



Australian Government

National Health and Medical Research Council

**Post-Coma Unresponsiveness
(Vegetative State):
A Clinical Framework for Diagnosis**

An Information Paper

Endorsed 18 December 2003

© Commonwealth of Australia 2004

Paper-based publications

This work is copyright. Apart from any use permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from the Commonwealth available from the Department of Communications, Information Technology and the Arts. Requests and inquiries concerning reproduction and rights should be addressed to the Commonwealth Copyright Administration, Intellectual Property Branch, Department of Communications, Information Technology and the Arts, GPO Box 2154, Canberra ACT 2601 or posted at <http://www.dcita.gov.au/cca>.

© Commonwealth of Australia 2004

Electronic documents

This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, non-commercial use or use within your organisation. Apart from any use as permitted under the Copyright Act 1968, all other rights are reserved. Requests for further information should be addressed to the Commonwealth Copyright Administration, Intellectual Property Branch, Department of Communications, Information Technology and the Arts, GPO Box 2154, Canberra ACT 2601 or posted at <http://www.dcita.gov.au/cca>.

ISBN Print: 1 86496 252 6 Online 1 86496 258 5

Disclaimer

This document is an information paper only and does not constitute clinical guideline recommendations.

The information paper is designed to provide information to assist health professionals involved in the assessment and diagnosis of post-coma unresponsiveness. The document is based on the best information available at the date of compilation (September 2003).

It is planned to review this information in December 2008. For further information regarding the status of this document, please refer to the NHMRC web address: <http://www.nhmrc.gov.au>.

To obtain details regarding NHMRC publications contact:

Email: nhmrc.publications@nhmrc.gov.au

Phone: Toll Free 1800 020 103

Internet: <http://www.nhmrc.gov.au>

CONTENTS

Summary	v
Overview and advisory points.....	v
Framework for the diagnosis of post-coma unresponsiveness (VS).....	ix
Considerations in diagnosing post-coma unresponsiveness (vegetative state).....	xii
Introduction	1
1 Current understanding of post-coma unresponsiveness (VS)	3
1.1 Review of the literature.....	3
1.2 Research needs.....	5
1.3 Existing guidelines.....	6
2 Pathology	9
2.1 Causes of post-coma unresponsiveness (VS).....	9
2.2 Neuropathological findings.....	9
2.3 Summary of evidence on pathology.....	12
3 Differential diagnosis	13
3.1 Loss of brain function.....	13
3.2 Coma.....	14
3.3 Locked-in state.....	14
3.4 Limited or minimal responsiveness.....	15
3.5 Akinetic mutism.....	17
4 Diagnosis and clinical management during diagnosis	19
4.1 Diagnosis of post-coma unresponsiveness (VS).....	19
4.2 Clinical management during the course of diagnosis.....	21
4.3 The welfare of patients and the role of the family.....	21
4.4 Future developments.....	23
5 Imaging and other tests	25
5.1 Computed tomography, magnetic resonance image scanning and angiography.....	26
5.2 EEG and cerebral electrical potentials.....	26
5.3 SPECT and PET scanning.....	28
5.4 Future developments.....	29
5.5 Quality of the evidence.....	31

6	Prognosis and emergence	33
6.1	Prognosis of patients who remain unresponsive	33
6.2	Emergence from post-coma unresponsiveness (VS)	35
6.3	Quality of the evidence on emergence.....	38
6.4	Continuing care.....	38
Appendices		39
A	Membership and terms of reference of the Working Party.....	40
B	Review of the evidence	42
C	Summary of existing guidelines	43
D	Process report.....	47
E	Dissemination and implementation	52
Acronyms and abbreviations		54
Glossary		55
Bibliography		57
	Additional reading.....	62

SUMMARY

OVERVIEW AND ADVISORY POINTS

The National Health and Medical Research Council (NHMRC) has issued this information paper to assist health professionals involved in the assessment and diagnosis of post-coma unresponsiveness. The term *post-coma unresponsiveness* is intended to be synonymous with the more established term *vegetative state* (VS). Both terms avoid the use of a time-based qualifier such as persistent or permanent (see further discussion on terminology below). Post-coma unresponsiveness (VS) encompasses clinical states that follow emergence from coma in which there is apparently complete lack of purposeful responsiveness, with preservation of sleep-wake cycles and cardiorespiratory function, and partial or complete preservation of hypothalamic and brain-stem autonomic (vegetative) functions.

Post-coma unresponsiveness (VS) is a manifestation of severe brain damage. It can be considered part of a continuous spectrum of impaired responsiveness that includes other forms of altered consciousness such as coma, death determined by loss of brain function, 'locked-in' syndrome, minimally responsive state (or minimally conscious state) and dementia (Bernat 2000). These states are sometimes very difficult to diagnose.

The incidence and prevalence of post-coma unresponsiveness (VS) are not known because of inconsistencies in assessment criteria and difficulties in assessing the effects of severe brain damage. Estimates of the likelihood of the *vegetative state* developing in patients in prolonged coma caused by trauma vary widely from 1 to 14 per cent (Multi-Society Task Force 1994a). The *vegetative state* has been rarely diagnosed in Australia (Dr I Baguley, personal communication) and few specialists have experience of large numbers of cases.

The diagnosis of post-coma unresponsiveness (VS) is an iterative process that should occur over a long period of time. There is a need to maintain care throughout this process. The ethics of managing patients in a state of post-coma unresponsiveness (VS) are the same as the ethics of managing any other highly dependent patient.

Terminology

The term *persistent vegetative state* and its acronym *PVS* are widely established in medical, legal and ethical literature, but other terms have been defined by various professional medical organisations. In several countries, the terms *vegetative state* or *continuing vegetative state* are used, with the modifier *permanent* applied when there is no prospect of emergence (Jennett 1997). However, none of these terms is defined or used consistently, and usage and definitions vary between countries.

There are increasing concerns in the literature and the clinical community about these terms and their potential to be misunderstood or to be prejudicial to the care of patients with the condition. Through the consultation process to develop this paper, comment was sought on the practicality of changing the terminology in this field (see page 51). Submissions received were largely supportive of the use of the term *post-coma unresponsiveness*. The advantages of this term are:

- it usefully excludes unresponsive states that do not follow a period of coma, such as the terminal stages of Alzheimer’s disease, or the unresponsiveness seen in developmental abnormalities such as anencephaly;
- it avoids the potentially pejorative term *vegetative*; and
- it has no time-based qualifiers — that is, it could apply as soon as emergence from coma occurs and for as long as the patient remains unresponsive (ie a clinical diagnosis of post-coma unresponsiveness would be the same as that of *persistent vegetative state*, but without the implication of a time-base).

Advisory point

- Through this paper, the NHMRC aims to discourage the use of terminology that may be misunderstood or be prejudicial to the care of patients with the condition (eg *persistent vegetative state*, *permanent vegetative state*, and *continuing vegetative state*). *Post-coma unresponsiveness* is proposed as an alternative term and is used in this report. The abbreviation for the more established term *vegetative state* (VS) is given after each use of *post-coma unresponsiveness* to reinforce the synonymy of the terms.

Diagnosis

For patients who survive severe brain damage with more or less intact autonomic functions but without cognitive responses, clinical requirements include the following:

- Assessment of the cause and extent of the brain damage and the nature of the neurological impairments, which often change over time.
- Repeated neurological assessments which involve the multidisciplinary team caring for the patient. The initial assessment should be undertaken by a medical practitioner with experience in assessing very severe brain injury.
- Standardised application of tests to enable measurement of change over time.
- Optimised circumstances for assessment which take into account the context for the individual.
- Repeated efforts to establish communication with the patient.
- Sensitive collaboration with the patient’s family and carers.

Ancillary diagnostic testing is helpful in amplifying clinical assessment but no ‘gold standard’ test for diagnosis is available or imminent.

Advisory points

- Given the uncertainties that may surround assessment, and the grave prognostic implications of a diagnosis of post-coma unresponsiveness (VS), it is important that decisions are made with great care over a sufficient length of time, and that the patient's best interests remain central to the process.
- It may not always be possible to distinguish clinically (as distinct from conceptually) between a state where a patient is minimally responsive because there is minimal cognitive capacity and a state where a patient has cognitive capacity but is effectively 'locked in' by damage to afferent or efferent pathways.

A framework to assist with assessment and diagnosis is given on pages ix to xii.

Prognosis and return of responsiveness

In the first few months of the condition, around 90 per cent of patients will either emerge from the unresponsive state or die. After this time the likelihood of emergence (ie the return of responsiveness) progressively decreases, but there is no evidence from studies of emergence of a change in this situation at any particular time. While it is rare for patients to emerge from an unresponsive state beyond the acute phase, there is some evidence for emergence after this time and the possibility, however remote, cannot be discounted.

Recent guidelines (Royal College of Physicians 2003) have suggested that a *vegetative state* lasting at least one year in trauma cases and six months in non-traumatic cases may be considered *permanent*, while acknowledging that such a state cannot be diagnosed with absolute certainty.

Even when emergence from post-coma unresponsiveness (VS) does occur, the outlook for these patients is often poor. Especially in patients who have been unresponsive for longer periods, there may be substantial residual disability with varying levels of dependence on others. The chance of a person regaining independence after being unresponsive for more than six months is extremely small.

Advisory points

- Factors that determine outcomes of post-coma unresponsiveness (VS) include the cause, extent and type of brain injury, the length of time that the person has been unresponsive, and his or her age (prognosis is even more uncertain in children than in adults).
- Determining the prognosis of a patient in an unresponsive state is very difficult. Due to methodological limitations of outcome studies, and variation in the many determining factors involved, prognosis should be based not on combined outcomes for all patients but on patients matched for cause and stage at assessment.

Evidence

Studies of post-coma unresponsiveness (VS) are confounded by a range of factors associated with the nature of the condition. Evaluation of the available evidence is further limited by the small number of published studies, and by methodological issues with the studies that have been done. As very prolonged post-coma unresponsiveness (VS) is rarely diagnosed, prospective cohorts of patients have not been studied in detail. The existing literature is therefore largely descriptive rather than investigative.

Due to the quality of the literature, it is necessary to take a more critical approach to evidence on post-coma unresponsiveness (VS) than for conditions with a stronger evidence base.

Advisory points

- The accurate collection of data relating to patients in states of coma and post-coma unresponsiveness (VS) is an essential prerequisite both for understanding the natural history of these conditions and for planning the most effective medical responses to them. It is recommended that a nationally coordinated coma register be established.
- Research needs include:
 - methods to overcome the heterogeneity of the patient group, including refinement of technologies to identify subclasses of patients with different prognoses;
 - further development of imaging techniques to assist in diagnosing manifestations of severe brain damage; and
 - an improvement in the management of people in a state of post-coma unresponsiveness (VS) with further studies of optimal stimulation and its efficacy.

Research needs are discussed in Section 1.2.

FRAMEWORK FOR THE DIAGNOSIS OF POST-COMA UNRESPONSIVENESS (VS)

The term post-coma unresponsiveness (VS) may generally be applied to patients emerging from coma in an apparently wakeful unconscious state in which there is:

- a complete lack of responses that suggest a cognitive component;
- preservation of sleep-wake cycles and cardiorespiratory function; and
- partial or complete preservation of hypothalamic and brain-stem autonomic functions.

Post-coma unresponsiveness (VS) can be considered as part of a spectrum of impaired responsiveness. As a clinical entity, post-coma unresponsiveness (VS) is conceptually well-defined. However, there may be difficulties in diagnosing the condition, sometimes due to poor understanding of the assessment criteria, and sometimes due to inherent limitations in assessing the effects of very severe brain damage.

Preconditions

1 To whom does this framework apply?

Adults and children aged more than one year, emerging from coma resulting from traumatic or non-traumatic brain injury, in a state of wakefulness but without signs of regaining responsiveness to the environment. The framework does not apply to unresponsive states that do not follow a period of coma, such as those resulting from the terminal stages of a chronic neurological disorder (eg Alzheimer's disease) or from developmental abnormalities such as anencephaly.

Diagnosis of post-coma unresponsiveness (VS) in infants aged less than one year is extremely difficult, and beyond the scope of this report. With unresponsive states arising as part of the relentless progression of a chronic neurological disorder, a fatal outcome is generally inevitable, and diagnosis of unresponsiveness has no therapeutic relevance. This framework is appropriate to those emerging from coma resulting from traumatic or non-traumatic brain injury.

2 What is the cause of the unresponsive state?

Determining the precise cause of the brain damage is important for prognosis of emergence and ultimate outcome.

Patients whose brain damage is caused by hypoxia or ischaemia generally have a worse prognosis than patients whose injury is caused by trauma.

3 When should the framework first be applied?

The framework should first be applied approximately four weeks after the appearance of unresponsive wakefulness. Regular reassessment is required.

Appearance of wakefulness may occur a few days or as long as six weeks after the onset of coma. The tests outlined below should be applied four weeks after the first evidence of wakefulness. Reassessment should initially be carried out at least every four weeks thereafter. If it is decided to reduce the frequency of formal reassessments, then the date of the next reassessment should be stated and recorded. The findings of the tests and the reassessments form the basis of future decisions and should be clearly documented on an appropriate chart.

4 Who should carry out the clinical examination?

It is important that medical practitioners who care for patients with severe brain injury be well informed about the assessment of altered consciousness and post-coma unresponsiveness (VS). Such practitioners include specialists in intensive care, neurologists, neurosurgeons and specialists in rehabilitation medicine (see Section 4.1).

Ideally, repeat assessments should be carried out by the multidisciplinary team caring for the patient, which might include medical practitioners, nurses, occupational therapists, physiotherapists, psychologists, speech pathologists and other allied health professionals. Assessments should take account of the continuing observations of the patient's family as well as the health professionals involved in the care of the patient.

Prolonged post-coma unresponsiveness (VS) is apparently not common in Australia and few medical practitioners have experience of large numbers of cases. Applying tests reliably and repeatedly, and optimising the circumstances under which tests are conducted, requires both time and expertise.

While the initial assessment should be undertaken by an experienced medical practitioner, repeat assessments should take into account the varying perspectives of the family and health professionals involved in the care of the patient.

Clinical assessment

Accurate assessment is vital for diagnosis of post-coma unresponsiveness (VS). Assessment involves excluding other manifestations of severe brain damage as well as identifying signs of post-coma unresponsiveness (VS).

Diagnosis of post-coma unresponsiveness (VS) can only occur after repeated clinical examination which obtains consistent results for a range of questions and supplementary tests and which takes into account the context for that individual. It is vital that the diagnosis is not made quickly.

Answers to the following questions should be consistently 'Yes'

1 Is the patient in good general health?

Febrile illness, sedation, intoxication and metabolic abnormalities should be excluded.

2 Are the conditions for testing optimal?

The patient should be out of bed with supportive seating (if practicable) in a familiar environment. Different times of day may be selected on different occasions. As patients can become habituated to noise and activity, high levels of stimulation should be avoided.

3 Are relatives or carers available to give extra information?

Relatives and carers can be useful sources of information about the state of responsiveness and subtle changes in patients. Information they provide is always valuable, even when it conflicts with observations made by medical staff. Examination of the patient with a relative or carer present is highly recommended as it is unlikely that patients in a totally dependent condition will otherwise be sufficiently reassured and able to provide a reliable indication of their capacity to respond.

Answers to the following questions should be consistently 'No'

4 Are there signs of responsiveness to the environment?

In patients in a post-coma unresponsive state, behaviour is not purposeful, movement appears stereotyped, recognition appears absent, attention appears absent and learning appears absent.

5 Are there purposeful responses to auditory, visual or tactile stimuli? Noxious stimuli can also elicit responses but must be used with care as they can cause patients to 'shut down'.

Reflex responses and movements do not exclude a state of post-coma unresponsiveness (VS). Visual tracking is usually absent but this may be very difficult to confirm. If a cold caloric test is carried out, the fast correcting phase of nystagmus will usually be absent. While the 'menace response' is usually absent, the following non-purposeful reflexes may be preserved:

- gag, cough, sucking and swallowing reflexes
- startle reflex, and primitive orientation reflexes (eg towards a loud noise)
- smiling, crying and groaning
- non-purposeful movements
- corneal reflex.

The context for the individual patient will influence emotional and other responses. Regular, consistent results are required to determine whether a response is purposeful or a reflex.

6 Is there any evidence of language comprehension or expression?

Responses of minimally responsive patients are often delayed. This may result in the response being discounted. It is also common for such patients to have a short attention span and to tire rapidly.

