nor did other large mite-intervention trials conducted around this time.

Physiology of AHR

Not all allergic people, however, have asthma. As Ann Woolcock explained at the beginning of the 1990s, ‘There seem to be two different asthma phenotypes: being allergic and having some other abnormality that turns the airways into being hyperresponsive.’

During the focus on epidemiological investigation of asthma in the 1980s, work on the physiology of the airways had continued.

In 1985, Ann’s AHR research team led by Cheryl Salome and Kwok Yan established that normal airways are qualitatively different from those with asthma. No matter how much you stimulate them, normals never narrow as much as asthmatics. Instead, they reach a plateau in their response beyond which there is no further reaction (Fig. 2). This finding is still highly cited by researchers (84).

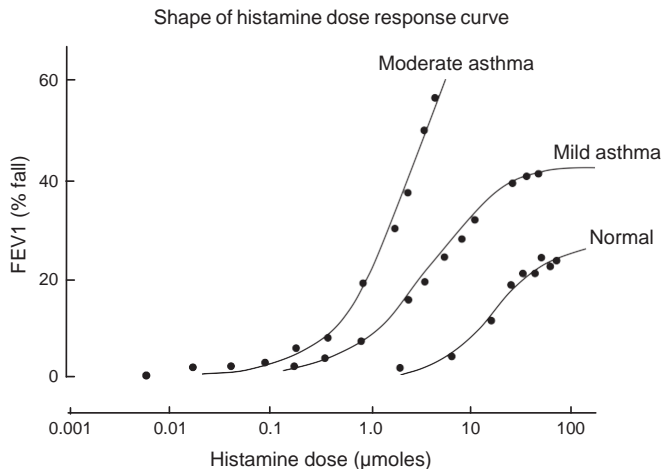


Figure 2. In a normal person, increasing concentrations of histamine lead to a fall in lung function that reaches a plateau, whereas in a person with asthma this fall does not reach a plateau.

Between 1989 and 1993, Watchara Boonsawat, a respiratory physician from Thailand, completed a doctorate under Ann's supervision that advanced knowledge of the plateau. His study showed that inflammation associated with allergen exposure increases the level at which the plateau occurred (that is, makes it worse) (144).

Between 1994 and 1997 Greg King, who was one of Ann's last postgraduate students, demonstrated that airway closure increased in asthma (205, 217). Greg valued Ann's 'light touch' as a supervisor: 'She allowed great intellectual freedom', he recalled. He was also encouraged by her lasting enthusiasm for the area of research in which she had begun so many years before: 'She was still driven by a desire to understand airway hyperresponsiveness in asthma from a mechanistic and physiological point of view.'

By 1999, this further research into asthma physiology meant that Ann Woolcock could describe how establishing allergy as the basis for asthma led to recognition that, in addition to using inhaled corticosteroids, one needed to stop the triggers but that there were other factors to consider as well. Speaking at the Asthma Workshop that year, she said: 'Throughout the 1990s, it became clear, with the advent of the longer-acting β -agonists, that there are in fact two abnormalities in everybody with asthma, that is, virtually everyone: the allergic inflammation and abnormal behaviour in their airway smooth muscle.' (Asthma Foundation Archives).

Pharmacology, Biology, Cells & Molecules

Meanwhile the science of pharmacology had become important to asthma researchers in Australia. In Sydney during the 1980s, assays were set up to measure the mediator histamine under the auspices of Diana Temple, then Head of Pharmacology at the University of Sydney. Judy Black and Carol Armour both trained with Diana Temple and in the course of this, Judy Black encountered Ann Woolcock: 'I was bowled over by her enthusiasm for research in general, basic research in particular, especially encouraging in someone who was in essence a clinical researcher.' Carol Armour went to work with Professor James Hogg in Canada. In Sydney, Ann Woolcock facilitated Judy's investigation into the way asthmatic patients' airways behaved *in vivo* and the way their tissue 'bits' contracted and relaxed in the laboratory. Ann described this work as 'the best smooth muscle studies in the world', something she believed was achieved by Judy Black's insistence on studying human muscle obtained from airways removed during lung surgery rather than airway muscle from laboratory animals (73, 80, 92).

