Jewels in the crown: *The Medical Journal of Australia*'s 10 most-cited articles

Ann T Gregory

According to data from the Institute for Scientific Information (ISI), the most-cited MJA *article is Cade's ground-breaking report on the effect of lithium in mania (1949; 888 citations), followed by Marshall et al's reports on the role of* Helicobacter pylori *in gastroduodenal disease (1985; 766 and 523 citations, respectively). Others in the "top 10" span decades and disciplines; all have a common grounding in Australian data of global relevance.* **(MJA 2004; 181: 9-12)**

For the year 1995, shortly after the 80th anniversary of *The Medical Journal of Australia* (*MJA*), researchers from the Australian National University used citation analysis to determine Australia's contribution to new knowledge in medical and health sciences. They found that Australians contributed 2.5% of all publications in the Science Citation Index — 18 390 publications, which had been cited over 88 000 times.[1,2] In 2003, the *MJA* used citation data provided by Thomson ISI (www.isinet.com) to identify the "top 10" articles published in the *MJA* — that is, the articles which had been cited most often. Data comprised citations within journal articles covered by the database of the Institute for Scientific Information (ISI) for the years 1945–2002; thus, articles published before 1945 could be cited.

The *MJA* top 10 articles span more than 60 years (Box 1). They have in common a grounding in Australian data, but a global relevance. In addition, all provide evidence of the importance of basic as well as clinical research, and of that endangered species the physician–scientist.

Simple cation holds promise as psychotropic agent

John Cade (1912–1980), the author of our most-cited article, once described himself self-deprecatingly as "an unknown psychiatrist, working alone in a small chronic [*sic*] hospital with no research training, primitive techniques and negligible equipment".[3]

Born in Murtoa, a small country town in Victoria, Cade seemed destined to enter psychiatry. His father was a psychiatrist, and as a child Cade lived in the grounds of various "lunatic asylums". He entered psychiatry in 1936, shortly after graduating in medicine (with honours in all subjects), but spent much of the Second World War as a prisoner of war in Changi, Singapore, returning to Australia as a 40 kg "walking skeleton".[4,5]

Cade's interests included all the sciences, and his "enquiring mind" stayed with him throughout life. The coauthor of his first article (published in 1940), detailing the serological response to influenza virus infection, was none other than Frank Macfarlane Burnet.[6]

While Cade was investigating potential anticonvulsant agents in guinea-pigs, he came to suspect that the cation lithium had a sedative effect which might be useful in treating mania. He demonstrated this sedative effect in guinea-pigs, and then took lithium himself, before extending his study to patients.[3] In his *MJA* article, Cade reported the results of a study of the effect of lithium salts in 10 patients with mania (as well as six with schizophrenia and three with "melancholia"). Lithium had a clear effect in mania.

He published no further research on lithium, but did search for other cations with psychotropic activity.[3] In commenting on his research career, he said: "My own research efforts have been

1 The *MJA*'s top 10 articles, by citation analysis

Number 1 (888 citations)
Cade JFJ. Lithium salts in the treatment of psychotic excitement. *Med J Aust* 1949; 2: 349-352.

Number 2 (766 citations)
Marshall BJ, Armstrong JA, McGechie DB, Glancy RJ. Attempt to fulfil Koch's postulates for pyloric campylobacter. *Med J Aust* 1985; 142: 436-439.

Number 3 (523 citations)
Marshall BJ, McGechie DB, Rogers PA, Glancy RJ. Pyloric campylobacter infection and gastroduodenal disease. *Med J Aust* 1985; 142: 439-444.

Number 4 (299 citations)
Derrick EH. "Q" fever, a new fever entity: clinical features, diagnosis and laboratory investigation. *Med J Aust* 1937; 2: 281-299.

Number 5 (267 citations)
Swan C, Tostevin AL, Moore B, Mayo H, Barham Black GH. Congenital defects in infants following infectious diseases during pregnancy. *Med J Aust* 1943; 2: 201-210.

Number 6 (203 citations)
George LL, Borody TJ, Andrews P, Devine M, Moore-Jones D, Walton M, Brandl S. Cure of duodenal ulcer after eradication of *Helicobacter pylori*. *Med J Aust* 1990; 153: 145-149.