Answers to the following questions should be consistently 'Yes'

7 Is there evidence of cycles of eye opening and closing (sleep-wake cycles)?

8 Is there preservation of respiration and circulation (brain-stem function)?

9 Is the patient incontinent?

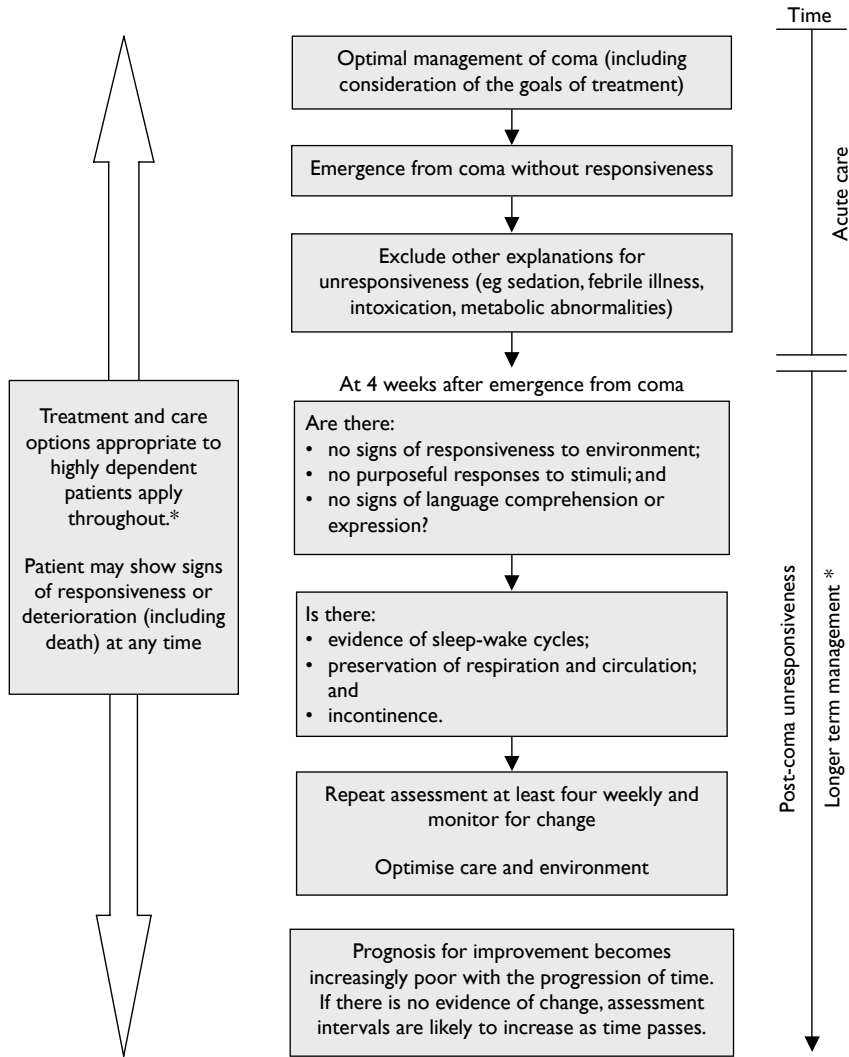
Imaging and other tests

There is a range of ancillary diagnostic aids that aim to amplify clinical assessment by demonstrating irreversible structural brain damage or absence of normal cerebral function, by helping to give a prognosis, or by excluding the presence of treatable lesions that might perpetuate the unresponsive state.

Structural, functional and electrophysiological tests are helpful in establishing the site and extent of brain injury. More extensive injuries, especially where connectivity between different cortical areas or between the cortex and subcortical areas is involved, are more strongly associated with post-coma unresponsiveness (VS). No 'gold standard' test is available or imminent.

It should always be kept in mind that awareness cannot be reliably excluded by any of these tests.

CONSIDERATIONS IN DIAGNOSING POST-COMA UNRESPONSIVENESS (VEGETATIVE STATE)



* Decisions about the treatment of highly dependent patients (including decisions about withholding or withdrawing treatment and the continuing provision of artificial nutrition and hydration) should be informed both by what, if anything, is known about their wishes and by a broad consideration of their best interests, and should reflect the best contemporary standards of care for people who are highly dependent.

In all instances the question is never whether the patient's life is worthwhile, but whether a treatment is worthwhile.

INTRODUCTION

This report aims to assist health professionals involved in the assessment and diagnosis of post-coma unresponsiveness (VS). It is applicable to adults and children aged more than one year, emerging from coma in a state of wakefulness, but without signs of regaining responsiveness to their environment.

The focus of the report is on post-coma unresponsiveness (VS) resulting from traumatic or non-traumatic brain injury. It does not apply to impaired responsiveness resulting from terminal degenerative causes (eg Alzheimer's disease) or from developmental abnormalities (eg anencephaly).

Discussion in the report is confined to the diagnosis of post-coma unresponsiveness (VS). The report does not include guidance on continuing care following such a diagnosis.

Development of a national report on diagnosis of post-coma unresponsiveness (VS)

This paper was developed in response to a request to the National Health and Medical Research Council (NHMRC) for assistance on the diagnosis of *persistent vegetative states* following brain injury. The request came from the New South Wales Health Department, arising from *Northbridge v Central Sydney Area Health Service* (2000) NSWSC 1241 revised 17/01/2001.

In August 2000 the Health Advisory Committee (HAC) of the NHMRC proposed that guidelines be developed as a joint initiative of HAC and the Australian Health Ethics Committee (AHEC). AHEC agreed to this approach in September 2000.

It was originally envisaged that the Terms of Reference for the project would be met through a two-stage process involving two working parties; one with expertise appropriate to addressing the assessment and diagnosis of the *vegetative state* and a second with appropriate expertise to focus on the clinical and ethical issues involved in continuing care. The Working Party that developed this paper focused its attentions on the area of diagnosis and therefore did not address Term of Reference 4 which concerns continuing care.

The membership and terms of reference of the Working Party are given in Appendix A.

Assessing the evidence

The Working Party conducted a review of available studies on diagnosis, neuropathology, ancillary testing, prognosis and emergence, with additional expert advice sought where necessary (see Appendix B). The paper was also informed by review of existing guidelines (see Appendix C) and by a systematic review of the literature on ongoing care of patients with post-coma unresponsiveness (VS).

Due to a lack of studies and methodological issues with the studies that have been undertaken (see Chapter 1), it is not possible to gather a level of evidence that would be regarded as adequate to justify clinical guideline recommendations. The NHMRC therefore decided to issue the report as an information paper which provides a synthesis of available evidence and expert opinion, and provides advice for clinicians on assessing patients in a post-coma unresponsive state (VS).

Consultation process

A multifaceted process of consultation was used to inform the development of this information paper:

- as a first stage of consultation, submissions were sought from relevant stakeholders. Thirteen submissions were received and issues raised were incorporated into the draft report;
- a workshop to obtain comment from health professionals was held to further inform the development of the information paper;
- a second-stage consultation draft was developed and comments sought through advertisements and dissemination of the paper. Eight submissions were received; and
- State and Territory health departments and other relevant organisations were invited to comment on the consultation draft.

The consultation process is discussed in greater detail in Appendix D.

Structure of the report

The report is structured as follows:

- description of the literature review, discussion of the limitations of the evidence and a summary of existing guidelines (Chapter 1);
- outline of the pathological basis of post-coma unresponsiveness (VS) (Chapter 2);
- clinical differentiation of post-coma unresponsiveness (VS) from other similar conditions (Chapter 3);
- discussion of studies into the assessment of post-coma unresponsiveness (VS), the clinical management that needs to occur while the assessment process occurs, and other perspectives of management, such as the welfare of the patient and the role of the family and other carers in the assessment process (Chapter 4);
- discussion of the use of tests and imaging (Chapter 5); and
- discussion of the issues surrounding prognosis and emergence (Chapter 6).

I CURRENT UNDERSTANDING OF POST-COMA UNRESPONSIVENESS (VS)

An early study gave a clinical account of emergence from deep coma into a state of unresponsiveness, with appearance of eye opening, at first only in response to pain, but later spontaneously, giving an apparent alternation of wakefulness and sleep (Jennett & Plum 1972). The authors of the study coined the term *persistent vegetative state*. While terminology varies, many authors have since confirmed the original description.

The essential features of such a state have been described as (Jennett 1996):

- long periods of wakefulness without responsiveness;¹
- roving eyes, sometimes briefly tracking a moving object;
- spastic limbs, with withdrawal in response to pain, and often grasp or grope reflex in the hands;
- no words uttered or mouthed, no commands obeyed; and
- no purposeful emotional responses — frowning, crying, tears, smile-like movements and laughter may occur but are divorced from appropriate stimuli.

This description is generally accepted. However, Jennett (2002) has recently published a critical review of the relevant literature, and has tabulated the diagnostic criteria used in a number of authoritative declarations. He has emphasised divergences of opinion on the significance of ocular responses and has noted the impossibility of wholly excluding some residual awareness in persons without any behavioural responses to suggest that they are aware.

There are many difficulties inherent in defining post-coma unresponsiveness (VS) and in reviewing the evidence regarding its assessment. This chapter describes the literature review undertaken for this paper, discusses the limitations of the evidence, and summarises diagnostic criteria from overseas guidelines.

I.1 REVIEW OF THE LITERATURE

To ensure that the literature reviewed in this information paper was complete and up to date, searches of the Medline, Embase and Cochrane databases were carried out using a range of medical subject headings (MeSHs). The initial search aimed to include all relevant studies with abstracts published in English in peer-reviewed

¹ While 'lack of awareness' is often used as evidence when assessing continuing unresponsiveness, an absence of awareness can only be inferred by lack of responsiveness to the environment. For this reason, *responsiveness* has been used rather than *awareness* wherever appropriate in this document.

journals before July 2001. Additional papers published after that date were located by Working Party members and considered in the development of this information paper.

The evidence used to inform the development of this information paper was classified according to the NHMRC level of evidence ratings (NHMRC 1999a), to enable readers to judge the strength of the evidence on which the paper is based. However, it should be noted that the questions dealt with in this paper concern pathology, diagnostic tests and prognosis rather than interventions so the levels of evidence are sometimes difficult to apply. This is why most evidence listed in this paper is level IV.

NHMRC levels of evidence

I:	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II:	Evidence obtained from at least one properly designed randomised controlled trial.
III-1:	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2:	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.
III-3:	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
IV:	Evidence obtained from case series, either post-test or pre-test and post-test.

Source: NHMRC (1999a).

The review process is discussed in greater detail in Appendix B.

Limitations of the literature

Studies of post-coma unresponsiveness (VS) are confounded by a range of factors associated with the nature of the condition. Evaluation of the available evidence is further limited by the small number of published studies, and by methodological issues with the studies that have been done.

As very prolonged post-coma unresponsiveness (VS) is rarely diagnosed, prospective cohorts of patients have not been studied in detail. Problems caused by the small number of patients are exacerbated by incomplete follow-up and a high death rate. The literature is also limited by:

- the heterogeneity of the patient group, which is caused by variation in the terminology used to describe the condition;
- the lack of a diagnostic test;
- difficulties in distinguishing between the various manifestations of impaired responsiveness; and
- the report of misdiagnosis in up to 40 per cent of cases (Andrews et al 1996).

In addition, post-coma unresponsiveness (VS) is associated with a variety of pathological causes and it has not been practicable to establish clear, objective structure-function relationships. The existing literature is therefore largely descriptive rather than investigative.

Methodological limitations of individual studies

Most reported studies of series of patients who remain in a state of post-coma unresponsiveness (VS) are further limited by methodological problems. These include:

- the heterogeneity of the cohort;
- inadequate description of processes for follow-up;
- loss of subjects to longer term follow-up that is not adequately accounted for;
- inconsistent intervals between evaluations; and
- failure to make allowance for variations in patient management within a series.

Due to the quality of the literature, it is necessary to take a more critical approach to evidence on post-coma unresponsiveness (VS) than for conditions with a stronger evidence base.

1.2 RESEARCH NEEDS

The accurate collection of data relating to patients in states of coma and post-coma unresponsiveness (VS) is an essential prerequisite both for understanding the natural history of these conditions and for planning the most effective medical responses to them.

It is therefore recommended that a nationally coordinated coma register be established.

The literature review identified a range of gaps in current knowledge.

- There is a paucity of long-term outcome studies both for individuals in a state of post-coma unresponsiveness (VS) for prolonged periods and/or those in states of minimal responsiveness. Accuracy of diagnosis and prognosis are important issues that need to be addressed through large prospective studies (Bates 1997).
- There is a need for further comparative autopsy studies on cases of apparent post-coma unresponsiveness (VS) and on cases of apparent minimal responsiveness. Quantitative estimates of the extent of damage may be illuminating. There is also need for correlative pathological and radiological studies to assess the prognostic value of neuroradiological images of brain damage.
- The availability of a standardised form for recording the progress of patients in states of post-coma unresponsiveness (VS) would allow harmonisation of information collected across Australia and greater comparability of single-case studies.

- The development of a research project into the effects of having a close relative (eg spouse, child, parent) who has a diagnosis of minimal responsiveness or post-coma unresponsiveness (VS) would provide further understanding of the needs of this group.
- There has been some research into evoked cerebral activity. It would be worth exploring recent refinements in this area that have emerged from the studies in cognitive psychology in this group of patients.
- Studies of optimal stimulation and its efficacy may provide an improvement in the management of people in a state of post-coma unresponsiveness (VS).

1.3 EXISTING GUIDELINES

Due to the medical, ethical and legal considerations presented by the state of post-coma unresponsiveness (VS), several professional medical organisations have developed standards for assessment of patients (World Medical Association 1989; American Medical Association 1990; ANA 1993; Multi-Society Task Force 1994a; 1994b; AAN 1995; British Medical Association 1996; Royal College of Physicians of London 1996; 2003). The terms used by these groups and their definition of terms vary markedly. The definitions and assessment criteria proposed by the groups are summarised in Appendix C.

Preconditions

Some guidelines (British Medical Association 1996; Royal College of Physicians of London 1996; 2003) stress the need to:

- define the cause of the *vegetative state*;
- exclude treatable causes of the *vegetative state*, particularly metabolic disturbance or the effects of drugs; and
- exclude other related conditions, including locked-in syndrome.

Clinical assessment

Explicit assessment criteria are given in five of the guidelines (American Medical Association 1990; ANA 1993; Multi-Society Task Force 1994a; British Medical Association 1996; Royal College of Physicians of London 1996; 2003). Inclusion of the following criteria is common to all of these:

- no evidence of responsiveness to the environment;
- no evidence of purposeful responses to stimuli;
- no evidence of language comprehension or expression;
- the presence of wake-sleep cycles; and
- preserved hypothalamic and brain-stem function sufficient to ensure the maintenance of respiration and circulation.

As well, guidelines include criteria concerning bowel and bladder incontinence, cranial nerve reflexes, eye tracking and nystagmus in response to cold caloric testing. Guidelines also describe features that may be present but are not indicative of responsiveness (eg inconsistent, non-purposeful motor activity, sporadic movements of facial muscles).

Most guidelines specify that a longer interval be allowed for assessment of post-coma unresponsiveness (VS) when it follows trauma than when it follows anoxia.

Imaging and other tests

Some of the guidelines considered the role of technology in the assessment of the *vegetative state* (American Medical Association 1990; ANA 1993; Multi-Society Task Force 1994a; British Medical Association 1996; Royal College of Physicians 1996; 2003). It is evident that although results of these studies may be of value in diagnosis in excluding related conditions, and in prognosis, no particular study is itself diagnostic of post-coma unresponsiveness (VS) and that diagnosis should be based on clinical assessment. This remains the current situation despite important advances since the development of many of the guidelines (Andrews 1999; Laureys et al 2000a; Rudolf et al 2000).

2 PATHOLOGY

The cause of the brain injury is a major determinant of both diagnosis and prognosis for patients surviving in states of post-coma unresponsiveness (VS). This chapter discusses the main causes of post-coma unresponsiveness (VS) and discusses its neuropathological basis. The terms *vegetative state* and *persistent vegetative state* are used in this chapter as they are the terms most often used in the literature.

2.1 CAUSES OF POST-COMA UNRESPONSIVENESS (VS)

Mechanical trauma and hypoxia are the chief causes of the *persistent vegetative state* in clinical practice, if degenerative conditions (eg Alzheimer's disease) and other progressive processes are excluded. The clinical course depends to a considerable extent on the particular underlying disease process (Multi-Society Task Force 1994a). In general, the prognosis is worse when the clinical state results from hypoxic-ischaemic brain damage.

2.2 NEUROPATHOLOGICAL FINDINGS

The *vegetative state* has been attributed to 'overwhelming damage to the cerebral hemispheres' (World Medical Association 1989). More recent studies indicate that the neuropathological findings are variable, though frequently there is severe damage to the thalamus and subcortical white matter (Kinney & Samuels 1994; Adams et al 2000). It is suggested that such lesions render even a structurally intact cortex unable to function.