Clinical Applications of AHR

Ann Woolcock was always as much a clinician as she was a scientist. For example, under her supervision in 1980–3 Kwok Yan undertook an

MD into the nature of AHR in subjects with asthma, COPD and rhinitis. His work showed that tight control of asthma with standard treatment reduced AHR (90).

In 1985 Christine Jenkins had begun her MD in thoracic medicine at Concord Hospital. As a trainee physician at Sydney Hospital, she was full of trepidation that she might have Ann Woolcock as her examiner: 'She had a reputation as a ferocious interrogator.' In fact she was not allocated to Ann but she experienced the full impact of the Woolcock personality when in the second year of her MD, she submitted an abstract to the Thoracic Society in which she described work she had done on the effect of respiratory infections on airway hyperresponsiveness in normal people. Of course, this was a topic of great interest to Ann who, with her usual single-minded albeit tactless enthusiasm for improving someone's work, took to the abstract with a red pen. Ann was not Christine's supervisor but the abstract was returned to Christine covered in comments and with 'a big fat red line' through the title and the exhortation, 'Don't be timid! Say what you mean!' Christine revised the title from a question to a forthright statement, 'Viral infections do not increase airway hyperresponsiveness in normal people', but she was devastated by what felt like overwhelming criticism. Unknown to her, word of her distress reached Ann. Despite this setback or perhaps challenged by it, Christine began attending Ann's legendary Friday morning meetings, which were open to researchers from all over Sydney and not confined to particular hospitals or universities. At them, researchers not only learned what others were doing but were required to report progress on their own work. 'Although I started going with fear in my heart', Christine recalled, 'it proved a rich intellectual experience where we could see how intelligent academics with a passion for their subjects could interact in a meaningful way.'

Christine's first personal experience of Ann occurred when they both attended a meeting in Canberra in 1986. They were there to advise government on the use of peak-flow meters in asthma management and whether it was appropriate for government to subsidize these to improve asthma self-management. On the steps of the Department of Health, Christine was taken aback when Ann apologized for the way she had treated her work: 'She said, 'I'm so sorry, I upset

you about that Abstract. I would never want to discourage somebody who was doing work like that.' I saw that she was genuinely deeply upset and it made me realise that it mattered to her. One of her key characteristics was wanting to make sure people stayed with research and also to help them do it better. She meant to be helpful.' It was during that time in Canberra that Ann asked Christine to join the Institute of Respiratory Medicine. After its somewhat rocky start, the relationship between the two women settled into a mutually supportive working partnership that lasted over a decade until Ann's death.

From her early days at RPAH and at Concord, Ann Woolcock had never stopped running a regular asthma clinic. From the mid-1980s she was joined by Christine Jenkins and together they ran a weekly clinic at the Asthma Centre at RPAH. Ann, who was travelling frequently during those years, would often come to the clinic straight from a long overseas flight. The clinic was always multi-disciplinary with a dietician such as Linda Hodge in attendance, a technician from the respiratory science laboratory at the Page Chest Pavilion and an asthma educator. Depending on individual needs, the patient could leave with a personalized asthma management plan or be given advice about diet or lessons on how to use an inhaler. Sometimes all three.

The Asthma Management Plan

Ann Woolcock believed, as she put it, in 'a dialogue with the consumers. We care about them and they tell us their cares.' She made a major personal contribution to that dialogue with the development of individualized management plans for asthmatics, an idea that was subsequently copied world-wide. A key element in the plan was a yearly diary in which asthmatics could record their condition daily and, in the process, understand and manage their asthma better. Ann's colleague from Montreal, Peter Macklem, described it as perhaps her greatest achievement: 'It is probably the most important therapeutic advance for asthma since the introduction of steroids, and all it took was common sense, which Ann had in abundance' (Smith 2003, p. 243).

