Research In Dementia in Australia

Henry Brodaty
Professor of Psychogeriatrics &
Director, Primary Dementia Collaborative Research Centre,
UNSW; & Aged Care Psychiatry
POW Hospital, Sydney
Auguste D in 2006??

- How would she be treated today?
- Use of cholinesterase inhibitor, memantine, atypical antipsychotics
- Multidisciplinary Mx
- Carer support and training
- Managed at home

Health R&D: Benefits vs Costs

• Returns on money spent on health R&D in Australia are 5 – 8 fold annually
• e.g. R&D that reduced cancer deaths by 20% = saving of $184bn to Australia
• Investment in health R&D = biggest source of rising living standards
• R&D is the greatest hope to reduce burden of chronic diseases of ageing which are set to place unprecedented demands on Australian health care system

ASMR; Access Economics 2003: Exceptional Returns
The Cost of Dementia In Australia

- Total cost of dementia (direct & indirect) = AU $6 576 million in 2002
Burden of Disease: Dementia

- 5th (women) & 11th (men) cause of total burden (DALYs)
- 7th cause of mortality burden in women
- 3rd (women) & 5th (men) cause of incident non-fatal burden

Neurological & sense disorder burden (DALYs) expressed as proportions of total

AIHW 2007: The burden of disease & injury in Australia 2003
Direct Costs 1993-1994: Disease Comparisons

- Circulatory: $3.7 b
- Cancer: $1.9 b
- Dementia: $1.4 – 1.5 b*

*estimated direct cost based on underestimation of NH costs in 1993-94

Access Economics 2003
Projected Financial Impact of Dementia with No Revenue Increase

Access Economics 2003
The Increase in World Wide Dementia Research: 1960-2007*

*Medline and PsycINFO searched for abstracts with 'dementia' or 'Alzheimer$'
The Increase in Australian Dementia Research: 1960-2007*

*Medline and PsycINFO searched for abstracts with 'dementia' or 'Alzheimer$' and 'Australia$' or 'Australia' or 'Australian' in the author address
NHMRC Grants Awarded: 2000-07

Calculated from NHMRC data
NHMRC funding and % of Australian disease burden
Proportion of funding to proportion of burden ratio

- Dementia and AD
- Asthma + COPD
- Diabetes
- Cardiovascular disease
- Cancer
Spending on research

• $\$\$\$\$\$ on medical & health research per year
  – In Australia 0.255% of GDP
  – In USA 0.6% of GDP

• NHMRC funding for dementia in 2006: AUD$0.54 per Australian

• NIH funding for dementia in 2006: AUD$2.57 per USAmerican

• Annual rates of return to Australia health R&D were $5 for every $1 spent on R&D
  (Australian Society for Medical Research, 2003)
Dementia: A National Health Priority

- Australian government initiative announced in 2005
- $320.9m including $26m for research over 3 years, including:
  - Two rounds of NHMRC grants $16m
  - Three Dementia Collaborative Research Centres total of $7m over 3 y
Fields of research

- Epidemiology
- Diagnosis
  - Instruments
  - GP training
- Pathology
- Therapeutics
- Carers
- BPSD & Nursing homes
- Clinical research
- Legal aspects
- Special populations
  - Aboriginal people
  - CALD
Epidemiology

- Henderson
- Jorm
  - Eurodem
  - Canberra
  - Path through life
  - Honolulu Asian Aging Study
- Broe – Sydney Older Persons’ Study
- Memory and Ageing Study
- AIBL
ε4 allele is a risk factor for dementia, but not sufficient for its development

• Dementia prevalence rates double every 5.1 years\(^1\)
• Cognitive deficits frequently present 3-6 years prior to dementia onset \(^2\)

\(^2\) Jorm AF et al. (2005) Cognitive deficits 3 to 6 years before dementia onset in a population sample: The Honolulu-Asia Aging Study. JAGS. 53(3): 452-455
Eurodem: Depression & AD

- Hx of depression associated with AD
- Association held for episodes of depression more both ≥ 10 yrs before AD onset, & ≤ 10 yrs following onset
- No association was found with anti-depressant treatment or death of spouse, death of a child and divorce.