There are, however, few published reports of large series of clinico-pathological correlations in cases of survival in the *vegetative state*. To have good evidential value, such studies should provide clinical descriptive assessments confirming the diagnosis of *vegetative* survival for an acceptable time; a minimum of one month has been adopted in the most authoritative study of this kind (Adams et al 2000). The neuropathological methodology should assess the whole brain and especially the nuclear structures supposedly concerned with arousal and wakefulness, and should give attention to the integrity of neurons and axons, using appropriate microscopic techniques. Ideally, a neuropathological study of the brains of patients in a *vegetative state* should provide comparisons with those of conscious patients with a similar degree of other neurological impairments. An unavoidable confounding factor when attempting to correlate the neuropathological features observed at autopsy with the clinical features on which the original diagnosis of *vegetative state* was based can be introduced by the occurrence of additional abnormalities during an extended interval between diagnosis and death.

Some earlier neuropathological studies were done before immunochemical staining techniques became available; these stains may demonstrate more extensive abnormalities than are shown by older staining methods. An early study investigating the pathological basis of prolonged states of unresponsiveness (termed extreme dementia by the author) reported on autopsy studies on five patients with severe head injury (Strich 1956). The study found diffuse damage to the subcortical myelinated fibres of the cerebral hemispheres. Strich relied heavily on histological stains visualising degenerating myelin rather than axonal injury, though silver stains were also used. A later study by the same author reported on 20 cases with similar pathological lesions in the white matter of the brain (Strich 1961). Most of the cases described in the studies did not conform exactly with the original definition of the *vegetative state* (Jennett & Plum 1972) as they manifested some speech and responsiveness at various times after their injuries. However, the studies clearly identified the usual finding in autopsied cases of the post-traumatic *vegetative state*, namely massive irreparable damage to the subcortical white matter of the cerebral hemispheres.

That the *vegetative state* might occur as a result of cortical necrosis due to severe hypoxia following cardiac arrest was recognised in the first study defining the condition (Jennett & Plum 1972). Two cases were described where patients survived in a *persistent vegetative state* for several months with isoelectric electroencephalograms (Brierley et al 1971). At autopsy, there was very extensive destruction of the cerebral neocortex and the basal ganglia (striatum); the thalami were also involved but to a lesser extent. In these and other autopsied cases of post-hypoxic *vegetative state*, there was extensive damage to the cerebellar cortex, but presumably this does not relate to loss of responsiveness.

Neuropathological findings in the case of Karen Ann Quinlan (who survived for 10 years in a *vegetative state* following cardiopulmonary arrest) included massive damage in both thalami (Kinney et al 1994). Although there was also much cortical atrophy, the authors concluded that the bilateral thalamic destruction was the chief cause of the loss of cognition and responsiveness. The brain stem, basal forebrain and hypothalamus were relatively well preserved, and the authors associated this with the patient's intact arousal and autonomic functions. This study gave a clear clinical description conforming to the criteria of the *vegetative state*, based on examination by one of the authors. The neuropathological investigation embodied serial sections of most of the cerebral hemispheres, with histological stains appropriate for both neurons and myelinated fibres. The findings were digitised, permitting the preparation of a three-dimensional atlas showing the damaged areas. As evidence, this study comes close to providing a gold standard; however, the reported staining methods did not include immunohistochemical stains for degenerating axons. These stains may not have been available when the study was performed.

Relkin et al (1990) reported on the autopsy findings made in three cases surviving 2–5 weeks after cardiac arrest. In two cases, multiple microscopic sections showed bilateral extensive neuronal damage in all the thalamic nuclei, while in the third the damage was most evident in the dorsomedial nuclei.

A review of findings in 11 published reports of the pathology of the *persistent vegetative state* concluded that cases showing loss of responsiveness showed three different sites of widespread bilateral damage: in the cerebral cortex, the subcortical white matter, or the thalami (Kinney & Samuels 1994). The authors related these distributions to current thoughts on the neuroanatomy of consciousness. However, the reports reviewed were of very diverse quality. In some series tabulated as reports of cases in the *persistent vegetative state*, it is evident that the clinical criteria were not always met.

A recent study has extended understanding of the *persistent vegetative state* occurring after trauma and acute hypoxia (Adams et al 2000). These authors reported on the neuropathological study of the brains of 49 patients who remained unresponsive until death (one month to eight years after an acute brain insult). In 25 of the 35 traumatic cases, the brains showed widespread axonal degeneration. In the other 10 traumatic cases, examination showed intracranial haemorrhage and/or anoxic brain damage. In the 14 cases of non-traumatic brain injury, the most common finding was laminar necrosis in the neocortex, and in every case there was also profound bilateral damage in the thalami and hippocampi. These studies did not include volumetric studies of the amount of damaged brain.

The authors followed this publication with a comparison of 35 brains from cases of post-traumatic *persistent vegetative state* with 30 cases of severe brain damage not in a *vegetative state* (Jennett et al 2001). Importantly, there were striking relative differences between the two series: half of the cases surviving with preservation of consciousness showed neither severe diffuse axonal damage nor large thalamic lesions, and contusion and haemorrhage were more frequent findings than in cases in the *persistent vegetative state*.

The cases of severe brain damage were selected from a large data bank of traumatic cases. It appears that the selection was on the basis of well-documented severe disability, which included patients surviving with minimal responsiveness. There was no age matching; the control series had a higher average age. The methodology in both series is well-known and reproducible (Adams et al 1982); brain slices are taken at 1 cm intervals and sections are stained with a range of methods visualising neurons, myelin and axons. Findings are plotted on standardised diagrams, permitting semi-quantitative evaluations. A criticism of the method is that the estimation of severity of axonal damage relates to the anatomical sites of injury rather than to the density of damage. Developments in immunochemistry and automated lesion counting should remedy this.

Thus, it appears that the relevant pathological findings in patients dying after survival in the *vegetative state* are extensive damage in the thalami, the cerebral cortex and the white matter of the cerebral hemispheres, in various combinations. Patients dying after hypoxia typically show laminar cortical necrosis and bilateral thalamic neuronal damage. Post-traumatic cases may show similar lesions, but more characteristically show massive bilateral damage to axons in the white matter of the hemispheres, suggesting that the cerebral cortex might be isolated by disconnection. In both groups, the brainstem and the hypothalamus are usually preserved.

2.3 SUMMARY OF EVIDENCE ON PATHOLOGY

None of the studies considered in this chapter entailed a clinical or other trial and all were classified as level IV evidence using NHMRC criteria. However, the paper by Jennett et al (2001) attempted to compare the neuropathological findings in cases of severe brain injury with and without survival in a *persistent vegetative state*. There was some overlap between the groups, with some of the severely disabled, but conscious, group having lesions as severe as those 'characteristic' of the unresponsive group.

3 DIFFERENTIAL DIAGNOSIS

As a clinical entity, post-coma unresponsiveness (VS) is conceptually well-defined. However, difficulties in recognising the condition do occur, sometimes due to poor understanding of assessment criteria and sometimes due to inherent limitations in the assessment of the effects of very severe brain damage.

The presence of sleep-wake cycles has been repeatedly seen as a diagnostic feature of the *vegetative state*. However, it is theoretically possible that this sign might be absent or inconspicuous in patients with facial and oculomotor paralysis due to a high midbrain lesion. Isono et al (2002) have recently reported four cases of otherwise typical *vegetative state* in which no sleep-wake cycles were detected; all had evidence of brainstem lesions.

It is essential to distinguish the unresponsive state from other manifestations of severe brain damage. The differentiation of these conditions is on clinical grounds, with limited evidence available to support the use of imaging and other tests (see Chapter 5). The following clinical states should be considered:

- death determined by loss of brain function;
- coma;
- locked-in state;
- limited or minimal responsiveness (or *minimally conscious state*);
- severe brain damage with expressive and/or receptive impairments; and
- akinetic mutism.

3.1 LOSS OF BRAIN FUNCTION

The development of the concept of 'brain death' has involved identifying the clinical criteria that indicate that integrated brain function has been lost. Based on the statutory definition of death (where applicable) and on professional codes of practice, the certification of death by reference to loss of brain function has become reasonably standardised in Australia (NHMRC 1997; ANZICS 1998).

After all preconditions have been satisfied, death as determined by loss of brain function is confirmed by clinical testing of brain-stem function. Preconditions are:

- diagnosis of severe brain injury and coma consistent with progression to loss of brain function (this may be confirmed by neuro-imaging);
- exclusion of coma caused by drugs or metabolic conditions such as hypothermia, hypoglycaemia or hyponatraemia; and
- confirmation of intact neuromuscular conduction.

Clinical testing of brain-stem function is then required to ensure that the patient has lost all reflex action involved in coughing, gagging, eye movement, blinking and pupillary responses. Finally the complete absence of the ability to breathe is established. Formal testing may be repeated up to 24 hours later.

Irreversibility is established in the light of the nature of the injury to the brain, the period of observation prior to the performance of formal testing, a period during which the complete absence of brain function in response to standard clinical testing is established and by repetition of the testing process where necessary.

Occasionally, clinical testing of brain function cannot be reliably completed and so death cannot be established according to the brain function criterion on clinical grounds alone. This might be so if anaesthetic drugs have been administered as part of normal treatment or if injury to the head prevents the very detailed clinical examination required. If this is the case, then death may be established by demonstrating that all blood flow to the brain has ceased. An angiogram of brain blood vessels or a radioisotope study is required to be sure that blood flow to the brain has ceased.

3.2 COMA

Coma is deep, sustained pathologic unconsciousness that results from dysfunction in either the brain stem or both cerebral hemispheres (Multi-Society Task Force 1994a). Coma is usually the immediate result of a cerebral insult such as trauma, anoxia, intoxication or infection.

In the Glasgow Coma Scale (GCS) (Teasdale & Jennett 1974), the level of consciousness is quantified in terms of eye opening, verbal response and motor response (see Glossary). Absence of eye opening on painful stimulus, any verbal or vocal response, and any motor response constitute the lowest level of consciousness and the deepest level of coma.²

Recovery from coma usually goes through levels of improving consciousness to normality. In unfavourable cases, the process of recovery may reach the unresponsive state and go no further.

3.3 LOCKED-IN STATE

The locked-in syndrome refers to a state in which consciousness and cognition are retained but movement and communication are impossible due to severe paralysis of the voluntary motor system (Plum & Posner 1972; AAN 1993a; Jennett 2002). This state may result from peripheral nerve disease but is most characteristically seen after a stroke affecting the brain stem.

² The usefulness of both the Glasgow Coma Scale and the Glasgow Outcomes Scale in defining emergence from an unresponsive state has been questioned.

Patients in a locked-in state typically show isolated lesions in the ventral pons with sparing of the cerebral hemispheres (Bauer et al 1979). Other structural bases for the typical clinical picture have been reported. In theory, a locked-in state might result from an isolated traumatic lesion or lesions in the brain stem, but in fact such cases are rare. Primary brain-stem lacerations usually cause instant death, though there are a few cases of survival, sometimes in a locked-in state (Simpson et al 1989; Blumbergs et al 1991). Survival after brain-stem lesions due to raised intracranial pressure is not uncommon, and conceivably might result in a locked-in state. These possibilities may justify magnetic resonance imaging (MRI) in cases of prolonged unresponsiveness (see Chapter 5). Although electroencephalography (EEG) findings have been used in the diagnosis of the locked-in state (Bauer et al 1979), it is questionable whether it can be confirmed by EEG evidence alone.

Patients may be able to communicate by some residual means of motor signal, such as eye movements, a twitching muscle, or vocal sound. When consistent responses are secured, communication can be established with letters of the alphabet, morse code, or other means (Andrews et al 1996). The success of such communication may be variable due to fatiguability.

The term *locked-in state* would be equally applicable to some cases misdiagnosed as in a state of post-coma unresponsiveness (VS), in whom careful assessment has shown some capacity to communicate (Andrews et al 1996). For obvious reasons, it is most important that such persons are not thought to be in an unresponsive state. There is little likelihood of this diagnostic error when the cause is a localised vascular lesion of the pons or brain stem. There is however a risk of misdiagnosis after severe brain injury. Trauma is not a common cause of a locked-in state from isolated brain-stem lesions, though this has been recorded (Blumbergs et al 1991). Much more frequent is a locked-in state after severe brain damage that interrupts major efferent pathways but leaves sufficient motor innervation to permit some kind of signalling, such as eye blinking, vocal noise, or muscular activation of a buzzer. In such cases, there may be in addition damage to afferent pathways, resulting in blindness or deafness.

3.4 LIMITED OR MINIMAL RESPONSIVENESS

Severe brain injuries may result in a state of severely limited responsiveness, with minimal but definite evidence of consciousness. Some patients may suffer from damage to the neural substrate of speech (eg dysphasias and dysarthrias) and/or other means of communication (eg quadriplegia). Though they may represent a part of the spectrum of unresponsiveness, these patients are not considered to be in a state of post-coma unresponsiveness (VS).

Minimal responsiveness has recently been defined as the *minimally conscious state* by Giacino et al (2002), who developed consensus-based guidelines on the definition and diagnostic criteria of this condition. According to their definition, this state is characterised by “severely altered consciousness, in which minimal but definite evidence of self or environmental awareness is demonstrated. To make the diagnosis, there should be one or more of the following:

- following simple commands;
- gestural or verbal yes/no responses (regardless of accuracy);
- intelligible verbalisation;
- purposeful behaviour including movements or affective behaviours that occur in contingent relation to relevant environmental stimuli and are not due to reflexive activity.”

Examples of qualifying purposeful behaviour include:

- appropriate smiling or crying in response to linguistic or visual content of emotional stimuli, but not to neutral topics or stimuli;
- vocalisations or gestures that occur in direct response to the linguistic content of questions;
- reaching for objects that demonstrates a clear relationship between object location and direction of reach;
- touching or holding objects in a manner that accommodates the size and shape of the object; and
- pursuit eye movement or sustained fixation that occurs in direct response to moving or salient stimuli.

It is emphasised that such evidence of awareness must be reproducible on repeated testing, though allowance is made for fatigue and other limiting factors. In people suffering from severe brain injuries, responsiveness may fluctuate and be absent when the patient is tired, ill or depressed. Moreover, a patient who has learned to make some kind of signal may fail to reproduce it with a different examiner.

These criteria have been given in more succinct form by Jennett (2002), who endorsed the term *minimally conscious state* to distinguish the condition from *vegetative states* showing reflex responses but no evidence of cognitive function. The Royal College of Physicians of London in its most recent memorandum on the *vegetative state* (2003) also cited the paper by Giacino et al and interpreted the term *minimally conscious state* as “the condition of patients who showed minimal but definite evidence of awareness despite profound cognitive impairment”.

Clearly where minimal consciousness is evident only by limited or intermittent communications, the degree of cognitive impairment may be hard to assess. A patient whose level of consciousness exceeds the ability to communicate could simultaneously be described as *minimally conscious* and *locked in*. The terms *limited* or *minimal responsiveness* have therefore been used in this paper.

Persons showing minimal responsiveness may emerge from this state to higher states of consciousness, though usually with severe disabilities. To monitor emergence, Giacino et al (2002) provide parameters for demonstrating functional communication and functional object use. However, the state of minimal responsiveness may be apparently static; Jennett (2002) mentions two cases that remained thus for 11 and 4 years. It also seems possible that signs of responsiveness may wax and wane over time.

Bernat (2002), commenting on the paper by Giacino et al, accepted the descriptive benefit of delineating the *minimally conscious state*, but stressed the importance of acknowledging the limitations of diagnostic categories within the spectrum of impaired responsiveness, and of maximally protecting the interests and welfare of such patients.

3.5 AKINETIC MUTISM

Akinetic mutism has been regarded as a form of unresponsive state, typically due to a localised lesion or lesions, and sometimes recovering dramatically. The term has been used to describe a trance-like state of severe but sometimes reversible unconsciousness with periods of seeming wakefulness and periods of sleep (Cairns et al 1941). The syndrome typically includes absence of speech or any other sound in response to stimuli, though some patients in this state have spoken or whispered a few words. There is absence of all voluntary motor activity (Cairns 1952), but spastic limb postures are not seen and grasp reflexes may be present (Freemon 1971). The eyes are periodically wide open, and may rove. Various pathological findings have been described (Plum & Posner 1972 p 23), including lesions in or near the third ventricle (Cairns 1952), but also bilateral lesions involving the territories supplied by the anterior cerebral arteries, with infarction of the anterior cingulate gyrus or its connections (Freemon 1971; Guetling et al 1992; Ackerman & Ziegler 1995). In one case of traumatic haemorrhage, there was negativism and a state suggesting catatonic schizophrenia (Cairns 1952).

Reports of similar cases have included the so-called Sleeping Beauty syndrome, an apathetic-akinetic-mutistic state, which may be, at least in part, a psychoreactive response (Todorow 1975). This interpretation has encouraged rehabilitationists to persevere with attempts to establish communication with children in unresponsive states soon after head injury.

