First Steps

In 1995, Trustees of the Sir Zelman Cowen Fund, Professor Stone, convened a meeting of
cognate scientists, to serve as a Scientific Advisory Committee\(^1\). The meeting considered, and
supported, a proposal that the Fund's support for medical research should become focussed on a
specific issue, the role of inflammation in Alzheimer's disease (AD). Minutes of this meeting and of
subsequent meetings of these scientists, held in 1996 and 1997, show the stimulus for suggestion.
Reports were appearing around the world which noted a relationship between long-term treatment
with anti-inflammatory drugs, and the incidence of AD.

The earliest observations in this sequence were made in the UK, and in Sydney. The UK
group\(^2\) reported a negative correlation between chronic rheumatoid arthritis; it raised the question
why AD was uncommon in those suffering arthritis. The Sydney group, headed by G.A. Broe at
Concord Hospital (and part of the University of Sydney's Faculty of Medicine) noted the inverse
relationship, that arthritis was uncommon among Alzheimer sufferers\(^3\)

In the decade since, this seemingly obscure observation led to the broader hypothesis, that it
was drugs taken by arthritis sufferers which provided protection against Alzheimer's disease. By the
mid-1990's, the hypothesis that non-steroidal anti-inflammatory drugs (NSAIDS) are protective
against AD was recognised as a potentially valuable hypothesis in the search for treatment for AD,
though the idea had to fight for consideration and grant support with a growing range of scientific
findings related to AD, concerning the tau and beta-amyloid proteins, and genetic causes, as for
example in the alleles of the gene for apolipoprotein E. The Committee took the view that if
inflammation does play a role in AD, and that NSAIDS are protective, this carried such potential
benefit to at least those likely to develop AD, that it was an appropriate focus for SZCUF funding.

The Fund's Alzheimer's Disease and Inflammation Initiative was officially launched at a
function in May 1996.

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\(^1\) Professor J.G. McLeod FAA FRS (Chairman)
Professor Max Bennett B Eng, D Sc, FAA,
Emeritus Professor William Burke BSc PhD,
Professor Bogdan Dreher DSc
Dr John Mc Avoy PhD
Professor Ian Mc Closkey FAA, FTS, FRACP

\(^2\) ML Jenkinson, MR Bliss, AT Brain, and DL Scott. Rheumatoid arthritis and
senile dementia of the Alzheimer's type Rheumatology 1989 28: 86b-88b

### Grants Funded under ADI Program

**SZCUF GRANTS AND GRANTEES 1996 - 2001**

<table>
<thead>
<tr>
<th>Year</th>
<th>Name(s)</th>
<th>Project Description</th>
<th>Amount</th>
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<tr>
<td>1996</td>
<td>Dr Glenda Halliday</td>
<td>Inflammation and Alzheimer's Disease - Clinicopathological Correlations</td>
<td>$30,000</td>
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<td></td>
<td>Dr Jonathon Sedgwick</td>
<td>Microglial cell activation. Effect of anti-inflammatory agents and immunosuppressants.</td>
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<td>Prof G A Broe</td>
<td>Anti-inflammatory Drugs and Alzheimer's Disease</td>
<td>$52,194</td>
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<td>Dr Philip Penfold</td>
<td>Microglia mediated cytotoxicity against neural cells: influence of beta-amyloid proteins</td>
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<td><strong>1996 Total</strong></td>
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<td>1997</td>
<td>Drs Glenda Halliday &amp; Jillian Kril</td>
<td>Is there a relationship between inflammatory and vascular pathologies and cognitive performance in prospectively studied patients with Alzheimer's disease?</td>
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<td>Prof G A Broe</td>
<td>Anti-inflammatory Drugs and Alzheimer's Disease</td>
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<td>Dr Philip Penfold</td>
<td>The Role of Microglia in Neuronal Cell Death</td>
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<td>Inflammation and microvascular degeneration in Alzheimer's disease: relationship to senile plaque progression and neurofibrillary degeneration</td>
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<td>Dr Elizabeth Milward</td>
<td>Ant-inflammatory drugs: Regulators of oxidative damage in Alzheimer's disease?</td>
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<td>1999</td>
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<td>Dr Jillian Krill</td>
<td>Genes regulating inflammatory processes and their role in dementia.</td>
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<td><strong>Total funding 1996-2000</strong></td>
<td><strong>$396,875</strong></td>
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**Studies Reported**

The following publications have resulted from studies supported by the ADI

**Journal Articles**

1. **Waite**, LM; Broe, GA; Creasey, H; Grayson, DA; Cullen, JS; O'Toole, B.; Edelbrock, D., and Dobson, M. Neurodegenerative and other chronic disorders among people aged 75 years and over in the community. Medical Journal of Australia. 1997; 167:429-32.