PATH Through Life study

- 20 year longitudinal study of 7,485 community residents aged 20-24, 40-44 and 60-64 randomly selected from the Electoral Rolls of Canberra and Queanbeyan
- Follow-up every 4 yrs
- Aims to investigate the causes of 3 classes of common mental health problems:
  1. Anxiety and depression
  2. Alcohol and other substance abuse
  3. Cognitive functioning and dementia
Professor Tony Broe

- Epidemiological studies in Scotland
- Sydney Older Persons Study (SOPS)
- Rise of neurodegenerative disorders with age and relative reduction in systemic disorders
- Mix of pathologies in late age
Systemic diseases: Prevalence
(N=522. Age trends: * p < 0.05; ** p< 0.01)
Neurodegenerative disorders: Prevalence

(N=522. Age trends: * p < 0.05; ** p< 0.01)
The Australian Biomarker and Imaging Lifestyle (AIBL) Flagship Study of Ageing

- 3 yr prospective longitudinal Study of 1000 volunteers (60 yrs+)
- Not cognitive impaired, (600), MCI (200), AD (200)
- Aims:
  - To improve understanding of causes and diagnosis of AD
  - To examine lifestyle and diet factors that may influence the onset of AD
  - To help develop Rxx & preventative strategies


David Ames
Memory and Ageing Study

- To determine prevalence of mild cognitive impairment, MCI, in 1000 community dwellers
- Electoral Roll, 70-90 years
- Follow-up 12 months and every 2 years
- To determine incidence of MCI
- To examine disease burden of MCI
- To determine progression of MCI

1 Brodaty, Sachdev, Broe, Draper, Trollor, Slavin, Kochan, Schnier, Schofield
2 Sachdev, Brodaty, Andrews NHMRC Program grant
Memory and Ageing Study

• What predicts healthy cognitive ageing?
• What predicts cognitive decline?
  – Genes
  – Past and present life style
  – Diet
  – MRI scan findings
  – Neuropsychological performance
  – Physical signs eg walking, smell
  – Subtle signs noted by other person (CICAQ)
Diagnosis

• Amyloid β protein in blood (Ralph Martins)
• MRI, PET with PIB
• New diagnostic instruments
• GP training (Pond)
Measurement tools

- IQCODE
- PAS
- COGSTATE
- GPCOG
- RUDAS
- KICA
- Abbey Pain Scale
IQCODE\textsuperscript{1} & Short IQCODE\textsuperscript{2}

- IQCODE (26 items) & Short IQCODE (16 items):
  - Informant questionnaire
  - Assesses changes in patient’s cognitive performance over previous 10 yrs
  - Rated on a 5 point scale from “much improved” to “much worse”
  - Lower scores better

Examples of Short IQCODE Items

Compared with 10 yrs ago, how is this person at:

1. Remembering things about family & friends e.g. occupations, birthdays, addresses?
2. Remembering things that have happened recently?
3. Recalling conversations a few days later

Responses on 5-point scale ranging from much improved to much worse
Psychogeriatric Assessment Scale (PAS)

- Assesses dementia and depression on scales
  - Subject interview, 3 scales
    - Stroke
    - Depression
    - Cognitive Impairment
  - Informant i/view, 3 scales
    - Stroke
    - Cognitive Decline
    - Behaviour change
- Gives results as a percentile rank within the population