Reasons for not equating akinetic mutism with the behaviour of patients in a vegetative/unresponsive state have been advanced (Jennett 1996; 2002), but it is easy to believe that the differential diagnosis may be difficult, and several writers have implied that akinetic mutism may merge into the *vegetative state*, or into inert apathy associated with frontal lobe lesions and sometimes called abulia [loss of willpower]. The paucity of reports of akinetic mutism since the term *persistent vegetative state* was proposed may suggest that subsequent cases with akinetic-mutism features have been subsumed diagnostically into the newer entity, or into the state of minimal consciousness/responsiveness when a few words are spoken. However, the term akinetic mutism may be reappearing as a description for some patients with variant Creutzfeldt-Jakob Disease (Blasco et al 2001; Tumani et al 2002).

4 **DIAGNOSIS AND CLINICAL MANAGEMENT DURING DIAGNOSIS**

Based on studies of pathology and differential diagnosis of impaired responsiveness, it is possible to develop a framework to guide diagnosis of post-coma unresponsiveness (VS). The framework on pages ix to xii outlines the assessment of patients who are in an unresponsive state and what to look for during the assessment process. Due to the nature of the condition and the lack of a specific diagnostic test, this process is based on continuing observation over time. This chapter discusses studies into assessment of post-coma unresponsiveness (VS) and outlines the clinical management that needs to occur during the assessment process. It also discusses other important factors in the assessment process, such as the welfare of the patient and the role of family and others who know the patient well.

4.1 **DIAGNOSIS OF POST-COMA UNRESPONSIVENESS (VS)**

Although there are guidelines giving assessment criteria for post-coma unresponsiveness (VS) (see Section 1.3), concerns have been expressed over the accuracy of assessment and the consequent potential for misdiagnosis. These concerns are supported by studies illustrating the difficulties in excluding minimal residual cognitive functions, for example:

- a study of patients referred to a neurological hospital under the diagnosis of *persistent vegetative state* (n = 40) (Andrews et al 1996) of whom 43 per cent proved to have been wrongly diagnosed by specialist practitioners, in that they were able to respond purposefully and to communicate by signals. All were severely disabled by unspecified physical impairments and 10 were blind or had severe visual impairment; and
- the recent reporting of three cases in which there was preservation of stereotyped, repetitive behavioural activity, including speech, in the absence of any evidence of cognitive activity or interaction with the environment (Plum et al 1998). One person had remained in an unresponsive state for 20 years, but exhibited the capacity to speak four or five meaningless words in two languages, without any descriptive or object-related content.

These cases fit well with the concept of post-coma unresponsiveness (VS) as a clinical expression of devastating but anatomically heterogeneous brain damage. The fact that such behavioural activity can be compatible with prolonged unresponsive existence has important implications for the diagnosis of unresponsiveness and emphasises the need for repeated observations carried out by experienced clinicians.

Professions involved in the diagnosis

A range of health professionals is likely to be involved in the diagnosis of post-coma unresponsiveness (VS).

- Intensivists are likely to be involved in the early care of comatose patients, and to be familiar with the signs of emergence from coma.
- Neurologists are concerned in the evaluation and treatment of patients who are unresponsive from such causes as vascular disease and hypoxia/ischaemia; neurologists are expert in the interpretation of electrodiagnostic and other special investigations.
- Neurosurgeons are also involved in the diagnosis and management of patients in unresponsive states, especially those unresponsive after head injury or acute intracranial haemorrhage.
- Specialists in neurorehabilitation are frequently responsible for the long-term care of patients with severe brain damage from all causes, and are familiar with the evaluation of changes in responsiveness over long periods.

In all these disciplines, it is important that specialist teaching should include awareness of the diagnostic difficulties discussed in this report. Wherever possible, it is advised that medical practitioners without personal experience in diagnosing post-coma unresponsiveness (VS) consult with a practitioner who has such experience.

Standardising the assessment process

As diagnosis of post-coma unresponsiveness (VS) is based on repeated assessments over time, it is important that observations are as accurate and consistent as possible. This includes:

- involving the patient's family and carers in observing the patient (discussed further in Section 4.3);
- considering individual patient requirements (eg in determining assessment intervals);
- timing the assessments to take account of treatment (eg sedative therapy) and other factors;
- involving the multidisciplinary team caring for the patient in the assessment process; and
- using consistent scales and tests at each assessment.

Tools have been developed for assessing patients with severe brain injury and refining diagnosis (eg SMART, developed at the Royal Hospital for Neuro-disability in London, which provides a structured program to assess the senses, movement, communication and wakefulness [Gill-Thwaites 1997]). The use of scales that are insensitive to assessing severe brain injury, such as the Glasgow Outcome Scale, may actually lessen the prospects of rehabilitation for unresponsive patients.

A nationally coordinated coma register would assist research in this area and should also benefit individual patients by promoting follow-up and regular reassessment.

4.2 CLINICAL MANAGEMENT DURING THE COURSE OF DIAGNOSIS³

The lack of certainty of diagnosis and long duration needed for determining diagnosis and prognosis have resulted in adoption of a cautionary approach to providing treatments and therapies for patients in a state of post-coma unresponsiveness (VS). However, it has been suggested that rehabilitative treatments be provided until there is practical certainty of diagnosis and prognosis or there is no further sign of progress. In some health care systems, it is also recommended that management of the patient be regularly reviewed by the hospital ethics committee (Whyte & Glenn 1986; Young et al 1989; Andrews 1993; Freeman 1997).

Basic nursing and medical care during the course of diagnosis is likely to include measures to maintain the optimal clinical state of the patient, prevent secondary complications and obviate suffering and discomfort. Such measures may include artificial nutrition and hydration, pressure care, range of movement exercises, and bowel and bladder care (Oboler 1986; Whyte & Glenn 1986; Ashwal 1994; Giacino & Zasler 1995; Gustafson 2000).

Some descriptive papers have identified complications experienced by patients in the *persistent vegetative state* (Arts et al 1985; Heindl & Laub 1996; Kluger et al 2000). A higher incidence of epileptic seizures was found in patients whose *persistent vegetative state* resulted from hypoxic causes rather than from trauma (Heindl & Laub 1996). Heterotopic ossification (Heindl & Laub 1996; Kluger et al 2000) and pressure sores (Tresch et al 1991) were also identified as complications associated with being in a *persistent vegetative state*.

4.3 THE WELFARE OF PATIENTS AND THE ROLE OF THE FAMILY

The need for medical practitioners to take into account the observations of the patient's family and carers has been recognised by a number of authors (Andrews 1996; Freeman 1997; Andrews 1999; Wade & Johnston 1999). The NHMRC strongly supports this view, and further recommends that, in the interests of the patient's welfare, decisions about treatment and care are made with great care over a sufficient length of time.

Considering the patient's welfare

Given the uncertainties that may surround assessment of post-coma unresponsiveness (VS), and the grave prognostic significance once it is diagnosed, the patient's best interests must be central to any decisions that are made. Assessment should be made in good faith, that is, to further the care of the patient:

- with honesty about practical uncertainty, where this exists;
- with consultation intended to reduce the risk of error;

³ Information in this section was drawn from the *Systematic Review of the Literature in Relation to Continuing Care of People Diagnosed with a Persistent Vegetative State* carried out by Queensland Centre for Evidence Based Nursing and Midwifery Mater Misericordiae Health Services Brisbane.

- recognising the role of the family and carers, and the burdens they bear and are prepared to continue to bear; and
- honouring the prior views of the patient (if these are known).

The patient's views about medical treatment in this situation may not be known, even to his or her family. During life, people need to be encouraged to talk with their family, doctors and other relevant people about their hopes for, and fears of, medical treatment, particularly that which may be administered to them in a situation in which they are unable to make their wishes known. An expression of such projected wishes could best be written in documents such as diaries or prior medical or hospital records, and ideally in an enduring power of attorney. In addition, people need to be better informed of the value of appointing someone to make decisions on their behalf should a situation arise in which they are unable to do so themselves.

The role of the family and others who provide care for the patient

The patient's family should always be respected and supported. So too should other people who are bonded to the patient by emotional or other ties of care. Health care facilities should always strive to be places of welcome and outreach to a patient's family and 'significant others'. The holistic care of patients involves, where possible, support and assistance for family, friends and others who care for dependent people. Sensitivity should always be shown to the patient's religious or cultural background.

Assessment of post-coma unresponsiveness (VS) is an iterative process. As the patient's family and significant others are likely to know the patient well, they may be able to assist health care practitioners in assessing the patient's condition. It can be beneficial to involve family members during examinations, as they may facilitate interactions with the patient and allow more accurate assessment of the patient's condition. Conveying a diagnosis of post-coma unresponsiveness (VS) to family and carers should be undertaken with great care and sensitivity.

As well as making observations to assist assessment, the family will also be involved in decisions about continuing care. This is because the assessment process may take place over a period of several months, during which many decisions are made about testing, support and an appropriate level of care.

Generally, the responsibility for health care decision-making belongs to each person in his or her own right. That is why health care practitioners must take care to explain clearly and accurately to a patient (NHMRC 1993)⁴:

- his or her condition;
- the nature of treatment options;
- the patient's prognosis with and without treatment;
- the risks and harms inherent in any proposed treatment which the patient would be likely to think significant in making a decision.

⁴ These guidelines are currently under review. It is anticipated that the review will be finalised in 2004.

In the case of patients who are either temporarily or permanently unable to make their own health care decisions, the patient's family, primary care givers or those legally appointed (by public authorities or by the patient's own prior decision) to represent the patient should be consulted about both proposed tests and proposed treatment. Indeed, except in the case of emergency, tests or treatment should not be administered to such patients until all relevant information has been disclosed and considered by the person (or persons) who constitute the patient's legitimate representative or guardian.

When health care practitioners seek the assistance of the patient's representative(s) or guardian(s) in the decision-making process, they should encourage them to base their decisions on the patient's best interests. Health care practitioners can help family and relevant others in their thinking about what would be in the patient's best interests by encouraging them to take into account not only the patient's medical condition and prognosis but also (first) the patient's previously expressed wishes and (second) their own views about what would be appropriate treatment in the circumstances.

In situations where family members and relevant others have conflicting views about appropriate treatment, health care practitioners should try to help them to understand the rationale for proposed tests and treatments.

4.4 FUTURE DEVELOPMENTS

Research directed to the diagnosis of post-coma unresponsiveness (VS) may be considered in two general categories, namely the distinction of post-coma unresponsiveness (VS) from other conditions and the possibility of separating patients meeting the clinical diagnostic criteria for post-coma unresponsiveness (VS) into subgroups with differing prognoses. While this paper is exclusively concerned with the *diagnosis* of post-coma unresponsiveness (VS), some of the procedures that have been trialled for that purpose overlap with the *management* of patients diagnosed as in post-coma unresponsiveness (VS). Specifically, procedures utilised in attempts to delineate subgroups of post-coma unresponsiveness (VS) may achieve this by eliciting clinical improvements in the condition of the selected subgroup. To this extent, these procedures could be classed as "therapeutic".

An example of a research procedure that did not entail any potentially therapeutic intervention was reported by Owen et al (2002). Three patients who were clinically diagnosed as in a *persistent vegetative state* were found, using PET (see Chapter 5), to be undertaking "covert cognitive processing". Cerebral blood flow increased reproducibly in association with face recognition but not with control stimuli. All three patients had a significant improvement some months later and it was inferred that the PET responses presaged this.

Research procedures that have a potential therapeutic component, apart from the possible identification of prognostically more favourable subgroups, have incorporated administration of pharmacologically active agents and deep brain electrical stimulation. Some of the experimental psychology approaches that

have been applied to post-coma unresponsiveness (VS) patients, such as operant conditioning, may also have potential for therapeutic benefit. The use of drugs in management of post-coma unresponsiveness (VS) patients with the intention of stimulating brain activity has probably been undertaken intermittently by clinicians on a “one-off” basis as it does not require the technical facilities needed for brain stimulation with implanted electrodes. A report of the effect of administering bromocriptine to post-coma unresponsiveness (VS) patients suggested that improvement may have been facilitated (Passler & Riggs, 2001). Reports of electrical stimulation deep in the brain have appeared over more than 20 years. Some recent reports suggest that such stimulation may be effective in poorly identified, subgroups of post-coma unresponsiveness (VS) (Yamamoto et al 2002).

As a general observation, it is not feasible to determine the extent to which any of these experimental approaches entails the *initiation* of improvement in a responsive subgroup of patients or the *acceleration* of a previously undetected process which would have occurred in any case, albeit at a slower pace, without intervention. Another general observation is that the recruitment of subjects incompetent to give consent for participation in invasive and highly experimental procedures requires careful consideration. The two general issues relevant to these procedures are those of the use of innovative therapy and its application to subjects incapable of giving consent. These issues have been considered in the *National Statement on Ethical Conduct in Research Involving Humans* (NHMRC 1999). Section 13 of the National Statement deals with “Innovative Therapy or Intervention” and Section 6 considers research involving unconscious patients.

5 IMAGING AND OTHER TESTS

A growing number of experts rely on imaging and/or neurophysiological tests to diagnose post-coma unresponsiveness (VS). However, as there is no evidence that any existing test can be used to diagnose the condition, the NHMRC considers that post-coma unresponsiveness (VS) must be diagnosed primarily through clinical examination. This supports the conclusions of the US Multi-Society Task Force on PVS and the Royal College of Physicians of London. This may change as technology evolves further and new tests are developed.

However, certain procedures can be used to amplify the assessment process by demonstrating irreversible structural brain damage or absence of normal cerebral function, helping to give a prognosis, or excluding the presence of treatable lesions that might perpetuate the unresponsive state. These include:

- images of brain structure — computed tomography (CT), MRI and angiography;
- records of cerebral electrical activity — EEG, visual-evoked responses (VERs), auditory-evoked responses (AERs) and somatosensory-evoked responses (SERs); and
- images of cerebral metabolic activity — single photon emission computed tomography (SPECT) and positron emission tomography (PET).

Ancillary diagnostic technology, while it is assisting understanding of unresponsiveness on a research basis, has yet to provide diagnostic or prognostic information with a high degree of certainty.

In evaluating quality of diagnostic tests (NHMRC 1999b), two criteria were particularly relevant to diagnostic tests for post-coma unresponsiveness (VS). These were diagnostic accuracy of the ‘gold standard’ of clinical diagnosis and, for prognostic tests, a sufficiently long and complete follow-up for the outcome of interest (*persistent* or *permanent vegetative state*) to occur, with this not being biased by intervening events.

Three systematic reviews of prediction of outcome in severe brain injury grouped *vegetative state* with other adverse outcomes. Nevertheless, these reviews of somatosensory-evoked potentials (SEPs) after severe brain injury (Carter & Butt 2001), early neurological examination, EEG or SEPs after anoxic ischaemic coma (Zandbergen et al 1998) and biochemical markers after anoxic ischaemic coma (Zandbergen et al 2001) concluded that these tests, particularly bilateral absence of SEPs, were powerful though imperfect predictors of outcome.

5.1 COMPUTED TOMOGRAPHY, MAGNETIC RESONANCE IMAGE SCANNING AND ANGIOGRAPHY

CT and MRI studies are in routine use to exclude a remediable disease process underlying an unresponsive state due to head injury (eg obstructive hydrocephalus or a chronic subdural effusion) and angiography may be used in the evaluation of cerebral blood flow. It is unusual for treatment of such conditions to rescue a victim from an unresponsive state, though it is possible that the onset of the unresponsive state may be prevented by proper treatment during the period of coma. In established cases of the *vegetative state*, imaging studies may illustrate the underlying pathology (Kampfl et al 1998a), but contribute only marginally to understanding of function. Neuroimaging has also been used extensively in studies predicting cognitive and functional outcome after brain injury (Azouvi 2000).

CT scanning

Except in extreme cases, CT scanning is essential in the management of acute brain injuries but plays little part in diagnosis of unresponsive states. CT scanning has been trialed as a prognostic indicator of outcome in unresponsive states (Reider-Groswasser et al 1997). However there have been a number of instances in which extreme CT changes have been followed by emergence. Most notably, a 60 year old man in a *vegetative state* after cerebral hypoxia with *generalised cerebral atrophy* on CT scan emerged from the state after eight weeks and was subsequently able to resume his academic career (Falk 1990).

MRI

Areas of structural damage shown on MRI do not always correlate with areas of poor function. Kampfl et al (1998a) reported the presence of widespread brain lesions in individuals in post-traumatic *vegetative state*, with diffuse axonal injury being the commonest form of brain injury. However, for individuals in post-traumatic *vegetative state* in the subacute stage after head trauma more than six areas of damage, and corpus callosum and dorsolateral brain stem lesions have a significant association with continuing post-coma unresponsiveness (VS) (Kampfl et al 1998b). Functional MRI measures regional blood flow, and thus, indirectly, neural activity. Widespread reductions in blood flow are consistent with diagnosis of a post-coma unresponsiveness (VS).