The asthma management plan was developed after a multi-disciplinary session on asthma chaired by Ann Woolcock at a pharmacology

congress held in Australia in 1987 (Armour & Black 1988). A similar session was delivered to physicians attending the 1989 annual meeting of the Royal Australasian College of Physicians, held in conjunction with the Thoracic Society of Australasia. Encouraged further by their interest, Ann and her colleagues Paul Seale, Professor of Pharmacology at the University of Sydney, Abe Rubinfeld, a respiratory physician from Melbourne, and Richard Ruffin, later Dean of the Faculty of Medicine at the University of Adelaide, decided that the session should be refined into an actual management guide that could be disseminated to general practitioners. The resulting ‘Six Step Asthma Management Plan’ was published in the *Medical Journal of Australia* and has since been regularly updated to reflect new developments (120).

A decade later, Ann was still planning improvements that would make it easier for asthmatics to manage themselves: ‘We’re moving towards giving people electronic diaries where they record data about their symptoms in the last 24 h. How much bronchodilator they’ve taken. Then they blow into this machine which can record a month’s worth of data and downloads it. They can see for themselves what has happened over the last month and adjust their therapy. If you can get rid of paper and pencil and just have one piece of equipment ... it seems to work extremely well.’

The Institute of Respiratory Medicine

In 1984, Ann Woolcock was promoted to a Personal Chair in Respiratory Medicine at the University of Sydney. Since 1980, she and Ruthven Blackburn had been discussing the benefits of an independent body for funding research into asthma and associated diseases. Through the efforts of Ruthven and Sir James Vernon, the necessary legal and administrative structure was created and a formal relationship with the University of Sydney defined. In 1985, the Institute of Respiratory Medicine (later re-named the Woolcock Institute) began operation at RPAH. The Institute embodied Ann’s philosophy that it would undertake research with important practical applications to improve the diagnosis, treatment, management and quality of life of asthmatics. The culture Ann created there and the attitude of researchers who have worked under

the Institute’s umbrella was eloquently summarized by Guy Marks: ‘One of the good things about the Woolcock is the sense that people value each other, both for the contributions they make and also personally. It is not an intensely competitive environment; rather it is a collaborative and very supportive environment. I always enjoyed coming to work at the Woolcock, in part, because I enjoyed working with my colleagues there...’

Considering the Institute in the year 2000, Ann was clear about her hopes for its future but she was worried about money: ‘I would like to see us not only bridging the gap between the university and the hospital while being independent and giving people freedom, but also running the whole gamut in respiratory disease from basic science – cellular science, basic physiology – through clinical science, epidemiology through public health, and so into commercialisation.’ Before Ann died, the Woolcock’s research teams expanded to include the Sleep Clinical Trials Network, initiated by Professor Colin Sullivan and subsequently led by Professor Ron Grunstein.

Not long before Ann died, Norbert Berend took over as Director of the Woolcock Institute. In the overlap period, he heard echoes of Ann’s childhood reaction when she was straining to do something perfectly, what her sister described as ‘keyed up’. Now it was the challenge of being an administrator. Crushed by some organizational problem or funding disappointment, she would cry out: ‘I’m doing it all wrong. I’m so terrible.’ More than once Norbert and his deputy, Paul Seale, took her out to dinner to brainstorm the problems. After Ann’s death from cancer on 17 February 2001, Norbert spent twelve years as Director. He was succeeded in 2012 by Carol Armour who faced the same challenge as Ann in making a transition to administration and financial management. ‘Of course I worry about money. And I do very little research now,’ said Carol, ‘Ann was the same. The Woolcock is all-consuming. Her family told me she found that very hard. In the end, her role was encouraging others. But she saw her own patients to the very end.’

In 1999, the Institute was awarded funding as part of a new Co-operative Research Centre for asthma which, jointly with the Institute’s partners, had a research programme of thirteen projects over seven years. As usual Ann was

thinking of her patients when she described its potential:

Our aim is to reduce the burden of asthma working mainly from what we know about asthma right now, but also developing new techniques, new methods of diagnosis, new ways of drug delivery. We want to get better diagnostic tools for the GP. It is going to take us into the community more, and towards networking with other people. It has only just started and there is a huge amount of work to do to set it up.