• A/Prof David Darby - Chief Medical Officer
• CogState = a range of computerised cognitive tests to measure reaction time, attention, visual memory & learning, social cognition, verbal memory & learning, planning and problem solving
• Used to determine the effect of drugs etc on cognition
• Used in > 30 clinical trials

http://cogstate.com/
**General Practioners Assessment of Cognition (GPCOG)**

- Designed for GPs; for efficiency in screening
- Two sections:
  - Cognitive Testing (range 0-9; 6 items, $\uparrow$ better)
  - Informant interview (6 items, $\uparrow$ better)
- <4.5 minutes to administer; several languages
- Informant can be contacted by telephone
- If cognitive score is $> 8$ or $< 5$, informant interview not needed
- Valid and reliable, sensitivity/specificity $> 0.85$

RUDAS

- Designed to be free of cultural bias
- 10 minutes to administer
- Items divided into:
  - Memory
  - Visuospatial Orientation
  - Praxis
  - Visuoconstructional Drawing
  - Language

Kimberley Indigenous Cognitive Assessment tool (KICA)

Difficulties associated with cognitive testing of older indigenous Australians:

- Limited access to formal education
- English is often 3\textsuperscript{rd} or 4\textsuperscript{th} language
- Indigenous languages generally oral
- Different concepts of number, time & space
- Inappropriate to discuss personal/family issues
- Poor vision highly prevalent

Prof Nicola Lautenschlager
University of Western Australia

Prof Leon Flicker
University of Western Australia
Kimberley Indigenous Cognitive Assessment tool (KICA)

- KICA-Cog: 16 questions
- Score: 0 – 39 (31/32; sens = 97, spec = 82)
- Higher scores better
- 30 – 40 minutes to administer
- Walmajarri language specific to Kimberly
- Orientation, free & cued recall, language, verbal fluency, copying sequence pattern & ideational praxis

Examples of KICA Items

• Hold up 3 items in turn: comb, pannikin (cup) & matches, and ask “What do you call this?”, “What is this one for?”

• “Tell me the names of all the animals that people hunt” – time: 1 minute

• “I’ll show you some pictures, you tell me what they are”: boy, emu, crocodile, billy on fire, bicycle
GP training

Dimity Pond leading an NHMRC funded consortium from 4 universities to answer these Qs:

1. Does GP training improve:
   • Diagnosis rate
   • Adequacy of management

2. Does earlier diagnosis lead to positive outcome?
Abbey Pain Scale

- Measures pain in PWD
- 6 items:
  - Vocalisation; Facial expression; Change in body language; Behavioural change; Physiological change; Physical change
- Measured on 4-pt scale for severity (absent to severe)
Pathology
Masters and his team were among the first to isolate & characterise amyloid in AD
Masters championed the amyloid theory of AD
> 800 papers on amyloid published annually
Characterised the cerebral amyloid prNn that forms the plaque core in AD and in aged individuals with Down syndrome

• Novel insight into metabolic processes underlying age-related neurodegenerative diseases
• Disruption in metabolism of critical biological metal ions, such as Cu and zinc
• Uncovered interactions of biometals (Cu, Zn & Fe) & β-amyloid that contributes to both oxidation damage and amyloid accumulation in AD
Therapeutics

- AC4R
- PBT2 (Bush, Masters, Ritchie, Ames)
- Testosterone (Martins)
- Current drug trials in Australia
PBT2: 2nd Generation Clioquinol

- Designed to modify the course of AD by preventing metal-dependent aggregation, deposition & toxicity of Aβ
- FDA Phase: Phase II/IIa/IIb

The Australasian Consortium of Centres for Clinical Cognitive Research (AC4R)

- Peak body representing Dementia Research Centres in Australasia
- Goal is to bring together all centres throughout Australasia involved in treatment studies for dementia
- 80 members in 2006
- Geriatric medicine, neurology, psychiatry, psychopharmacology, psychogeriatrics, neurobiology, nuclear medicine and neuropathology
AC4R: drug trials in Australia