5.2 EEG AND CEREBRAL ELECTRICAL POTENTIALS

As the absence of reactivity to stimuli appears to be the abnormality most strongly associated with post-coma unresponsiveness (VS), it might be expected that the absence of cerebral electrical potentials (either in a resting state or evoked by stimuli) could be used to support its diagnosis. However, even the SER, the most sensitive

and reliable marker of cortical activity, may be normal in cases of the *vegetative state*, and absent in cases later recovering minimal cognitive activity (Multi-Society Task Force 1994a).

Electrophysiological studies do not provide a diagnostic gold standard. However, such studies can be of value and will usually be done as part of a neurological evaluation, especially when there is doubt about the patient's visual, auditory and tactile functions.

EEG

Isoelectric EEG records have been reported in two cases of post-anoxic necrosis of the cerebral cortex (Brierley et al 1971). In both cases, auditory and visual-evoked potentials showed no evidence of cortical activity, and one case also showed a lack of significant response to peripheral stimuli.

However, this absence of normal cerebral activity is not a consistent finding in cases of post-coma unresponsiveness (VS). During her first six months in a *vegetative state*, Karen Ann Quinlan's EEGs showed cortical activity (predominantly low-voltage fast activity [beta] when she was awake and intermittent low-voltage theta activity [3–7 Hz] during sleep and even some infrequent alpha activity) (Kinney et al 1994).

Other studies have reported a lack of correlation between EEG recordings and clinical status (Hansotia 1985; Rothstein et al 1991). Review of the published literature noted that 'in approximately 10 per cent of patients in a *vegetative state*, the EEG is nearly normal late in the course of illness, but without evidence of vision-induced alpha blocking' (Multi-Society Task Force 1994a). Reactivity, if present, suggests a better prognosis, but its absence does not reliably predict post-coma unresponsiveness (VS) or death. Similarly, reactivity on EEG may well herald emergence from post-coma unresponsiveness (VS), while its absence does not rule out the possibility of emergence at some point in the future.

Evoked electrical potentials

Computer-averaged cortical-evoked electrical responses have been used both in the diagnosis of post-coma unresponsiveness (VS), and for prognosis for patients in coma. SEPs have good positive predictive value for poor outcomes in trauma, anoxia and cerebrovascular accident. Bilateral absence is particularly accurate in predicting death or a state of unresponsiveness (Carter & Butt 2001; Zandbergen et al 1998). SEPs may be normal in locked-in syndromes. Brain-stem auditory-evoked potentials are less investigated.

The continued absence of an SEP over the cortex following median nerve stimulation has been found to be a useful predictor of an unfavourable outcome (Rothstein et al 1991). However it was pointed out that the absence of activity over one location did not necessarily indicate lack of activity over the entire cortex. Glass et al (1998) reported the presence of auditory event related potentials in patients with *post-coma unawareness*. They also point out that absence of N200 and P300 cognitive-evoked

potentials correlated strongly with *post-coma unawareness* and death, while presence of these responses had an association with emergence from coma. These results warrant further investigation.

SEPs have been used as a prognostic aid in determining the likelihood that patients in an acute stage of coma after trauma or hypoxia will ultimately enter an unresponsive state. Both bilateral and unilateral absence of cortical potential has been shown to be associated with an unfavourable outcome (death, *vegetative state* or inability to live independently) (Judson et al 1990). Of 45 patients lacking potentials at an early stage after cerebral trauma (n=100), 36 died, 2 were in a *persistent vegetative state* and 7 were incapable of independent living six months later.

VERs and brain-stem evoked responses (BSERs) have not been found of great diagnostic value (Keren et al 1994), but are often undertaken in cases of supposed locked-in states, as blindness or deafness may affect responsiveness.

5.3 SPECT AND PET SCANNING

Cerebral metabolic activity has been examined as a possible guide to outcome in patients considered to be in a post-coma unresponsive state. SPECT and PET scanning measure cerebral metabolic activity, indirectly by measuring cerebral blood flow (CBF), or directly by measuring cerebral oxygen metabolism (CMRO₂) and other metabolic activities. A 1996 study (Oder et al 1996) reviewed the status of these investigations.

SPECT scanning

SPECT provides a cost-effective and simple means of imaging CBF; the isotope used is technetium and the imaging device a gamma camera.

SPECT has been widely used in studies on the unresponsive state, and it has been shown that a global reduction of cortical blood flow is a predictor of poor outcome (Oder et al 1991; Oder et al 1996). Impaired perfusion in the frontal region is said to be especially predictive of poor outcome. However, SPECT abnormalities are not specific.

PET scanning

PET scanning is able to detect regional variation in cerebral glucose metabolism. It is especially used as a prognostic tool. An overall reduction in glucose metabolism is usual in unresponsive states, with certain areas more profoundly affected.

A study of CBF and CMRO₂ in seven cases of *vegetative state* and three of locked-in syndrome has shown impressive results (Levy et al 1987). CBF was measured through inhalation of CO₁₅O, and CMRO₂ with intravenous 18F fluorodeoxyglucose;

the study used normal subjects as controls. In the *vegetative* patients, cortical glucose metabolism was less than half the normal value, whereas the locked-in patients showed only a 25 per cent reduction.

However, in some cases of *chronic unconsciousness*, PET has shown small areas of relatively higher metabolic activity, suggesting the possibility of islands of functional brain tissue (Plum et al 1998; Schiff et al 2002). The extent to which depression of cerebral metabolism — other than its absence — can be interpreted as equivalent to any specified level of loss of consciousness remains undefined. The neuronal metabolic activity responsible for the presence of consciousness may represent a very small part of the total metabolic activity. Rudolf et al (1999) reported no statistically significant association between reduced global or regional glucose metabolic rate and degree of alteration in evoked potentials or EEG findings in patients with *vegetative states*.

Nevertheless, it remains to be demonstrated that PET is infallible either in diagnosis or in prognosis. In a study of five relatively early cases of *persistent vegetative state*, PET was able to image the primary auditory cortex after auditory stimulation. It was concluded that in these cases the cortex was intact but isolated, presumably by subcortical or intercortical interruption (Laureys et al 2000b). Three of the five cases improved to states of moderate disability or good recovery, and two did not. PET scan findings did not help in predicting outcome. Laureys et al (2002) subsequently used high intensity stimulation of the median nerve to demonstrate changes in the somatosensory cortex on PET in vegetative patients, even when cortical evoked potentials were absent.

5.4 FUTURE DEVELOPMENTS⁵

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS), which can be performed on standard MRI scanners, provides biochemical information about brain tissue, which frequently demonstrates the presence of pathological processes in brain tissue which may appear normal on standard MRI studies. N-acetyl aspartate (NAA) appears to be a unique neuronal marker, which is found in neuronal cells and their axons. Choline is a marker of cell membrane turnover and lactate indicates abnormal anaerobic metabolism.

In the past MRS was limited in that only one voxel at a time could be examined and the voxels measured anywhere between 2 and 8 cc in volume. Most modern MRI scanners allow the simultaneous examination of multiple voxels, which are 1 cc or less in volume. Although particularly used in the assessment of suspected tumours and stroke, it has already been used in vegetative patients. The NAA/Choline ratio has been reported to reach statistical significance in discriminating between patients with a poor outcome (death or a prolonged *vegetative state*) and those who regained

⁵ Information in this section was kindly provided by Dr Brian Tress, Department of Radiology, University of Melbourne.

awareness (Ricci et al 1997). It has certainly been used to help predict outcome in neonates, infants and children after acute central nervous system injury. It was reported to increase the correct prediction of outcome on the basis of clinical findings and standard imaging findings alone to 91 per cent (83 per cent before MRS) for neonates and 100 per cent (84 and 93 per cent before MRS) in infants and children (Holshouser et al 1997). No satisfactory prospective longitudinal randomised study with adequate numbers has yet been performed, but the technique appears promising and is a practical addition to most modern MRI scanners' protocols.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an extension of the widely used diffusion weighted sequence used by all modern scanners. It requires the acquisition of at least double the number of rapid sequences required for standard diffusion weighted sequences and appropriate post processing algorithms, but still takes only a few minutes to acquire the data. It detects the anisotropic diffusion of water molecules, which under normal circumstances is the form of diffusion seen in intact axons. The diffusion direction can be pictorially represented as a colour-coded white matter "map". Wallerian degeneration has been well demonstrated before it can be identified by conventional MRI (Pierpaoli et al 2001) and there have been case reports of DTI-demonstrated subtle white matter tract traumatic injury (Werring et al 1998). The technique appears ideally suited to the assessment of white matter shearing injury.

5.5 QUALITY OF THE EVIDENCE

Study	Level of evidence
Carter & Butt (2001)	Systematic review*
Multi-Society Task Force (1994a)	Systematic review*
Zandbergen EG et al (1998)	Systematic review*
Zandbergen EG et al (2001)	Systematic review*
Azouvi P 2000	Review
Brierley 1971	Level IV
Falk 1990	Level IV
Glass 1998	Level IV
Hansotia 1985	Level IV
Holshouser et al 1997	Level III-2
Judson 1990	Level IV
Kampfl 1998 (b)	Level III 2
Kampfl et al (1998a)	Level IV
Keren 1994	Level IV
Kinney 1994	Level IV
Laureys 2000 (b)	Level IV
Laureys 2002 (c)	Level IV
Levy 1987	Level IV
Oder 1991	Level IV
Oder 1996	Level IV
Pierpaoli et al 2001	Level III-2
Plum 1998	Level IV
Reider-Groswasser 1997	Level IV
Ricci et al 1997	Level IV
Rothstein 1991	Level IV
Rudolf 1999	Level IV
Schiff 2002	Level IV
Werring et al 1998	Level IV

* Systematic reviews but not of randomised controlled trials.

6 PROGNOSIS AND EMERGENCE

Many attempts have been made to determine prognosis of patients who remain in an unresponsive state and to predict the probability of emergence from such a state, on the basis of studies of its natural history, and of neuroanatomical structure and neurophysiological functions. However, many of these studies have methodological shortcomings which limit their usefulness. Long-term cohort studies of people with post-coma unresponsiveness (VS) commonly fail to take the variable quality of their life support into account. Technologically advanced studies of structure and function have provided probabilities for survival and emergence, and for ultimate disability, but so far have not achieved certainties.

Emergence is not synonymous with full recovery. Especially in patients who have been unresponsive for longer periods, there may be substantial residual disability with varying levels of dependence on others. There is general agreement that emergence is less probable in older people, and in the victims of hypoxic brain damage (Jennett 2002).

6.1 PROGNOSIS OF PATIENTS WHO REMAIN UNRESPONSIVE

The capacity for survival in a state of post-coma unresponsiveness (VS) has been found to require preservation of hypothalamic and brain-stem autonomic functions (Multi-Society Task Force 1994a). Factors that determine outcome are the cause, extent and type of brain injury, the length of time that the person has been unresponsive, and his or her age.

Studies into prognosis

A number of attempts to formulate prognostic criteria for unresponsive patients have been published. One study (n=210) proposed an algorithm based on clinical signs on the first two days after entry into coma (Levy et al 1985). The study compared outcomes from coma caused by cerebral hypoxic-ischaemia with serial neurological findings.

However, the proposed algorithm has been criticised on several grounds, including the rapid decrease in size of the subpopulation for whom an unfavourable outcome had been predicted (in one group of 70 patients only 36 per cent remained alive at the end of the first week and 9 per cent remained after a year) (Shewmon & De Giorgio 1989). A necessary consequence of this rate of loss was that a very large starting group would be required in order to estimate prognosis for a patient at an early stage. Some indication of the difficulty of meeting this requirement is provided by an earlier report (Levy et al 1981), in which only 5 per cent of patients predicted on admission to have no chance of regaining independent function (n=120) survived for more than two weeks.

Identifying and measuring outcomes

As in any other medical condition, identifying the outcome to be used as the basis for making predictions is necessary. Regaining responsiveness is the main outcome that can be objectively defined, even if not objectively measured. However, other endpoints of recovery are commonly selected. These may range from ‘minimally responsive with high dependency’ to independent living. The frequency of these outcomes decreases with progression along the range, with the chance of a person regaining independence after being unresponsive for more than six months being extremely small.

In any individual case, the likelihood of achieving the selected outcome, and hence the prognosis, will depend not only on the nature of the outcome, but also on the interval before it is measured. Any improvement that occurs, as well as determination of that improvement, may be both gradual and prolonged. For instance, an individual who is assessed as minimally cognitive at one time may have regained additional capacity to communicate if re-assessed a year later.

In attempting to formulate advice to guide estimation of prognosis of patients in an unresponsive state, a confounding factor is the wide range of treatment (or its lack) given to different individuals. The condition of some patients may never improve, irrespective of the care that is provided. The condition of others may improve under optimal conditions but not if they are given the minimal level of care. Experimental psychology studies with normal subjects point to the potentially detrimental effects of sensory deprivation on unresponsive patients. In addition, secondary complications may preclude the potential for spontaneous emergence.

Due to variation in the many determining factors involved, a prognosis based on combined outcomes for all patients may have little applicability to individual cases. This fact differentiates post-coma unresponsiveness (VS) from other states such as paraplegia.

Furthermore, it is difficult to differentiate the influence of quality of patient care into the two categories of facilitating detection of improvement and facilitating the improvement itself. This is likely to make estimating the probability of alternative outcomes even more complex.

Other difficulties

As well as these general principles, assessing prognosis in unresponsive states is complicated by specific difficulties, including:

- lack of any grading (or staging) of clinical entry criteria;
- lack of reliable ancillary technology that is suitable for diagnosis or grading of cases;
- rarity, if not complete absence, of groups of patients accessible for long-term follow-up;
- absence of quantifiable types of treatment or support which could be factored into estimates of prognosis (reflecting the great variability in management of different patients);

- disagreement about, and variability in, assessment of return of responsiveness (although acceptance of coma exit scales might alleviate this); and
- frequent failure when calculating prognosis to separate death from post-coma unresponsiveness (VS). There are likely to be two large exit groups from unresponsive states, namely death and recovery of consciousness, with the number of patients who remain unresponsive at the end of the first year being much less than either of these.

Generalisations about prognosis

Despite these difficulties, several generalisations about the likelihood of emergence from post-coma unresponsiveness (VS) have been made:

- the prognosis for emergence is better in cases following trauma than it is after those caused by hypoxia/anoxia (most existing guidelines specify that a longer interval be allowed for assessment of post-coma unresponsiveness [VS] when it follows trauma than when it follows anoxia);
- younger patients may have a better chance of emergence than older ones (especially in post-traumatic cases); and
- the preceding duration in coma (ie before eye opening) may provide some indication of the likelihood of emergence from a subsequent unresponsive state.

6.2 EMERGENCE FROM POST-COMA UNRESPONSIVENESS (VS)

Many of the prerequisites for diagnosis of an unresponsive state also apply to detecting emergence from it. These include:

- maintaining the patient in the best attainable physical condition;
- being prepared to listen to family, nurses and paramedics (especially physiotherapists and speech pathologists) and pay attention to their observations of the patient;
- being aware of a range of communication strategies and equipment; and
- having the patience to make serial brief examinations.

Diagnosis of emergence requires the existence of something to detect and the availability of someone who can detect it.

Studies into emergence

Some studies of patients in an unresponsive state have provided information about emergence from the state. However, this was frequently not the primary aim of the studies and, consequently, their contribution to assessing emergence is variable.

A number of caveats apply in the interpretation of these studies as follows:

- The limited information available has been presented in the form of outcomes at arbitrarily determined regular intervals, which may present an unrealistic impression of discontinuity (the likelihood of emergence at 14 months may not differ much from that at 10 months, but most studies use 12 months as the cut-off for reviewing outcomes).

- Epidemiological information about emergence can only be obtained from examining a series of patients. The study design would need to include information about the current status of all of the patients who had been entered into the study, as at the time of its conclusion.
- The likelihood of emergence tends to be expressed in relation to the original (ie starting) population of patients in a series rather than the subpopulation remaining unresponsive at the time of interest (eg one study reported that less than 5 per cent of patients emerged after nine months; however when account is taken of the patients who either died or emerged within the nine months, it is apparent that 25 per cent of 'traumatic' and 20 per cent of 'hypoxic' patients who remained unresponsive at nine months had emerged by nineteen months [Heindl & Laub 1996]).