**Review Article**


**Articles Submitted**


**Conference Presentations**


8. **Milward**, EA; Grayson, DA; Creasey, H; Kyngdon; B; Janu, MR; Brooks, WS, and Broe, GA. Anaemia and dementia in community-dwelling Australian elderly. Aust Carer's Assoc/Aust Ass Geront. 1999

**Key Findings**

Three findings of the studies reported from the ADI stand out. They are distinct but complementary:

1. **The protective effect of NSAIDS is not dose related** (Broe et al. 2001)

The team led by GA Broe at Concord Hospital re-analysed their growing body of data yielded by the Sydney Older Persons Study. By both extending the length of this study to over 10 years, and re-designing their analysis, they confirmed their original 1990 finding (that the incidence of AD is inversely related to NSAIDS), and extended it by showing that the effect is not related to dose of NSAIDS. The implication of this finding is that the protective effect may not be related to the anti-inflammatory action of the NSAI drugs, but to some other action. The nature of that 'other' action is now a key question. One possibility, still speculative, arises from the well-established action of some NSAIDS, particularly aspirin, in maintaining the integrity of small vessels, the capillaries of the brain.

2. **NSAIDS do not reduce the pathology usually associated with Alzheimer's disease.**

(Halliday et al., 2000).

This was a surprising negative finding. In the latter part of the 20th Century neuropathologists had come to regard two features of the dementing brain as characteristic (and to some workers) definitive of Alzheimer's disease. These are known as 'plaques' and 'tangles'. Alzheimer had described plaques in his original (1911) paper, and he described a third pathology, the presence of cells which we would now call ‘active' microglia, a feature of inflammation. This aspect of the pathology of Alzheimer's disease was neglected until the late 1980's. Halliday and colleagues' study is a uniquely detailed assessment of brains (obtained largely from the cohort of patients followed for many years by the Concord group) whose cognitive history was well documented. In these patients the use of NSAIDS correlated with better cognitive status of the patients, but not with any lessening of plaques, tangles or markers of inflammation. These data confirm the prior studies (now about 20) which report a beneficial effect of NSAIDS on cognitive function in the aged. They suggest that the action of NSAIDS is not to reduce the plaques and tangles which many regard as
definitive of Alzheimer's disease, and also not to reduce inflammation. They suggest that some other pathology is important for cognitive function.

3. The early pathology of AD may be microvascular (Cullen, 2001)

Dr. Cullen's work has also addressed the neuropathology of Alzheimer's disease, but looked at the earliest stages of the cortical lesions which occur. The feature which her papers highlight is that, the earliest lesions always form around a small blood vessel. This is a novel hypothesis/finding, which will receive a lot of analytical attention. Its implication, that the degenerative changes which cumulatively cause dementia centre on blood vessels, complements the two other Sydney findings. NSAIDS may protect against dementia by stabilising the small blood vessels of the brain.

**Relationship to the Field**

World-wide, the literature exploring the relationship between Alzheimer's disease and inflammation has grown exponentially since 1996, when the ADI was launched (Figure 1). The Australian contribution to this literature amounts to approximately 15 papers, thus about 13% of the total. Major parts of this literature, particularly the step-by-step demonstration of inflammatory markers in Alzheimer's brains, have been generated in the USA and Europe. The Australian part of that literature, all from Sydney, has made the distinctive contributions identified above.

This line of enquiry is still, by any criterion, unfinished. The initial correlations which inspired it have been extensively confirmed. Neuropathologists have demonstrated inflammatory processes to be as reliable a feature of Alzheimer's disease as plaques or tangles. Initial prospective trials of NSAIDS have reported positive results; extensive clinical trials are under way. The mechanistic analysis – how NSAIDS stabilise cerebral function – is still a controversial and exciting field. This is where the *Alzheimer's Disease and Inflammation Initiative* has made a particular contribution.

I believe I can report to my fellow Trustees, to those who served on the Scientific Advisory Committee and to those who have supported us, that the Fund’s Alzheimer's disease and Inflammation Initiative was timely, focussed and, given our resources, was successful and influential.