Collaboration, Linking and ‘Playing Big’

The year before her death, Ann was asked to identify her most significant research findings. ‘Asthma’, she replied, ‘is a very very complicated disease. I [still] haven’t the foggiest idea of what causes it or how to define it.’ In her typical way, she went on to emphasize the collaborative nature of the work that had been done: ‘We’ve managed to have several teams running along parallel streams: an epidemiological team, an allergen team, a clinical team, a pathology team and a clinical drug trials team. These five teams talk to each other a lot. . . I’m very much for building networks and having people work together rather than reinvent the wheel.’

She omitted to mention her own role as catalyst, synthesiser and *provocateur*, the importance of her sheer energy and drive—the ‘push factor’. Equally important was her role as what Carol Armour called ‘a linker’: ‘She linked areas of research and came up with a new paradigm on several occasions. That’s what made her so exciting to talk to. . . That kind of intellect is rare and linking across areas is rare. She was an innovator. Very definite. And she was always right in her science.’ Creative energy and lateral thinking were among Ann’s most prominent characteristics. So was her ability to synthesise different topics and ideas into a coherent whole. These were aspects for which she was greatly respected by all who worked with her. John Reynolds, IT Manager at the Institute, recalled: ‘When I first met Ann, she managed to intimidate the daylights out of me with her ceaseless energy, her abrupt manner, and her constant air of impending chaos. Take it from me; anyone who can suddenly grab an opened envelope and start scratching her ideas on the back of it – and who does not recognise the clichés inherent in such an act – is not a person to mess with. . . Working for her was one

of the great experiences of my life; I loved it, and looked forward to it every day – chicken scratches on envelopes notwithstanding.’

These characteristics were evident whatever Ann was doing but they were most on public display at her Friday meetings, which were attended by researchers across the spectrum of asthma and sometimes included cardiologists too. With varying degrees of trepidation, junior researchers would present papers about their work and be given feedback in the discussion that followed. Occasionally, Ann took pity on someone who was stumbling by providing the answer in her question: ‘I don’t understand. . . Do you mean it’s such and such?’ One way or another, she took charge of the discussions. Even when she sat quietly at the back, not showing any sign that she was listening, she would then deliver a brilliant synthesis of what had been said. More often she was down the front, usually at the whiteboard, stimulating and provoking researchers to expand their ideas and demonstrating how their work could lead to future studies or link up with those already under way.

Ann Woolcock’s ability to see the wood and the trees simultaneously was greatly assisted by two inputs to her thinking. The first and most significant was from her husband Ruthven Blackburn. Eminent in the field of medicine and research himself, he understood the politics and funding difficulties of the environment in which a researcher operated. At a personal level, he was vital to Ann’s success and to her comfort in pursuing it. Nelson Mandela once wrote that ‘it doesn’t benefit the world to play small’. Ann was fortunate to have married someone who encouraged her to ‘play big’. She recognised her debt to him, telling people that ‘Ruthven’s the only man who’s ever understood me’. They shared many interests including bushwalking and living in the bush at their property on the Hawkesbury River. Medieval art, particularly in France, was another bond. A passion for opera had been first instilled in Ann by her mother. It continued as something special in her life with Ruthven.

The second influence, which may have been underrated, was her experience early in her career on the Board of the Asthma Foundation of New South Wales. She had been one of the Foundation’s first Fellows after a massive fund-raising effort in 1963 but in the following years she, along with John Read, immunologist

Don Wilhelm from the University of New South Wales and other leading medicos were on the receiving end of enormous pressure from the Foundation's President, Justice Martin Hardie, and its founders, particularly Mrs Mickie Halliday. Empowered by the money they had raised, these lay people kept insisting that their medical research advisors must not stop at their own specialty but must take account of what was being done in other fields and at other institutions as well as their own. Think nationally. And don't stop there. Think globally. The first National Asthma Workshop, organized by Ann in 1972, arose in that context (Smith 2003 *passim*).