• Rosiglitazone (recruiting)
• Lecozan (ongoing, recruitment closed)
• PBT2 (successor to clioquinol) (start soon)
• High dose, slow release donepezil (soon)
• Xaliproden (completed, results awaited)
• Memantine (soon)
• Leuprolide (abandoned, financial problems)
Testosterone & Dementia

- Are ↓ testosterone levels a causative factor in cognitive decline with ageing?
- Interaction between testosterone and APOE ε4
- ↑ testosterone associated with better general cognition in non- ε4 carriers
- ε4 carriers: ↑testosterone associated with ↓ executive functioning, working memory & attention

Burkhardt MS … Martins RN et al. (2006) Interaction between testosterone and apolipoprotein E epsilon4 status on cognition in healthy older men. Journal of Clinical Endocrinology & Metabolism.91(3); 1168-1172
Advances with carers
The Dementia Carers Program

- Ten day intensive residential program
- For persons with dementia and carers
- Intensive, comprehensive, extensive
- Counselling, skills & communication training, knowledge, mutual support
- Involve PWD and extended family
- Follow-up 2nd → 6th weekly by tel and quarterly in person for a year

Brodaty and Gresham (1989), BMJ; 299: 1375-1379
The Dementia CGs’ Program

Results: GHQ

Brodaty and Gresham (1989)
7 yr survival at home for patients of Carers undertaking Dementia Carer Training

Meta-analysis of psychosocial interventions for CGs

- CG interventions can reduce CG psychological morbidity (ES = 0.3) and help people with dementia stay at home longer
- Significant benefits in CG psychological distress, knowledge
- Success predicted by involvement of patients and their families, by “dose” of intervention
- Flexibility and constant therapist appear important

The three country study: Aricept + counselling

Manchester, UK - Alistair Burns

New York, USA - Mary Mittelman

Sydney, Australia - Henry Brodaty
The treatment group started off more depressed than control group and ended up less depressed.
Behavioural and Psychological Symptoms of Dementia (BPSD) & Nursing Homes
Depression in Part 3 Homes

- 390 (89%) residents of Part 3 homes (hostels) compared with previous survey
- ↑ residents now with dementia or depression
- Only 17% of those previously depressed had recovered
- Little use of antidepressant medication
- Under-treatment of depression
- Increasing rates of depression and dementia in residential care

BPSD in Sydney NHs

• >90% of NH residents exhibited ≥ 1 behavioural disturbance
• Psychosis = 60%, depressed mood = 42% & activity disturbances or aggression = 82%
• Rates higher if
  – NH larger; more residents in room
  – residents younger
  – residents more functionally impaired
  – chart diagnosis of psychosis

Risks of antipsychotics

• Australian RIS trial 1st to report increased risk of stroke with antipsychotics
• Many studies since demonstrated increased risk of stroke and of death
• Risk of death appears higher with typical antipsychotics
Survival curves for atypical anti-psychotics (& haloperidol) incident users

- AMIS (n=48)
- OLAN (n=2387)
- QUET (n=394)
- RISP (n=1451)
- HALO (n=4739)

# days survival

Cum. Survival Probability
High Rates of Psychotropic Use in NHs

- 47.2% ≥ 1 psychotropic drug regularly
- Compared to 1988, ↓ hypnotics (11.3%) & anxiolytics (4.1%), but ↑ antidepressants (20.5%)
- Psychotropics = 51.5%
- Multiple psychotropics = 22.7%
- Antidepressants = 19.8%

¹Snowdon J. et al. (2006); ²Draper B. et al. (2001)
Dementia Care Mapping

- Prospective RCT comparing
  - DCM
  - Person-centred care (PCC)
  - Usual care (UC)
- Primary outcome = CMAI
- PCC > DCM > UC
Clinical research
Kaarin Anstey: Cognition and falls

- MMSE & verbal reasoning at baseline predicted rate of falling over 8 yrs
- ↓ verbal ability, processing speed, & immediate memory associated with increases in risk & rates of falling