Published studies have described the following:

- 60 per cent of patients in an unresponsive state after brain injury who met the original criteria for diagnosis of a *vegetative state* recovered consciousness in the course of a year (n=15) (significantly the authors noted that initial patient responses to communication were not detectable using standard tests) (Najenson et al 1978);
- of 135 patients with severe head injuries who were either 'unresponsive two weeks after the onset of coma or incapable of executing simple commands or showing any rapport with their environment', 8 per cent of patients who survived for one year were considered to be in a *vegetative state* (Bricolo et al 1980);
- 13 per cent of patients in an unresponsive state from non-traumatic causes who were diagnosed as *vegetative* (n=23) after one month subsequently regained consciousness, although two of the three patients died in the first year (the number of the remainder who remained alive and unresponsive at 12 months appeared to be less than half of the starting population; it should be noted that patients were followed after discharge from hospital and management and assessment was therefore variable) (Levy et al 1981);
- 20 per cent of patients considered to be *vegetative* at three months after severe brain injury (n=49) regained consciousness by the end of the first year (Braakman et al 1988);
- 58 per cent of patients in a *vegetative state* resulting from brain injury who were followed up after discharge (n=84) (Levin et al 1991) regained consciousness during the following three years (10 per cent of these after more than 12 months), 24 per cent died and 18 per cent remained in a *vegetative state* at the conclusion of the study;
- 26 per cent of patients assessed as in the *persistent vegetative state* (n=43) emerged from this state at intervals in excess of four months after initial brain injury (range 4–36 months) with 55 per cent of the emergent group remaining dependent in non-verbal communication (Andrews 1993);
- 24 per cent of patients in a *vegetative state* in a consecutive series (n=179) regained consciousness as inpatients (range 31 days to 2 years) (Sailly 1994); and
- 33 per cent of patients in a *vegetative state* resulting from cardiorespiratory arrest, head trauma or brain ischaemia (n=6) regained consciousness (after two to four months) (Tommasino et al 1995).

Reports of individual cases

Reports of individual cases have been published primarily because they illustrated some feature of interest, most commonly the duration of the unresponsive state before emergence. Their significance lies in reporting what can happen rather than in providing an indication of the frequency with which it does happen. Reports on emergence have included description of complete recovery after seven weeks (Shuttleworth 1983) and after eight weeks (Falk 1990).

The following accounts of emergence, occurring after much longer intervals, were associated with severe residual disability:

- a case of intermittent unresponsive state (Thomasma & Brumlick 1984);
- first signs of returning responsiveness after 30 months (Arts et al 1985);
- return of responsiveness after six months (soon after a court approved the withdrawal of hydration and nutrition) (Steinbock 1989); and
- emergence after 15 months (Childs & Mercer 1996).

Anecdotal accounts of emergence

The extent to which the conventional wisdom on the rarity of late emergence from an unresponsive state has been called into question recently as a consequence of the availability of specialised care is illustrated by a succession of such cases at the Royal Hospital for Neurodisability in London. Following what has become common practice in the United Kingdom, all but one of this group of people were identified by name in the media. This had already been a cause for concern expressed in a *British Medical Journal* editorial (Smith 1996). A number of cases of emergence were reported in the lay press during 1996–1997,⁶ together with quoted comments from medical personnel asserting their assessment that emergence from an unresponsive state had occurred.

Frequency of emergence

In the absence of reliable data on the prevalence of post-coma unresponsiveness (VS), it is not possible to express the number of patients who emerge after any specified interval as a percentage of those affected. It is also difficult to make a reliable estimate, for several reasons:

- estimates of the frequency of occurrence of unresponsive state in the community have varied by an order of magnitude;
- the survival pattern of such patients is inadequately documented; and
- it is unlikely that cases of delayed emergence will continue to be reported in the medical literature.

Instances of emergence from post-coma unresponsiveness (VS) after longer than expected intervals, as well as cited numbers of unresponsive patients living in the community and their survival time, are often dismissed as anecdotal. This

⁶ *Standard Recorder*, Basildon, 11/1/96; *Daily Telegraph*, London 13/2/96; *Guardian*, London, 16/3/96 and 19/4/96; *Independent*, London, 27/3/97; and *Daily Mail*, London, 6/4/97.

is not surprising, given the lack of accepted methodology for recognising the condition. However, in the absence of an accurate denominator, any calculation of the frequency of emergence remains of little value. Jennett (2002) noted that no substantial traumatic series had been followed after one year. In a series of 25 cases of vegetative survival from the Traumatic Coma Bank, it was initially supposed that six patients had 'regained consciousness' after a year. However, enquiry showed that three individuals had improved before one year, and there were no clinical details of the other three individuals.

Disability after emergence

After emergence from post-coma unresponsiveness (VS), there is likely to be a varying degree of disability, resulting from irreversible brain damage and other adverse effects of prolonged unresponsiveness. Musculoskeletal complications, such as contractures, that develop as secondary complications while the patient is unresponsive may considerably exacerbate the severity of residual disability. The extent of the disability is sometimes also aggravated by earlier lack of care which may also impede attempts to establish communication. Experience with other neurological conditions such as cerebral palsy suggests that earlier intervention can lead to improved outcomes and reduced residual disability.

Disability following emergence is linked to the issues of quality of life for these patients. As coma emergence scales continue to improve, the degree of recovery assessed in this way will provide some indication of the likely quality of life following emergence. However, as two individuals with a similar degree of impairment may have vastly different appraisals of their quality of life, this judgement can only be made by the affected individual.

6.3 QUALITY OF THE EVIDENCE ON EMERGENCE

All papers cited in this chapter were classified as level IV evidence using the NHMRC criteria.

6.4 CONTINUING CARE

Patients with post-coma unresponsiveness (VS) constitute a subset of patients with severe brain injury.

Decisions about their treatment (including decisions about withholding or withdrawing treatment and the continuing provision of artificial nutrition and hydration) should be informed both by what, if anything, is known about their wishes and by a broad consideration of their best interests, and should reflect the best contemporary standards of care for people who are highly dependent.

In all instances the question is never whether the patient's life is worthwhile, but whether a treatment is worthwhile.

APPENDICES

- A MEMBERSHIP AND TERMS OF REFERENCE OF THE WORKING PARTY
- B REVIEW OF THE EVIDENCE
- C SUMMARY OF EXISTING GUIDELINES
- D PROCESS REPORT
- E DISSEMINATION AND IMPLEMENTATION

A MEMBERSHIP AND TERMS OF REFERENCE OF THE WORKING PARTY

Membership

Dr Michael O'Callaghan (Chair)	Health Advisory Committee representative Director, Child Development and Rehabilitation Services, Mater Children's Hospital
Dr Shabbir Ahmed	Australian Federation of Islamic Councils
Ms Mary Baumgarten	ACT Health Care Consumers' Association
Professor Adèle Green	Chair Health Advisory Committee Deputy Director, Queensland Institute of Medical Research
Dr Peter B Greenberg	Physician, Department General Medicine, Royal Melbourne Hospital and Principal Fellow, Department of Medicine, University of Melbourne
Dr Peter Joseph	General practitioner, Adelaide
Dr Peter McCullagh	Visiting Fellow, John Curtin School of Medical Research
Dr Peter Saul	Intensive Care Unit, John Hunter Hospital
Professor Donald Simpson	Road Accident Research Unit, University of Adelaide
Dr Bernadette Tobin	Director, Plunkett Centre for Ethics, St Vincent's Hospital Sydney
Dr Michael Wood	Neuropsychologist, Adelaide

Secretariat

Ms Kristine Fisher, Ms Darlene Lawler and Ms Sheryl-Ann Schaefer
(Health Advisory Section, NHMRC)

Technical writers

Ms Elizabeth Hall and Ms Jenny Zangger (Ampersand Editorial & Design, Canberra)

Terms of reference

1. Critically evaluate existing research and clinical evidence for the appropriate diagnosis of persistent vegetative states arising from developmental, acute and degenerative causes.
2. Critically evaluate ethical issues associated with the diagnosis of persistent vegetative states.
3. In accordance with the NHMRC *Guidelines for the Development and Implementation of Clinical Practice Guidelines* undertake the development of clinical practice guidelines about the diagnosis and management of persistent vegetative states. The guidelines are to be developed in two stages: the first stage, dealing with the appropriate diagnosis of persistent vegetative states; the second, will deal with the appropriate continuing care of people diagnosed with a persistent vegetative state.
4. Develop a framework for the use of health care workers and for families in order to enable informed decision making in the event of diagnosis of a persistent vegetative state.
5. Undertake wide consultation with relevant stakeholders and relevant overseas parties.
6. Develop an effective dissemination and implementation strategy for the guidelines.
7. Recommend future research needs.
8. Present a final report to HAC, AHEC and Council for issuing.

B REVIEW OF THE EVIDENCE

The focus of the Working Party was clinical diagnosis of *persistent vegetative state* (post-coma unresponsiveness). The review was informed by evidence, consultation and by a workshop with clinical specialists and consumers. Because of the limitations of the evidence this document is issued as an information paper and not an evidence-based guideline.

Members of the Working Party carried out independent examination of published literature in the areas of diagnosis, pathology, testing, prognosis and emergence. Searches of the Medline, Embase and Cochrane databases were carried out using the following search terms:

- Vegetative state(s)
- Persistent vegetative state
- Permanent vegetative state
- Post-coma
- Post-coma unawareness
- Post-trauma unawareness
- PVS

The search strategy aimed to include all studies concerned with the diagnosis of *vegetative states* with abstracts published in English before July 2001. The review focused particularly on literature published following the report of the Multi Society Task Force in the US (1994).

The citation lists were reviewed to ensure that:

- original data were used (ie primary studies rather than commentaries on patients reported elsewhere);
- outcomes were described (eg death or emergence);
- reliable assessment strategies were used;
- a critical approach was taken and the authors recognised the philosophical difficulties in assessing the condition; and
- diagnostic tests other than clinical assessment were used.

Larger cohorts were favoured but small samples not excluded.

A separate systematic review of the literature in relation to the continuing care of people diagnosed with a *persistent vegetative state* also informed the development of this report (Queensland Centre for Evidence Based Nursing & Midwifery Mater Misericordiae Health Services Brisbane, unpublished).

Definition/usage**Diagnosis**
Royal College of Physicians of London (2003)

The *persistent vegetative state* refers arbitrarily to a vegetative state that has continued for four weeks or more.

Patients in the vegetative state should be observed for 12 months after head injury (traumatic brain injury) and 6 months after other causes before the state is judged to be *permanent*.

1 The key requirement is that there must be no evidence of awareness of self or environment at any time; no response to visual, auditory, tactile or noxious stimuli of a kind suggesting volition or conscious purpose; no evidence of language comprehension or meaningful expression

2 There are typically cycles of eye closure and eye opening giving the appearance of a sleep-wake cycle

3 Hypothalamic and brainstem function are usually sufficiently preserved to ensure the maintenance of respiration and circulation

Conditions outlined in criterion 1 are all necessary for the diagnosis. Criteria 2 and 3 are usually satisfied by patients in the vegetative state but they are not obligatory for the diagnosis.

Compatible clinical features include chewing, teeth grinding, swallowing, roving eye movements, purposeless limb movements, facial movements (eg smiles or grimaces), brainstem reflexes, arousal response to various stimuli (usually noxious or noisy), fleeting eye movement to follow a moving object or towards a loud sound, grasp reflexes.

Testing

Brain imaging with CT or MRI often helps to clarify the cause of these clinical syndromes, but the findings on imaging are not specific. Cerebral atrophy is commonly seen in patients in the vegetative state.

PET, magnetoencephalography and evoked potential studies can be used to shed light on the physiology of the condition but their use is not required for diagnosis, which remains essentially clinical.

British Medical Association (1996)

Persistent vegetative state patients appear awake but show no psychologically meaningful responses to stimuli.

The British Medical Association retains the term *persistent* rather than *permanent* but continues to keep the arguments and evidence under review.

All appropriate clinical steps must be taken to eliminate other possibilities.

During the period of initial assessment, it is appropriate to provide aggressive medical treatment. The British Medical Association believes that it is vital that stimulation and rehabilitation be available for patients suspected of being in a persistent vegetative state as soon as their condition is stabilised.

Refers to Royal College of Physicians of London guidelines for assessment criteria (see below).

Diagnosis of an irreversible persistent vegetative state should not be confirmed until patient has been insentient for 12 months.

PET scanning may be helpful in diagnosis in some cases.

Definition/usage	Diagnosis	Testing
<p>Royal College of Physicians of London (1996)</p> <p><i>Continuing vegetative state</i> for an unresponsive state present for more than four weeks and the term <i>permanent vegetative state</i> when the vegetative state endures for at least 12 months following head injury, or 6 months following other causes of brain damage</p>	<p>A cause for the vegetative state should be established. Investigations should exclude reversible causes such as drugs or metabolic disorders.</p> <p>For diagnosis to be considered there must be:</p> <ul style="list-style-type: none"> • no evidence of awareness of self or environment, no volitional response to visual, auditory, tactile or noxious stimuli and no evidence of language comprehension or expression • presence of cycles of eye closure and eye opening • sufficient preservation of hypothalamic and brain-stem function to ensure maintenance of respiration and circulation <p>Other clinical features include:</p> <ul style="list-style-type: none"> • incontinence of bladder and bowel • no nystagmus in response to ice water caloric testing, no visual fixation or tracking, or menace response • any motor activity is inconsistent, without purpose and explicable as a reflex response to external stimuli 	<p>There is no evidence at present that EEG, evoked potentials, CT or MRI improve clinical diagnosis.</p> <p>Patients in a <i>permanent vegetative state</i> may show changes of cortical atrophy and hydrocephalus on CT scan and PET will show a reduction in metabolism; neither finding is diagnostic of a <i>permanent vegetative state</i>.</p>
<p>American Academy of Neurology (1995)</p> <p><i>Persistent vegetative state</i> is a vegetative state present at one month after acute traumatic or non-traumatic brain injury and present for at least one month in degenerative/metabolic disorders or developmental malformations.</p> <p>A vegetative state is termed <i>permanent</i> when a diagnosis of irreversibility can be established with a high degree of clinical certainty.</p>	<p>As for Multi-Society Task Force (see below)</p>	

Definition/usage**Diagnosis****Testing****The Multi-Society Task Force (United States) (1994a)**

A vegetative state is defined as a clinical condition of complete unawareness of self and the environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brain-stem autonomic function.

A vegetative state is termed *persistent*, if present one month after traumatic or non-traumatic brain injury. The qualifier *persistent* is defined as a diagnostic term and *permanent* as a prognosis.

- No evidence of awareness of self or environment and an inability to interact with others
- No evidence of sustained, reproducible, purposeful or voluntary behavioural responses to visual, auditory, tactile or noxious stimuli

- No evidence of language comprehension or expression
- Intermittent wakefulness manifested by the presence of sleep-wake cycles
- Sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival with medical and nursing care

- Bowel and bladder incontinence
- Variably preserved cranial-nerve reflexes and spinal reflexes

Neurodiagnostic tests alone can neither confirm the diagnosis of a vegetative state nor predict the potential for recovery of awareness. However, when used in conjunction with a clinical evaluation, laboratory tests may provide useful supportive information.

ANA Committee on Ethical Affairs (1993)

Persistent vegetative state is defined as a vegetative state that has continued or endured for at least one month. This does not imply permanency or irreversibility.

It is necessary to ascertain the causes (eg cardiac arrest, head trauma etc).

- No evidence of awareness of self or surroundings
- No communication
- No comprehensible speech or mouthing of words
- Smiling, frowning and crying may occur but are inconsistently related to stimulus
- Sleep-wake cycles are present
- Brain-stem and spinal reflex activity is variable
- No motor activity suggesting learned behaviour and no mimicry
- Blood pressure control and cardiorespiratory function intact
- Incontinence of bladder and bowel is present

Laboratory studies (CT, MRI, PET, evoked potentials and EEG) may assist in determining cause of some features of the persistent vegetative state, but are not essential to its diagnosis.

Definition/usage	Diagnosis	Testing
<p>American Medical Association (1990)</p> <p><i>Vegetative state</i> is a chronic state of unconsciousness in which the body cyclically awakes and sleeps but expresses no behavioural or cerebral metabolic evidence of possessing cognitive function or of being able to respond in a learned manner to external events or stimuli.</p> <p>The term <i>persistent vegetative state</i> applies when such cognitive loss lasts for more than a few weeks.</p>	<ul style="list-style-type: none"> • Chronic wakefulness without awareness • No evidence of coherent speech or comprehension or capacity to initiate or make consistently purposeful movements • No visual fixation or following of objects • Spontaneous eye opening, utterance of unintelligible, instinctive sounds as well as sporadic movements of facial muscles and unparalysed limbs • Tonic reflex oculo-vestibular movements • Impaired motor function • Incontinence of urine and stool • Preservation of cardiorespiratory activity, swallowing and digestive and other non-neurological vital functions 	<p>By themselves, no confirmatory tests provide an accurate diagnosis or prognosis; but PET in persistent vegetative state patients has shown severely depressed energy metabolism equivalent to that found during deep general anaesthesia in normal persons.</p> <p>Brain imaging studies may or may not reveal multifocal or diffuse lesions and cortical atrophy.</p>
<p>World Medical Association (1989)</p> <p><i>Persistent vegetative state</i> is defined as a chronic state of unconsciousness in which the body cyclically awakens and sleeps but expresses no behavioural or cerebral metabolic evidence of possessing cognitive function or of being able to respond in a learned manner to external events or stimuli.</p>	<p>Observed unawareness for at least 12 months (although cognitive recovery after 6 months is exceedingly rare in patients over the age of 50)</p>	<p>Not stated</p>

D PROCESS REPORT

Development of the draft

This paper was developed in response to a request to the National Health and Medical Research Council (NHMRC) for assistance on the diagnosis of *persistent vegetative states* following brain injury. The request came from the New South Wales Health Department, arising from *Northbridge v Central Sydney Area Health Service* (2000) NSWSC 1241 revised 17/01/2001.