Ann Woolcock was a global player from very early in her career, as her wide-ranging epidemiological studies in Asia and the South Pacific reveal. She also chose to take both her academic sabbaticals overseas. In 1977, she spent three months at McMaster University Medical School in Canada, accompanied by Ruthven and the boys, who went to school during their stay. In 1984–5, the family spent her sabbatical leave in Paris. Since that long-ago 'supplementary' in French through which she gained entrance to Medicine at the University of Adelaide, Ann had become fluent in the language. In Paris, she worked with Professor A. Lockhart at the Laboratoire d'Explorations at L'Hôpital Cochin. As her awards and the subsequent fellowships and prizes created in her name testify, Ann travelled constantly throughout her career. She took part in many conferences and symposia in Britain, across Europe, Scandinavia, Russia and, on one occasion, in Saudi Arabia. She was also well known as a speaker in Canada, the USA and Asia.

Ann Woolcock was instrumental in encouraging people to take up research or do further research, suggesting topics that might provide significant information and frequently supervising much of the process that followed. She powerfully influenced many with whom she came into contact. Peter Barnes, later a professor at the National Heart and Lung Institute in London and an exceptional research scientist himself, met her when he was a junior research fellow: 'I remember her sheer enthusiasm for research and her emphasis on doing research that was relevant to patients. This was useful advice to someone doing research on α receptors in guinea-pig lungs' (Smith 2003, p. 243).

For some people she could be overwhelming but Ann herself was apparently unaware that she affected them this way and remorseful if she found out. In Judy Black's experience, she was fine so long as you stood up to her: 'I had submitted my first smooth muscle study for publication in the 'Blue' journal. It came back with a request for some revisions which I took to Ann who said 'We'll do this. We'll do that.' She basically took over. I went away realising that in my naivety I had even named Ann as the last author when it should have been me.' After some indecision, Judy summoned up her fortitude and went back to Ann. 'This is my study,' she pointed out. Ann replied, 'You're absolutely right. It's yours.' According to Judy, she followed up by asking her to come to a major international meeting.

Ann's abrupt manner could be interpreted as rudeness by those who didn't know her. Judy Black tells the story of a pharmaceutical executive who was taken aback when Ann stood up in the middle of their conversation and began rifling through her filing cabinet: 'What a rude woman', he was thinking until she turned round and gave him a paper saying 'I think this will be of use to you.' She had been listening more closely than he realised – but she hadn't explained why she was turning her back on him either.'

Another of Ann Woolcock's notable qualities was her emphasis on teamwork and her loyalty. Stephen Leeder watched this phenomenon in some amazement: 'She had a team around her who used to regularly curse her demands, but were as loyal as if they were wired into her, largely teams of women, a few men but mainly women – just extraordinary. And she was incredibly loyal to them. When things were going wrong or they were unwell or something, Ann would be their staunch advocate. She had this sort of mother hen thing...' Loyalty, however, ran both ways. Euan Tovey recalled: 'We were part of her group and we circled around her and supported her. And she communicated our ideas and championed them widely.' And they learned a lot in return. Guy Marks described Ann Woolcock as 'a mentor and inspiration' who led by example. 'She worked extremely hard, thought very quickly. Research enquiry was intuitive for her. She taught me (and others) key skills and processes necessary for research. She was supportive and loyal, but she didn't suffer fools easily.' Jenny Peat agreed: 'Thanks to Ann,

I never went out in the world with a half-thought-through idea or a half-baked talk... she would push me that bit more to ensure the talk or grant application or journal article approached perfection... [and] she showed us that teamwork is everything to achieving professional and personal goals.' Judy Black echoed their comments: 'I learned much from Ann, including the fact that one needs to leave the planet a better place than one finds it and, in one's research environment, PhD students and publishing papers comes first! She also believed that it was our responsibility to 'have fun' while we were at it.'