PRIME

- Prospective naturalistic study
- Data base of patients attending 8 memory clinics around Australia (Ames, Boundy, Brodaty, Clarnette, Davies, Woodward, Kurrle, Mander)
- Target = 1000 patients with longitudinal data over 2 years
- Sponsored by Janssen but drug prescribing remains independent
- Participating clinicians can request analysis of data for research thro’ SAC
Legal aspects

• Darzins P, Strang D, Molloy W
  – Who Can Decide?: The Six Step Capacity Assessment Process

• Peisah C
  – Description of family disputes in cases coming before guardianship tribunal
  – Competency to marry
Economic/ Social

- Access Economics report 2003
- Access Economics report 2006 for Asia-Pacific
- Alzheimer Australia Prevention of AD strategy “Mind your mind”
Research only in Australia

- EACH, EACH-D, CACPs
- CALD
- Indigenous people
- Nursing Homes
Research gaps

• Culturally and Linguistically Diverse (CALD)
• Aboriginal people with dementia
  – KICA
  – Broe T (in progress)
  – Abbey J (in progress)
• Developmental disability
• Young onset dementia
• PWD in rural and remote communities
Cambridge residents diagnosed using CAMDEX

Reviewed approximately 12 months later:
- Dx confirmed in 97%
- Only 6 out of 29 survivors with progressive deterioration
- 13 reclassified as normal

Findings suggest that only small number of false negative diagnoses were made

CALD in Australia

Top 10 countries of birth:

1. Australia
2. UK
3. New Zealand
4. Italy
5. China
6. Vietnam
7. India
8. Philippines
9. Greece
10. Germany

ABS Year Book Australia 2007
Most common non-English languages are:
- Italian
- Greek
- Cantonese
- Arabic
- Vietnamese
- Mandarin
CALD in Australia

• 15% speak a language other than English

• Australians speak over 200 languages (including > 45 Indigenous languages)
Indigenous Australians and Dementia

• Aboriginal and Torres Strait Island people = 2.4% of Australian population\(^1\)
• Poorer quality of health than non-indigenous Australians\(^1\)
• Reduced life expectancy (\(~ 20\) years)\(^1\)
• 50 yrs+ used to plan health care for elderly indigenous Australians

\(^1\)Health & Ageing Factbook 2006
Indigenous Australians and Dementia

- 10% of 65yr+ diagnosed with dementia\(^1\)
- Cerebrovascular disease and alcohol abuse are major contributors\(^1\)

\(^1\)Henderson & Jorm (1998)
Indigenous and Non-Indigenous Age Profiles

Chart 50: Population age profile, by sex, indigenous and non-indigenous Australians as at 30 June 2001

Dementia Collaborative Research Centres
Dementia CRCs

- Australian Government Initiative
- $7m over 3 years for three CRCs:
  1. Assessment and better care outcomes
  2. Early Intervention, Prevention and Risk Reduction
  3. Consumers, Carers and Social Research
Assessment and Better Care Outcomes
Primary Dementia CRC

Dementia CRC Nº 2
Dementia CRC Nº 3

Prevention, Risk Reduction and Early Detection
Consumers, Carers and Social Research
<table>
<thead>
<tr>
<th>CRCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• UNSW</td>
</tr>
<tr>
<td>• U Syd</td>
</tr>
<tr>
<td>• U Newcastle</td>
</tr>
<tr>
<td>• UTS</td>
</tr>
<tr>
<td>• AIHW</td>
</tr>
<tr>
<td>• Hammond</td>
</tr>
<tr>
<td>• Monash</td>
</tr>
<tr>
<td>• Melb U</td>
</tr>
<tr>
<td>• Alz Australia</td>
</tr>
</tbody>
</table>