Number 7 (170 citations)
Trautner EM, Morris R, Noack CH, Gershon S. The excretion and retention of ingested lithium and its effect on the ionic balance of man. *Med J Aust* 1955; 2: 280-291.

Number 8 (169 citations)
Bower C, Stanley FJ. Dietary folate as a risk factor for neural-tube defects: evidence from a case–control study in Western Australia. *Med J Aust* 1989; 150: 613-619.

Number 9 (167 citations)
Wilson RMcL, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. *Med J Aust* 1995; 163: 458-471.

Number 10 (166 citations)
Borody TJ, Cole P, Noonan S, Morgan A, Lenne J, Hyland L, Brandl S, Borody EG, George LL. Recurrence of duodenal ulcer and *Campylobacter pylori* infection after eradication. *Med J Aust* 1989; 151: 431-435.

The Medical Journal of Australia, Sydney, NSW.
Ann T Gregory, MB BS, GradDipPopHealth, Deputy Editor.
Reprints will not be available from the author. Correspondence: Dr Ann T Gregory, *The Medical Journal of Australia*, Locked Bag 3030, Strawberry Hills, NSW 2012. medjaust@ampco.com.au

sporadic over many years. Most have ended in blind alleys. Some have been successful. All have been fun. In the process I have learned a greater deal . . ., and *en passant* something of the causes and effective treatment of manic–depressive illness."[7]

Cade's findings were not immediately accepted in the rest of the world (and not until the 1970s in the United States), so it is not surprising that further notable research on lithium was also conducted in Australia. Ranked seventh in the *MJA* top 10, *The excretion and retention of ingested lithium and its effect on the ionic balance of man* was published in 1955. The authors included Trautner, a physiologist at the University of Melbourne, and Noack, a psychiatrist at Melbourne's Mont Park Hospital. Their research, conducted on themselves and on patients with mania, showed that lithium is retained during the acute phase of mania, necessitating higher doses. These can be reduced as the mania resolves. They also showed that intercurrent illness increases the risk of lithium toxicity.

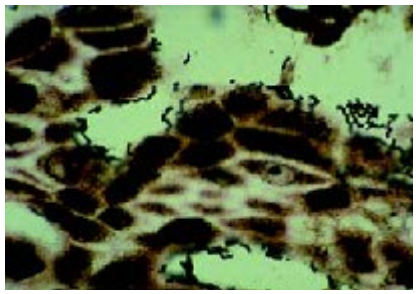
Spiral bacterium linked with gastritis and peptic ulcer

Today, we know that *Helicobacter pylori* colonises the stomach and infects about half the world's population.[8] Further, it has infected people since the dawn of human history, and its geographic variation is being used to map the earliest human migrations, including the arrival of Europe's first neolithic farmers.[9] However, as recently as two decades ago, notwithstanding reports suggesting otherwise ("dispersed over 100 years, in journals of different languages and subspecialities"[10]), the prevailing dogma was that the human stomach was sterile, and that bacteria could not survive in gastric acid.[10]

Gastroenterologist Barry Marshall and pathologist Robin Warren first described the association of a campylobacter-like organism with gastritis in two letters to the editor of *The Lancet*.[11,12] Marshall and colleagues later published two articles — in the 15 April 1985 issue of the *MJA* — providing evidence of a causal relationship. These articles rank second and third in the *MJA* top 10.

In the first *MJA* article, the researchers successfully fulfilled Koch's third postulate by demonstrating that *H. pylori* (then known as pyloric campylobacter) could colonise histologically normal mucosa. After trying to infect animal models without success, Marshall used himself as a "guinea-pig". About 5 days after drinking a pure culture of *H. pylori* (10^9 organisms), he became ill, with early-morning nausea, vomiting of acid-free gastric juice, and "putrid" breath. Although the illness resolved spontaneously after 14 days, culture and histological examination on the 10th day showed severe acute gastritis with many *H. pylori* organisms (Box 2A). The experiment allowed Marshall and colleagues to link *H. pylori* to epidemic gastritis with hypochlorhydria.