In August 2000 the Health Advisory Committee (HAC) of the NHMRC proposed that guidelines be developed as a joint initiative of HAC and the Australian Health Ethics Committee (AHEC). AHEC agreed to this approach in September 2000.

It was originally envisaged that the Terms of Reference for the project would be met through a two-stage process involving two working parties; one with expertise appropriate to addressing the assessment and diagnosis of the *vegetative state* and a second with appropriate expertise to focus on the clinical and ethical issues involved in continuing care.

Consultation

First-stage consultation

An initial round of consultation on the development of draft guidelines for the diagnosis of a *persistent vegetative state* took place during December 2000 to February 2001 and involved the following:

- a call for submissions on the development of the draft guidelines for the diagnosis of a *persistent vegetative state*, publicised in the *Government Notices Gazette* and *The Weekend Australian*; and
- invitations forwarded to all professional colleges and known interested parties.

Thirteen submissions were received and considered in the development of the first draft and are listed below.

Dr Leslie Bolitho
Consultant Physician in Internal Medicine

Ray Campbell
Queensland Bioethics Centre

Fiona Davies
Australian Medical Association, NSW

Reverend Dr Norman Ford
Caroline Chisholm Centre for Health Ethics, Melbourne

Alison Gaines
Executive Director
The Law Society of Western Australia

Professor Brendon Kearney
Executive Director
Department of Human Services, SA

Dr Long
Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Bishop ME Putney, DD
Auxiliary Bishop, Brisbane

Dr Warwick Neville
Research Fellow
Australian Catholic Bishops Conference

Professor Elsdon Storey
Department of Neuroscience
Alfred Hospital

Andrew Taylor
Executive Officer
Palliative Care Council of South Australia

Dr Nicholas Tonti-Filippini
Catholic Archdiocese of Melbourne

Frederick Khafagi FRACP
Chairman, Adult Medicine Division
The Royal Australasian College of Physicians

Workshop

A workshop was held in December 2001 to seek advice from experts in relevant fields to inform the development of the second-stage consultation draft. At the workshop, particular attention was paid to the following issues:

- terminology;
- testing;
- measurement and recording; and
- consumer and ethical issues.

Participants in the workshop are listed below.

Dr Peter Anastassiadis
Brain Injury Rehabilitation Unit
Hampstead Rehabilitation Centre

Dr Ian Baguley
Westmead Brain Injury Rehabilitation
Westmead Hospital

Ms Janet Budak
National Brain Injury Foundation

Neti Card
Brain Injury Rehabilitation Unit
Hampstead Rehabilitation Centre

Dr Leo Davies
Department of Neurophysiology
Royal Prince Alfred Hospital

Dr Geoff Dobb
Australian and New Zealand Intensive
Care Society
Intensive Care Unit, Royal Perth Hospital

Dr Ted Freeman

Dr James Gelder

Dr Joe Gurka
Department of Rehabilitation
Westmead Hospital

Professor Ross Harris
Department of Medicine
Royal North Shore Hospital

Dr Michael Hayes
Department of Neurology
Concord Hospital

Dr John Myburgh
Australian and New Zealand Intensive
Care Society
St George Hospital

Ms Jodie Nicholas
Westmead Brain Injury Rehabilitation
Westmead Hospital

Ms Sally Nelthropp

Ms Margaret Nottle
Hampstead Rehabilitation Centre
BIRU

Dr Chris Rowe
Department of Nuclear Medicine
Austin Hospital

Dr John Watson
Neuropsychology Unit
Royal Prince Alfred Hospital

Professor Brian Tress
Department of Radiology
University of Melbourne

Members of the NHMRC/AHEC Working Party who attended the workshop were Ms Mary Baumgarten, Dr Peter Joseph, Dr Peter McCullagh, Dr Michael O'Callaghan, Dr Peter Saul, Dr Bernadette Tobin and Dr Michael Wood.

Second-stage consultation

A second-stage consultation draft was developed which incorporated comments from first-stage consultation submissions and the expert workshop. This draft was advertised for comment and made available on the NHMRC website. Eight submissions were received and considered in the refinement of the draft and are listed below.

Cathy Clutton
Australian Health Ethics Committee

Elizabeth Heenan
President
The Law Society of Western Australia

Rev Dr Norman Ford SDB
Director
Caroline Chisholm Centre for Health Ethics Inc.

Professor Elsdon Storey
Professor of Neuroscience and Director
Van Cleef Roet Centre for Nervous Diseases

GAJ McCulloch
President
Neurosurgical Society of Australasia

Dr Robert Pollnitz FRACP
Consultant Paediatrician
Memorial Medical Centre

Ray Campbell LPh
Director
Queensland Bioethics Centre

Coalition for the Defence of Human Life

The consultation draft was also circulated to State and Territory health departments and submissions were received from:

Human Services Department, South Australia

NSW Health Department

Louise Sinclair
Principal Legal Officer
NSW Health

Issues arising through the consultation process

An ongoing theme during the consultation process was the terminology used to describe the condition. A range of concerns about current terminology were raised in submissions to the NHMRC and by participants at the Workshop:

- The medical term *vegetative* is potentially pejorative if misunderstood by families or carers as being synonymous with vegetable.
- The diagnosis of *vegetative state* depends on clinical observation of the presence or absence of behaviour that might indicate a functioning mind (Jennett & Plum 1972). As self-awareness cannot be measured, but only identified through an absence of purposeful responses to environmental stimuli, it has been suggested that the term *vegetative* be replaced by a clinical term descriptive of continuing unresponsiveness.
- Prediction of outcome may influence patient management (Murray et al 1993). Where the term *persistent vegetative state* is used inappropriately or taken to indicate permanence of an unresponsive state in an individual, it may lead to withholding of opportunities for rehabilitation and restriction or limitation of access to other treatments (Andrews 1996; Zasler 1996).
- The abbreviation *PVS* may be interpreted to mean either *persistent* or *permanent vegetative state*. Criteria for use of the qualifier *permanent* vary in overseas guidelines and some have suggested that there may be more than one type of *vegetative state* (Multi-Society Task Force 1994a; Andrews 1996; Royal College of Physicians of London 1996; 2003). It has been suggested that use of the qualifiers *persistent* and *permanent* be avoided and that, instead, the duration of the *vegetative state* be specified (American Congress of Rehabilitation Medicine 1995).
- Medical use of the term *permanent vegetative state* is based on the high statistical clinical probability of the *vegetative state* continuing indefinitely. It has been suggested that non-medical understanding of *permanent* is absolute, rather than statistical. Reports of late emergence or possible initial misdiagnosis (Tresch et al 1991; Childs et al 1993; Multi-Society Task Force 1994a; Andrews et al 1996) have heightened this concern.

Members of the Working Party share many of these concerns, along with bodies such as the International Working Party on the Vegetative State (Andrews 1996). The second-stage consultation draft therefore adopted the term *post-coma unresponsiveness*. Responses to the revised terminology in the second stage of the consultation process were largely positive.

E DISSEMINATION AND IMPLEMENTATION

Dissemination

Dissemination involves making guidelines accessible, advertising their availability and distributing them widely. Multiple dissemination strategies ensure greater coverage than a single strategy (NHMRC 1999a). The consultation process was used to determine how this report may best be disseminated and whether additional materials (eg consumer literature) should be derived from the report.

The dissemination strategy for this report includes distribution of the document to:

- State and Territory health departments;
- individuals and organisations who participated in the consultation process;
- workshop participants; and
- relevant professional Colleges.

Implementation

Dissemination alone is not enough to change the behaviour of health professionals (Field & Lohr 1992; EHCBC 1994; Oxman et al 1995; Bero et al 1998; Rubin et al 2000). For implementation of health advisory documents to be successful, they should be integrated with broader activities, such as continuing education and quality improvement (NHMRC 1999a).

Strategies that have been shown to be effective in changing clinicians' behaviour or health outcomes, or both (Lomas & Haynes 1988; Lomas 1993; 1994; Oxman et al 1995) include:

- promoting the report through endorsement by clinical groups, as well as conferences, seminars and workshops;
- education; and
- monitoring uptake of the report through reminder systems and continuing quality assurance and data feedback.

The following table summarises activities that may be appropriate for the implementation of this information paper.

Governments	• Developing and refining through consultation with stakeholders
Professional colleges and organisations	• Participating in consultations to refine the report and inform implementation • Endorsing the report through policy statements • Support for specialist teaching on diagnosis of post-coma unresponsiveness (VS)
Institutions	• Participating in consultations to refine the report and inform implementation • Supporting ongoing education of junior and senior clinical staff • Uptake of advisory points within institutions • Involving family and others who provide care to the patient in the process of assessment and in consent

Evaluation and review

Evaluation of guidelines aims to assess their validity and the effectiveness of their dissemination and implementation as indicated by their impact on professional behaviour, patient outcomes and health-care costs (Audet et al 1990). Areas that should be considered in evaluation of guidelines include (NHMRC 1999a):

- assessment of the dissemination process;
- assessment of whether or not clinical practice is moving towards the guideline's recommendations;
- assessment of whether or not health outcomes have changed (where baseline data allow);
- assessment of impact on consumer knowledge and understanding; and
- economic evaluation of the guideline process.

Implications of the report

This report presents the available evidence and expert opinion on the diagnosis of post-coma unresponsiveness (VS) and considers diverse clinical experience and consumer concerns in an attempt to promote more informed decision-making and improve patient care and outcomes.

If the report is implemented effectively, there will be a number of positive implications in a range of areas:

- consistency in approach to the diagnosis of post-coma unresponsiveness (VS);
- benefits to patients and their relatives from the use of the term post-coma unresponsiveness (VS) rather than *persistent vegetative state*;
- involvement of family and others who provide care for the patient in assessment;
- a broader understanding by the medical and allied health professionals as well as by consumers of the nature of post-coma unresponsiveness (VS); and
- patients with post-coma unresponsiveness (VS) receiving the same level of care as other highly dependent patients.

ACRONYMS AND ABBREVIATIONS

AAN	American Academy of Neurology
AER	auditory-evoked response
AHEC	Australian Health Ethics Committee
ANA	American Neurological Association
BSER	brain-stem evoked response
CBF	cerebral blood flow
CMRO ₂	cerebral oxygen metabolism
CT	computed tomography
DTI	diffusion tensor imaging
EEG	electroencephalography
EHCB	Effective Health Care Bulletin
fMRI	functional MRI
GCS	Glasgow Coma Scale
HAC	Health Advisory Committee
MeSH	medical subject heading
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAA	N-acetyl aspartate
NHMRC	National Health and Medical Research Council
PET	positron emission tomography
SEP	somatosensory-evoked potential
SER	somatosensory-evoked response
SPECT	single photon emission computed tomography
VER	visual-evoked response
VS	vegetative state

GLOSSARY

Anencephaly	Congenital absence of the cranial vault, with the cerebral hemispheres completely missing or reduced to small masses.
Anoxia	Deficiency of oxygen.
Axon	The usually single, long process of nerve cell that propagates a nerve impulse.
Brain stem	The portion of the brain immediately superior to the spinal cord, made up of the medulla oblongata, pons and mid-brain.
Caloric test	A test of the third, sixth and eighth cranial nerves. Ice water is instilled into the ear canal on one side. In a normal caloric test, the eyes will deviate to that side.
Cerebral cortex	The convoluted layer of grey matter covering the cerebral hemispheres, which governs thought, reasoning, memory, sensation and voluntary movement.
Dysarthrias	Imperfect articulation of speech due to disturbances of muscular control resulting from central or peripheral nervous system damage.
Dysphasia	Impairment of speech and other means of symbolic communication due to disease or injury of the brain, almost always in the left cerebral hemisphere if the patient is right handed.
Glasgow Coma Scale	A standardised system for assessing response to stimuli in a neurologically impaired patient. Reaction scores are depicted in numerical values, to minimise the problem of ambiguous or vague terms to describe the patient's neurological state. The total score is obtained by adding E, M and V; a score of 7 or less indicates coma and a score of 9 or more rules out coma.
Hydranencephaly	Absence of the cerebral hemispheres, their normal site being occupied by cerebrospinal fluid.
Hydrocephalus	A condition characterised by enlargement of the cranium caused by abnormal accumulation of cerebrospinal fluid within the cerebral ventricular system.
Hypothalamus	A part of the brain, lying beneath the thalamus and forming the floor and part of the wall of the third ventricle.

Hypoxia	Lack of adequate oxygen at the tissue level.
Necrosis	Death of a cell or group of cells as a result of disease or injury.
Nystagmus	Involuntary, rapid, rhythmic movement (horizontal, vertical, rotary or mixed) of the eyeball.
Persistent	This is a widely accepted but arbitrary qualifier which has been used to refer to a <i>vegetative state</i> that has continued for four weeks or more.
Permanent	This qualifier is often applied to a <i>vegetative state</i> lasting more than one year following traumatic head injury. While the chances of regaining awareness after this time are extremely low, any prediction that awareness will never recover cannot be made with absolute certainty.
Pons	The portion of the brain stem that forms a bridge between the medulla and mid-brain, anterior to the cerebellum.
Sleep-wake cycles	Cycles of eye opening and closing giving an apparent alternation of wakefulness and sleep.
Thalamus	A large oval structure located above the mid-brain, consisting of two masses of grey matter covered by a thin layer of white matter.
Trauma	An injury caused by an external agent or force.
Vegetative	Functioning involuntarily or unconsciously.

BIBLIOGRAPHY

- AAN (1993a) Position statement: certain aspects of the care and management of profoundly and irreversibly paralyzed patients with retained consciousness and cognition: Report of the Ethics and Humanities Subcommittee of the American Academy of Neurology. *Neurology* 43: 222–23.
- AAN (1993b) Position of the American Academy of Neurology on certain aspects of the care and management of the persistent vegetative state patient. *Neurology* 39: 125–26.
- AAN (1995) Practice parameters: assessment and management of patients in the persistent vegetative state. Summary statement. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 45: 1015–18.
- Ackerman H & Ziegler W (1995) [Akinetic mutism: A review of the literature.] *Fortschritte der Neurologie und Psychologie* 63: 59–67.
- Adams JH, Graham DI, Jennett B (2000) The neuropathology of the vegetative state after an acute brain insult. *Brain* 123: 1327–38.
- Adams JH, Graham DI, Murray LS et al (1982) Diffuse axonal injury due to nonmissile head injury in humans: an analysis of 45 cases. *Annals of Neurology* 12: 557–63.
- American Congress of Rehabilitation Medicine (1995) Recommendations for use of uniform nomenclature pertinent to patients with severe alterations in consciousness. *Archives of Physical Medicine & Rehabilitation* 76: 205–9.
- American Medical Association (1990) Persistent vegetative state and the decision to withdraw or withhold life support. Council on Scientific Affairs and Council on Ethical and Judicial Affairs. *Journal of the American Medical Association* 263: 426–30.
- ANA (1993) Persistent vegetative state: report of the American Neurological Association Committee on Ethical Affairs. *Annals of Neurology* 33: 386–90.
- Andrews K (1993) Recovery of patients after four months or more in the persistent vegetative state. *British Medical Journal* 306: 1597–600.
- Andrews K (1996) International Working Party on the Management of the Vegetative State: summary report. *Brain Injury* 10: 797–806.
- Andrews K (1999) The vegetative state — clinical diagnosis. *Postgraduate Medical Journal* 75: 321–24.
- Andrews K, Murphy L, Munday R et al (1996) Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. *British Medical Journal* 313: 13–16.
- ANZICS (1998) *Recommendations on Brain Death and Organ Donation*. 2nd edition, Australian and New Zealand Intensive Care Society, Melbourne.
- Arts W, van Dongen HR, van Hof-van Duin J et al (1985) Unexpected improvement after prolonged posttraumatic vegetative state. *Journal of Neurology, Neurosurgery & Psychiatry* 48: 1300–3.
- Ashwal S (1994) The persistent vegetative state in children. *Advances in Pediatrics* 41: 195–222.
- Audet AM, Greenfield S, Field M (1990) Medical practice guidelines: current activities and future directions. *Annals of Internal Medicine* 113: 709–14.
- Azouvi P (2000) Neuroimaging correlates of cognitive and functional outcome after traumatic brain injury. *Current Opinions in Neurology* 13: 665–69.
- Bates D (1997) Persistent vegetative state and brain stem death. *Current Opinion in Neurology* 10: 502–5.
- Bauer G, Gerstenbrand F, Rimpl E (1979) Varieties of the locked-in syndrome. *Journal of Neurology* 221: 77–91.
- Bernat JL (2002) Questions remaining about the minimally conscious state. *Neurology* 58: 337–38.