An appetite for fun was part of Ann's character. Her love of a joke, her ribald sense of humour and her urge to celebrate, to live life to the full, were well known to those who worked with her. 'Every time we had a success, we had a party', said Victoria Keena. Guy Marks agreed: 'Parties were a good feature of the Woolcock – always informal but fun and well attended. The 'big one' was the annual winter solstice party presided over by wizard Wes Green [who lived in the Blue Mountains] but every achievement, milestone or occasion was an excuse for a celebration.' Ann was renowned for always doing many things at once and this extended to fun as well. Somehow she found time each year to buy Kris Kringle presents for everyone at the Christmas party. John Reynolds remembered that he always received a very bad tie and a bottle of gin.

Ann's loyalty extended beyond her staff and her research teams to her patients and her colleagues. Stephen Leeder could not speak too highly of the support she gave him when, as Dean of Medicine at the University of Sydney, he was trying to reform medical education: 'She was a very staunch supporter when I was dean. It's a very tough job and there's no way you can please everybody. The snakes and vipers come out of the pit. But she was a loyal, loyal supporter.'

Dr Sandra Anderson, who broke new ground with her study of exercise-induced asthma, had known Ann since the days when they were two of the few women working in medical research. She praised the loyalty that Ann showed her as a colleague in 1979 when, at risk of her career, Sandy exposed a scientific fraud by an academic at Harvard. With help from Peter Macklem in Canada, Sandy's accusation was taken seriously and her credibility endorsed, but memory of the strain of that incident remained, along with the

importance of Ann's unwavering support: 'She stood by me all the time.'

Ann's loyalty encompassed her patients too and it was reciprocated, as Stephen Leeder observed: 'What always impressed me was her loyalty to her patients. And their loyalty to her. Although I wasn't involved in any of her clinical work, I was aware that it was a very significant quality.' Christine Jenkins watched as she farewelled her patients shortly before her death: 'She couldn't believe they were so upset for her and not just for themselves as patients... They had immense confidence in her but it was the great affection they showed which took her completely by surprise.'

In the end, Ann Woolcock's success came down fundamentally to the person she was. There were others who were brilliant scientists or great clinicians. And some—she would have said not enough of them—who combined both characteristics as she did. But her energy and, to most people, her magnetic personality merged with the ability to think laterally and strategically and in this she was unique. She attracted students in droves and, while she terrified many along the way, she inspired them too. Once she decided in 1973 to 'focus on asthma', she was constantly thinking and planning how and who could forward the goal of understanding and treating it for the benefit of patients. When she herself first researched the mechanics of lung function in the 1960s, asthmatic patients were often dismissed by doctors as 'over-emotional' and 'creating' an illness that was deemed by some specialists to be mainly psycho-somatic (Smith 2003 *passim*). By the end of Ann's life, the disease was respected for its complexity and people with asthma could play a part in their own care, thanks to the tests, drugs and education developed by Ann and her researchers in the intervening forty years.

Awards and Appointments

Ann Woolcock received numerous awards including in 1992 being made an Officer of the Order of Australia and becoming the first woman in clinical medicine to be elected a Fellow of the Australian Academy of Science, and being elected a Corresponding Member of the Académie de Médecine Française in 1993. In 1998, she was awarded both the Society Medal of the Thoracic Society of Australia and New

Zealand and the Distinguished Achievement Award of the American Thoracic Society. She received the European Respiratory Society Presidential Award in 2000 for ‘enhancing the profile of respiratory medicine worldwide’, and that same year was asked to give the Distinguished Fellow Honor Lecture at the American College of Chest Physicians meeting. In 2001, she received an Honorary Doctorate of Medicine from the University of Ferrara, Italy. She was a founding member and President of the Asian Pacific Society of Respiriology and was the Principal Scientist of the Co-operative Research Centre for Asthma (CRC for Asthma) in 1999.

In recognition of Ann Woolcock’s work in respiratory medicine there have been fellowships and endowments established in her name both nationally and internationally. In August 2003 the Institute of Respiratory Medicine changed its name to the Woolcock Institute of Medical Research in her memory (Mellor 2008).

Acknowledgements

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