2 Illustrations from Marshall et al's two "top 10" *MJA* articles



A. *Numerous* Helicobacter pylori *organisms in a gastric biopsy specimen from Barry Marshall, taken 10 days after he ingested a pure culture of the organism (Warthin–Starry silver stain; original magnification x 900).*

B. *Heavy growth of* H. pylori *from an antral biopsy specimen from a patient with duodenal ulcer. (Larger white colonies are commensal flora of the mouth.)*

In the second *MJA* article, Marshall and colleagues proposed that pyloric campylobacter infection was responsible for damage to the duodenal epithelium, as well as the gastric antral mucosa, based on gastroduodenal biopsy and culture findings from over 100 patients referred to their dyspepsia research clinic (Box 2B).

Looking back on these discoveries, Marshall later wrote that early reports of an association between peptic ulcer and *H. pylori* were met with extreme scepticism by many doctors, who were convinced that psychic stress, cigarette smoking and hyperacidity were the causes of peptic ulcer. Reports of the first therapy ever shown to heal gastritis received "a cool reception at gastroenterological meetings".[10]

Compared with Cade's era, communication among the world's scientific community had accelerated greatly, and, in 1991, the first convincing study of cure of duodenal ulcer through eradication of *H. pylori* was published in the United States. However, this was preceded by another pair of notable articles on the same topic in the *MJA*, from the Centre for Digestive Diseases in Sydney. In 1989, the study by Borody and colleagues, which ranks tenth in the *MJA* top 10, showed that "triple chemotherapy" with bismuth, tetracyline and metronidazole could lead to long-term eradication of *H. pylori* in most patients with duodenal ulcer or non-ulcer dyspepsia. Further, they suggested that this eradication could reduce recurrence of, or even cure, duodenal ulcer. The group subsequently reported such cure in their 1990 *MJA* article, which ranks sixth in the top 10.

H. pylori infection is now recognised as the major cause of peptic ulcer disease and an important risk factor for gastric malignancy. For discovering its role in peptic ulcer disease, Marshall was awarded the 1995 Albert Lasker Clinical Research Award.[13]

Mystery abattoir fever confirmed as new disease

In 1935, unexplained fevers in abattoir workers in Queensland were referred for investigation to Edward Holbrook Derrick, newly appointed director of the state's Laboratory of Microbiology and Pathology[14] (Box 3). He was unable to identify a cause but found that "abattoir's fever" had a distinctive natural history. The clinical resemblance to murine typhus led him to inoculate patients' blood into guinea-pigs, which became febrile. The agent could be transmitted serially from one to another, and, after recovery, the guinea-pigs remained resistant to infection.

These findings were reported in the *MJA* in 1937, in an article that ranks fourth in the top 10. Thirty years later, Macfarlane

3 Edward Derrick, who first described Q fever

In 1961, Derrick became director of the Queensland Institute of Medical Research.
(Illustration courtesy of the Brisbane Courier-Mail.*)*

Burnet wrote that "these findings provided a rather cumbersome, but perfectly adequate means of establishing that abbatoir's fever was a specific entity definable immunologically, and also of allowing laboratory diagnosis in a doubtful clinical case".[15]

Although Derrick described the disease and named it "Q" fever, it was Macfarlane Burnet who showed it was caused by a rickettsial agent, as described in his article, coauthored with Mavis Freeman, which followed Derrick's in the same issue of the *MJA*.[16] The causative organism is now known as *Coxiella burnetii*.

Derrick (1898–1976) received international recognition for discovering not only Q fever, but also the form of leptospirosis caused by *Leptospira pomona*.[17] When Derrick was made a Fellow of the Australian Postgraduate Federation, Macfarlane Burnet stated that "to have defined and elucidated the aetiology of two worldwide infectious diseases is something no other living scientist can claim."[17]

German measles in pregnancy may damage the fetus

In 1941, the teratogenic effects of rubella (German measles) were uncovered by the Australian ophthalmologist Norman Gregg.[18] At that time, it was generally believed that birth defects were inherited, and that the placenta was an absolute barrier to infectious diseases. Gregg's suggestion that maternal rubella played a causal role in congenital cataract was considered revolutionary, and several years passed before overseas medical journals commented on the idea.[19] However, in Australia only a year later, Charles Spencer Swan was appointed by the National Health and Medical Research Council to investigate the possible relationship.[19]

On 7 October 1942, a circular sent to all South Australian general practitioners informed them of Gregg's findings and asked them to complete a form for all children born to women who had an acute exanthem during pregnancy. From these data, covering the years 1939–1943, Swan and colleagues identified 49 infants whose mothers had been exposed to rubella during pregnancy; 31 had congenital malformations, including cataract, deaf-mutism, heart disease, microcephaly and mental retardation. In all but two of the 31 cases, rubella had been contracted in the first 3 months of pregnancy. Further, Swan and colleagues suggested that the type of congenital malformation depends on the stage of pregnancy at which the mother acquired rubella. Their *MJA* report ranks fifth in the top 10. The rubella virus itself was not identified for about another 20 years.