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• ANU</td>
</tr>
<tr>
<td>• U Canberra</td>
</tr>
<tr>
<td>• Melb U</td>
</tr>
<tr>
<td>• Edith Cowan Uni</td>
</tr>
<tr>
<td>• U Qld</td>
</tr>
<tr>
<td>• Alz Australia (Vic)</td>
</tr>
</tbody>
</table>

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• QUT</td>
</tr>
<tr>
<td>• Hammond</td>
</tr>
<tr>
<td>• Latrobe</td>
</tr>
<tr>
<td>• Griffith</td>
</tr>
<tr>
<td>• Alz Australia</td>
</tr>
</tbody>
</table>
Primary CRC (UNSW)

- Coordinating centre with formalised links and communication mechanisms to the two other linked Centres
- Coordinate reports from linked Centres to the Department through a Coordinating Committee
- Undertake specific research focus on Assessment and Better Care Outcomes
Management Team
Henry Brodaty
Perminder Sachdev
Tony Broe
Brian Draper
Project manager
Glenn Rees
Satellite Centre representatives

Satellite Nodes
- Dimity Pond (Newcastle)
- Diane Gibson (AIHW)
- Sue Kurrle (U Syd; Hornsby)
- Richard Fleming (Hammond)
- Daniel O’Connor (Monash)
- Lynn Chenoweth (UTS)
- Brian Draper (POW Hospital)

Centre Agreement

Consumers:
- AA
- COTA
- CALD rep
- ATSI rep

Service providers
- Hammond Group
- Baptist Community Homes
- Montefiore Nursing Homes
- Silver Chain Nursing
- PRIME
- AC4R

Research Advisors
- Kaarin Anstey (ANU)
- Mike Bird (ANU)
- Madeleine King (UTS)
- Janice Davies (NICS)
- Lisa J Pulver (NSW)
- Peter Schofield (NSW)
- AAG
- Jiska Cohen-Mansfield (Wash’ton)
- Alistair Burns (Manchester)
- Ken Rockwood (Canada)
Dementia CRC no. 2

Consortium of:
• Australian National Uni; Uni Canberra (ACT)
• Uni Melbourne, Alzheimer’s Association (Victoria)
• Edith Cowan Uni (Perth, WA)
• Uni of Queensland (Qld)

International:
• Montreal NI- BIC, Canada (Evans, Collins)
• Arrhus Imaging Centre, Denmark (Geddjes, Rodell)
Dementia CRC Nº 3: Consumers, Social Research, Carers and Carer Support

QUT
Hammond Care Group
Alzheimer's Australia
Latrobe University
Curtin University
Griffith University
Approach (Aims)

• Ensure that research is combined with implementation – for example, using guidelines already produced.

• Ensure that any research undertaken is collaborative and includes the main players in the respective fields.

• Where appropriate ensure regional, rural and remote areas are included in investigations.
Main Areas of Interest (Objectives)

To investigate best practice and to upskill and mentor young researchers in the following areas:

- Prevention of functional decline
- Pain – assessment and management
- Issues for consumers/carers
- Issues relating to residential care
- Palliative care and dementia
Auguste D in 2106??

- How will she be treated in 100 years time
- National Framework and policies √
- World leader in community care
- Research improving

Funding Opportunities

- NHMRC, ARC
- Alzheimer’s Australia
- Pfizer Neuroscience Grants
- Rebecca Cooper Foundation
- Gerontology
- CRCs
Auguste D in 2106??

- Australia punching above weight but...
- Still behind compared to other conditions & countries
- Research is
  - Academics
  - Government
  - $$ - NGOs, Philanthropy
  - You
  - Exciting
Help plant the seeds of dementia research and care for the next 100 years

- **THANKS to** Louisa Gibson and Lee-Fay Low
- **CRC**  www.dementia.unsw.edu.au
- Dept Old Age Psychiatry, UNSW and POWH  //adfoap.med.unsw.edu.au
- Alzheimer’s Australia  
  www.alzheimers.org.au
- Alzheimer’s Disease International  
  www.alz.co.uk