Although Gregg's landmark article on congenital cataract and maternal rubella was formally published in the *Transactions of the Ophthalmological Society of Australia*,[18] he had presented his observations at the annual meeting of the society in October 1941. A description of the proceedings was published with permission in the *MJA* in December 1941,[20] before the formal article appeared. In defence of the rapid publication, the *MJA* stated: "The series [of cases] is so striking and the sight of the children is so seriously affected that the facts must be made known without undue delay to the general body of the medical profession."[20]

Folic acid in pregnancy can prevent spina bifida

Fiona Stanley graduated in medicine from the University of Western Australia and trained in epidemiology at the London School of Hygiene and Tropical Medicine and the National Institutes of Health in the United States. In 1977, she returned to Perth for family reasons and, although a researcher at heart, became Senior Medical Officer in Child Health.[21] Yet, this chance worked in both her and our favour, as it allowed her to establish, with colleagues, the Western Australian Congenital Malformations Registry. The registry provided the data for her landmark *MJA* article, coauthored with Carol Bower, which showed that dietary intake of folate in early pregnancy protects against the occurrence of isolated neural-tube defects in infants. It ranks eighth in the *MJA* top 10.

In 1990, a year after her top 10 *MJA* article was published, Stanley became founding director of the Telethon Institute for Child Health Research in Perth. She continues to explore the promise of epidemiology and other scientific disciplines in tracking trends and preventing major childhood and maternal illnesses.[22] Stanley (Box 4) was Australian of the Year in 2003.

Healthcare can harm patients

The Quality in Australian Health Care Study (QAHCS) arose from the Tito Review of Professional Indemnity Arrangements for Health Care Professionals, established by the Australian government in 1991. The review was to examine the adequacy of compensation and funding arrangements for healthcare misadventures in Australia, but lacked the data to answer the fundamental questions: How many adverse patient outcomes arise from healthcare services? How severe are they? What impact do they have on those services? A consortium of the University of Newcastle, the University of Adelaide and Sydney's Royal North Shore Hospital

4 Fiona Stanley

Since her discovery of the role of folate in preventing neural-tube defects, Stanley continues to investigate the epidemiology of childhood and maternal illness.

was awarded the contract to provide these data, led by intensive care physician Ross Wilson.

The QAHCS, based on the Harvard Medical Practice Study, was set up to measure preventability rather than negligence. Nevertheless, it provided a national measurement of the safety of healthcare, a measurement many other countries still lack. The most-cited report from the QAHCS was published in the *MJA* in 1995 and ranks ninth in the top 10. It found that 16.6% of hospital admissions in Australia in 1992 were associated with an "adverse event" to patients, that those events meant patients were injured by their healthcare, and that the injury had caused them some disability. About half the adverse events were considered preventable. In 1999, also in the *MJA*, the consortium reported further on the preventability of these events.[23]

"The spirit of the researcher"

The *MJA*'s 10 most-cited articles are testimony to the power of clinical research to revise our understanding of disease and treatment methods, and to enhance prevention of disease and adverse events. Despite the refinements in clinical research methods over the decades, which will continue to evolve, these top 10 articles and the pioneering spirit of their authors should inspire new generations of doctors to make the most of any opportunities or insights that come their way.

Derrick, in his address to the inaugural meeting of the Queensland Branch of the Australian Society for Medical Research in 1969, quoted the American physiologist Walter Cannon:

> Phenomena, no matter how mysterious they may appear to be, have a natural explanation and will yield their secrets to the persistent, ingenious, and cautious efforts of the investigator.[24]

Cade, in his presidential address to the Seventh Annual Congress of the Australian and New Zealand College of Psychiatrists in 1970, said:

> Almost everyone can and should do research, both because almost everyone has a unique observational opportunity at some time . . . and also because the intellectual discipline and technical training that it imposes is an essential prerequisite to expertise in a professional field.[7]

Derrick was said to have had a feeling for the historical context in which his research was done, an awareness of the stepwise progress of knowledge to which all, "however ill-equipped", might hope to add. He was said to be fond of quoting the wisdom of Descartes:

> The last should commence where the preceding had left off, and thus by joining together the lives and labours of many, we should collectively proceed much further than anyone in particular would succeed in doing.[17]

References

1 Bourke PF, Butler L. Mapping Australia's basic research in the medical and health sciences. *Med J Aust* 1997; 167: 610-613.
2 Anderson WP. Funding Australia's health and medical research. *Med J Aust* 1997; 167: 608-609.
3 Mitchell PB. On the 50th anniversary of John Cade's discovery of the anti-manic effect of lithium. *Aust N Z J Psychiatry* 1999; 33: 623-628.
4 Cade JF. John Frederick Joseph Cade: family memories on the occasion of the 50th anniversary of his discovery of the use of lithium in mania. *Aust N Z J Psychiatry* 1999; 33: 615-618.
5 John Frederick Joseph Cade [obituary]. *Med J Aust* 1981; 1: 489.
6 Burnet FM, Cade JFJ, Lush D. The serological response to influenza virus infection during an epidemic, with particular reference to subclinical infection. *Med J Aust* 1940; 1: 397-401.
7 Cade JFJ. Contemporary challenges in psychiatry. *Aust N Z J Psychiatry* 1971; 5: 10-17.
8 Marshall BJ. *Helicobacter pylori*: a primer for 1994. *Gastroenterologist* 1993; 1: 241-247.
9 Falush D, Wirth T, Linz B, et al. Traces of human migrations in *Helicobacter pylori* populations. *Science* 2003; 299: 1582-1585.
10 Marshall BJ. The 1995 Albert Lasker Medical Research Award. Helicobacter pylori. The etiologic agent for peptic ulcer. *JAMA* 1995; 274: 1064-1066.
11 Warren JR. Unidentified curved bacilli on gastric epithelium in active chronic gastritis [letter]. *Lancet* 1983; 1: 1273.
12 Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis [letter]. *Lancet* 1983; 1: 1273-1275.
13 DeBakey ME, Gutterman JU. The Lasker Awards at fifty. *JAMA* 1995; 274: 1061.
14 Doherty RL. E. H. Derrick — his published record and its background. *Med J Aust* 1967; 2: 1069-1073.
15 Burnet FM. Derrick and the story of Q fever. *Med J Aust* 1967; 2: 1067-1068.
16 Burnet FM, Freeman M. Experimental studies on the virus of "Q" fever. *Med J Aust* 1937; 2: 299-305.
17 Edward Holbrook Derrick [obituary]. *Med J Aust* 1976; 2: 731-732.
18 Gregg NMcA. Congenital cataract following German measles in the mother. *Trans Ophthalmol Soc Aust* 1941; 3: 35-46.
19 Webster WS. Teratogen update: congenital rubella. *Teratology* 1998; 58: 13-23.
20 Congenital cataract following German measles in the mother [editorial]. *Med J Aust* 1941; 2: 651-652.
21 Big ideas. The wisdom interviews. Fiona Stanley, interviewed by Peter Thompson [transcript]. Australian Broadcasting Commission Radio National, broadcast 4 Aug 2002. Available at www.abc.net.au/rn/bigidea/stories/s636281.htm (accessed May 2004).
22 Australian Academy of Science's video histories of Australian scientists: interview with Professor Fiona Stanley by Dr Norman Swan, May 2000 [transcript]. Available at: www.science.org.au/scientists/fs.htm (accessed May 2004).
23 Wilson RM, Harrison BT, Gibberd RW, Hamilton JD. An analysis of the causes of adverse events from the Quality in Australian Health Care Study. *Med J Aust* 1999; 170: 411-415.
24 Derrick EH. Medical research — a continuing challenge. *Med J Aust* 1970; 1: 829-832.

(Received 10 May 2004, accepted 31 May 2004) ❑