- Bero LA, Grimshaw JM, Oxman AD et al (1998) Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. *British Medical Journal* 317: 465–68.
- Blasco OR, Yaya HR, Garces SM et al (2001) Creutzfeldt Jakob disease with unilateral onset: clinical profile and imaging. *Neurologia* 16: 381–84.
- Blumbergs PC, Oatey PE, Sandhu A et al (1991) Pontomedullary tear in a speedboat accident. Report of a case with MRI diagnosis. *Zentralblatt für Neurochirurgie* 52: 89–93.
- Braakman R, Jennett WB, Minderhoud JM (1988) Prognosis of the posttraumatic vegetative state. *Acta Neurochirurgica* 95: 49–52.
- Bricolo A, Turazzi S, Feriotti G (1980) Prolonged posttraumatic unconsciousness: therapeutic assets and liabilities. *Journal of Neurosurgery* 52: 625–34.
- Brierley JB, Graham DI, Adams JH et al (1971) Neocortical death after cardiac arrest. A clinical, neurophysiological, and neuropathological report of two cases. *Lancet* 2: 560–65.
- British Medical Association (1996) *Treatment Decisions for Patients in Persistent Vegetative State*. <http://www.bma.org.uk/public/ethics.nsf/webguidelinesvw?OpenView&Start=30>
- Cairns H (1952) Disturbances of conscious awareness with lesions of the brain-stem and diencephalon. *Brain* 75: 109–46.
- Cairns H, Oldfield RC, Pennybacker JP et al (1941) Akinetic mutism with an epidermoid cyst of the 3rd ventricle. *Brain* 273–
- Carter BG & Butt W (2001) Review of the use of somatosensory evoked potentials in the prediction of outcome after severe brain injury. *Critical Care Medicine* 29: 178–86.
- Celesia GG (1997) Persistent vegetative state: clinical and ethical issues. *Theoretical Medicine* 18: 221–36.
- Childs NL & Mercer WN (1996) Brief report: late improvement in consciousness after post-traumatic vegetative state. *New England Journal of Medicine* 334: 24–25.
- Childs NL, Mercer WN, Childs HW (1993) Accuracy of diagnosis of persistent vegetative state. *Neurology* 43: 1465–67.
- Choi SC, Barnes TY, Bullock R et al (1994) Temporal profile of outcomes in severe head injury. *Journal of Neurosurgery* 81: 169–73.
- Cranford R (1996) Misdiagnosing the persistent vegetative state. *British Medical Journal* 313: 5–6.
- EHCB (1994) Implementing clinical practice guidelines. Can guidelines be used to improve practice? *Effective Health Care Bulletin* 6. University of Leeds, UK.
- Falk RH (1990) Physical and intellectual recovery following prolonged hypoxic coma. *Postgraduate Medical Journal* 66: 384–86.
- Field MJ & Lohr KN (eds) (1992) *Guidelines for Clinical Practice: from Development to Use*. Institute of Medicine, National Academy Press, Washington DC.
- Freeman EA (1997) Protocols for the vegetative state. *Brain Injury* 11: 837–49.
- Freeman FR (1971) Akinetic mutism and bilateral anterior cerebral occlusion. *Journal of Neurology, Neurosurgery and Psychiatry* 34: 693–98.
- Giacino JT & Zasler ND (1995) Outcome after severe traumatic brain injury: coma, the vegetative state and the minimally responsive state. *Journal of Head Trauma Rehabilitation* 10: 40–56.
- Giacino JT, Ashwal MD, Childs MD et al (2002) The minimally conscious state. Definition and diagnostic criteria. *Neurology* 58: 349–53.
- Gill-Thwaites H (1997) The Sensory Modality Assessment Rehabilitation Technique — a tool for assessment and treatment of patients with severe brain injury in a vegetative state. *Brain Injury* 10: 723–34.
- Glass I, Sazbon L, Groswasser Z (1998) Mapping ‘cognitive’ event related potentials in prolonged post-coma unawareness state. *Clin. Electroencephalogr.* 29: 19–30.
- Grossman P & Hagel K (1996) Post-traumatic apallic syndrome following head injury. Part 1: clinical characteristics. *Disability & Rehabilitation* 18: 1–20.
- Gustafson L (2000) Persistent vegetative state. Internet source.

- Gütling E, Landis T, Kleihues P (1992) Akinetic mutism in bilateral necrotizing leucoencephalopathy after radiation and chemotherapy: electrophysiological and autopsy findings. *Journal of Neurology* 239: 125–28.
- Hansotia (1985) Persistent vegetative state. Review and report of electrodiagnostic studies in eight cases. *Archives of Neurology* 42: 1048–52.
- Heindl UT & Laub MC (1996) Outcome of persistent vegetative state following hypoxic or traumatic brain injury in children and adolescents. *Neuropediatrics* 27: 94–100.
- Holshouser BA, Ashwal S, Luy GY et al (1997) *Radiology* 202: 487–96.
- Isono M, Wakabayashi Y, Fujiki MM et al (2002) Sleep cycle in patients in a state of permanent unconsciousness. *Brain Injury* 16: 705–12.
- Jennett B & Bond M (1975) Assessment of outcome after severe brain damage. *Lancet* 1: 480–84.
- Jennett B & Plum F (1972) Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet* 1: 734–37.
- Jennett B & Teasdale G (1981) *Management of Head Injuries*. Philadelphia. Davis. 1981. p.80.
- Jennett B (1996) Clinical and pathological features of vegetative survival. In: *Catastrophic Brain Injury*. Levin HS, Benton AL, Muizelaar JP et al (Eds), Oxford University Press, New York, Chapter 1.
- Jennett B (1997) A quarter century of the vegetative state: An international perspective. *Journal of Head Trauma Rehabilitation* 12: 1–12.
- Jennett B (2002) *The Vegetative State. Medical Facts, Ethical and Legal Dilemmas*. Cambridge University Press, Cambridge UK.
- Jennett B, Adams JH, Murray LS, Graham DI (2001) Neuropathology in vegetative and severely disabled patients after head injury. *Neurology* 56: 486–90.
- Judson JA, Cant, BR, Shaw, NA (1990) Early prediction of outcome from cerebral trauma by somatosensory evoked potentials. *Critical Care Medicine* 18: 363–68.
- Kampfl A, Franz G, Aichner F et al (1998a) The persistent vegetative state after closed head injury: clinical and magnetic resonance imaging findings in 42 patients. *Journal of Neurosurgery* 88: 809–16.
- Kampfl A, Schmutzhard, E, Franz G et al (1998b) Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging. *Lancet* 351(9118): 1763–67.
- Kanno T, Kamei Y et al (1987) Neurostimulation for patients in vegetative states. *Lancet North American Edition* 351: 1763–67.
- Kanno T, Kamei Y et al (1989) Effects of dorsal column spinal cord stimulation (DCS) on reversibility of neuronal function — experience of treatment of vegetative states. *Pacing Clin Electrophysiol* 12: 733–38.
- Katayama Y, Tsubokawa T et al (1991) Characterization and modification of brain activity with deep brain stimulation in patients in a persistent vegetative state: pain-related late positive component of cerebral evoked potential. *Pacing Clin Electrophysiol* 14: 116–21.
- Keren O, Sazbon L, Groswasser Z et al (1994) Follow-up studies of somatosensory evoked potentials and auditory brainstem evoked potentials in patients with post-coma unawareness (PCU) of traumatic brain injury. *Brain Injury* 8: 239–47.
- Kinney HC & Samuels MA (1994) Neuropathology of the persistent vegetative state. A review. *Journal of Neuropathology & Experimental Neurology* 53: 548–58.
- Kinney HC, Korein J, Panigrahy A et al (1994) Neuropathological findings in the brain of Karen Ann Quinlan. The role of the thalamus in the persistent vegetative state. *New England Journal of Medicine* 330: 1469–75.
- Kluger G, Kochs A, Holthausen H et al (2000) Heterotopic ossification in childhood and adolescence. *Journal of Child Neurology* 15: 406–13.
- Laureys S, Faymonville M, Pergneux P et al (2002) Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage* 17: 732.
- Laureys S, Faymonville ME, Degueldre C et al (2000b) Auditory processing in the vegetative state. *Brain* 123: 1589–601.

- Laureys S, Faymonville ME, Luxen A et al (2000a) Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet* 355: 1790–91.
- Levin HS, Saydjari C, Eisenberg HM et al (1991) Vegetative state after closed-head injury. A Traumatic Coma Data Bank Report. *Archives of Neurology* 48: 580–85.
- Levy DE, Bates D, Caronna JJ et al (1981) Prognosis in nontraumatic coma. *Annals of Internal Medicine* 94: 293–301.
- Levy DE, Caronna JJ, Singer BH et al (1985) Predicting outcome from hypoxic-ischemic coma. *Journal of the American Medical Association* 253: 1420–26.
- Levy DE, Sittis JJ, Rottenberg DA et al (1987) Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. *Annals of Neurology* 22: 673–82.
- Lomas J & Haynes RB (1988) A taxonomy and critical review of tested strategies of the application of clinical practice recommendations: from ‘official’ to ‘individual’ clinical policy. *American Journal of Preventive Medicine* 4: 77–97.
- Lomas J (1993) Retailing research: increasing the role of evidence in clinical services for childbirth. *The Millbank Quarterly* 71: 439–75.
- Lomas J (1994) Teaching old (and not so old) docs new tricks. In E Dunn et al (eds) *Disseminating Research/Changing Practice, Research Methods for Primary Care*, vol 5. Sage Publications, Thousand Oaks, US.
- Multi-Society Task Force (1994a) Medical aspects of the persistent vegetative state (1). Multi-Society Taskforce on the Persistent Vegetative State. *New England Journal of Medicine* 330: 1449–508.
- Multi-Society Task Force (1994b) Medical aspects of the persistent vegetative state (2). Multi-Society Taskforce on the Persistent Vegetative State. *New England Journal of Medicine* 330: 1572–79.
- Murray LS, Teasdale GM, Murray GD et al (1993) Does prediction of outcome alter patient management. *Lancet* 341: 1487–91.
- Najenson T, Sazbon L, Fiselzon J et al (1978) Recovery of communicative functions after prolonged traumatic coma. *Scandinavian Journal of Rehabilitation Medicine* 10: 15–21.
- Narayan RK, Greenberg RP, Miller JD et al (1981) Improved confidence of outcome prediction in severe head injury. A comparative analysis of the clinical examination, multimodality evoked potentials, CT scanning, and intracranial pressure. *Journal of Neurosurgery* 54: 751–62.
- NHMRC (1993) *General Guidelines for Medical Practitioners on Providing Information to Patients*. Commonwealth of Australia. [This document is currently under review.]
- NHMRC (1997) *Certifying Death: the Brain Function Criterion*. Ethical Issues in Organ Donation Discussion Paper 4. National Health and Medical research Council, Canberra.
- NHMRC (1999a) *A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines*. National Health and Medical Research Council, Canberra.
- NHMRC (1999b) *How to Review the Evidence: Systematic Identification and Review of the Scientific Evidence*. National Health and Medical Research Council, Canberra.
- NHMRC (1999c) *National Statement on Ethical Conduct in Research Involving Humans*. National Health and Medical Research Council, Canberra.
- Oboler SK (1986) Brain death and persistent vegetative states. *Clinical Geriatric Medicine* 2: 547–76.
- Oder W, Goldenberg G, Podreka I et al (1991) HM-PAO-SPECT in persistent vegetative state after head injury : prognostic indicator of the likelihood of recovery. *Intensive Care Medicine* 17: 149–53.
- Oder W, Podreka I, Spatt J et al (1996) Cerebral function following catastrophic brain injury: relevance of single photon emission tomography and positron emission tomography. In: *Catastrophic Brain Injury*. Levin HS, Benton AL, Muizelaar JP et al (Eds), Oxford University Press, New York, Chapter 4.
- Owen AM, Menon DK, Johnsrude IS et al (2002) Detecting residual cognitive function in persistent vegetative state. *Neurocase: Case Studies in Neuropsychology, Neuropsychiatry, and Behavioural Neurology* 8: 394–403.

- Oxman AD, Thomson MA, David DA et al (1995) No magic bullets: a systematic review of 102 trials of interventions to help health care professionals deliver services more effectively or efficiently. *Journal of the Canadian Medical Association* 153: 1423–31.
- Passler MA & Riggs RV (2001) Positive outcomes in traumatic brain injury – vegetative patients treated with bromocriptine. *Archives of Physical Medicine and Rehabilitation* 82: 311–15.
- Pierpaoli C, Barnett A, Pajevic S et al (2001) Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *Neuroimage* 13: 1174–85.
- Plum F & Posner JB (1972) *The Diagnosis of Stupor and Coma*. 2nd ed. Davis, Philadelphia, p.24, 126.
- Plum F, Schiff N, Ribary U et al (1998) Coordinated expression in chronically unconscious persons. *Philosophical Transactions of the Royal Society of London — Series B: Biological Sciences* 353: 1929–33.
- Reider-Groswasser I, Costeff H, Sazbon L et al (1997) CT findings in persistent vegetative state following blunt traumatic brain injury. *Brain Injury* 12: 865–70.
- Relkin NR, Petito CK, Plum F (1990) Coma and the vegetative state associated with thalamic injury after cardiac arrest. *Annals of Neurology* 28: 221–22.
- Ricci R, Barbarella G, Musi P et al (1997) Localised proton MR spectroscopy of brain metabolism in vegetative patients. *Neuroradiology* 39: 313–19.
- Rothstein TL, Thomas EM, Sumi SML (1991) Predicting outcome in hypoxic-ischemic coma. A prospective clinical and electrophysiologic study. *Electroenceph Clin Neurophysiology* 79: 101–7.
- Royal College of Physicians of London (1996) The permanent vegetative state. Report by a working group convened by the Royal College of Physicians and endorsed by the Conference of Medical Royal Colleges and their faculties of the United Kingdom. *Journal of the Royal College of Physicians of London* 30: 119–21
- Royal College of Physicians of London (2003) *The Vegetative State. Guidance on Diagnosis and Management*. Royal College of Physicians of London.
- Rubin GL, Frommer MS, Vincent NC et al (2000) Getting new evidence into medicine. *Medical Journal of Australia* 172: 180–83.
- Rudolf J, Ghaemi M, Ghaemi M et al (1999) Cerebral glucose metabolism in acute and persistent vegetative state. *Journal of Neurosurgical Anesthesiology* 11: 17–24.
- Rudolf J, Sobesky J, Grond M et al (2000) Identification by positron emission tomography of neuronal loss in acute vegetative state. *Lancet* 355: 115–16.
- Sailly JC (1994) Economic aspects of the care of patients in the vegetative state. *Acta Neurologica Belgica* 94: 155–65.
- Sato et al (1989) *Neurol Med Chair (Tokyo)* 29: 389–94.
- Sazbon L & Groswasser Z (1990) Outcome in 134 patients with prolonged posttraumatic unawareness. Part 1: Parameters determining late recovery of consciousness. *Journal of Neurosurgery* 72: 75–80.
- Schiff ND, Ribary U, Morena DR et al (2002) Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain* 125(6): 1210–34.
- Shewmon DA & De Giorgio CM (1989) Early prognosis in anoxic coma. Reliability and rationale. *Neurologic Clinics* 7: 823–43.
- Shuttleworth E (1983) Recovery to social and economic independence from prolonged postanoxic vegetative state. *Neurology* 33: 372–74.
- Simpson DA, Blumbergs PC, Cooter RD et al (1989) Pontomedullary tears and other gross brainstem injuries after vehicular accidents. *Journal of Trauma-Injury Infection & Critical Care* 29: 1519–25.
- Smith R (1996) The importance of patients' consent for publication. *British Medical Journal* 313: 16–17.
- Steinbock B (1989) Recovery from persistent vegetative state? The case of Carrie Coons. *Hastings Center Report* 19: 14–15.
- Strich SJ (1956) Diffuse degeneration of the cerebral white matter in severe dementia following head injury. *Journal of Neurology, Neurosurgery & Psychiatry* 19: 163–85.

BIBLIOGRAPHY

- Strich SJ (1961) Shearing of nerve fibres as a cause of brain damage due to head injury. A pathological study of 20 cases. *Lancet* 2: 443–48.
- Teasdale G & Jennett B (1974) Assessment of coma and impaired consciousness. A practical scale. *Lancet* 2: 81–84.
- Thomasma DC & Brumlik J (1984) Ethical issues in the treatment of patients with a remitting vegetative state. *American Journal of Medicine* 77: 373–77.
- Todd Eachus H (2001) Generating responses in vegetative children. CSUM 2001 Conference Proceedings. www.csun.edu/cod/conf2001/proceedings/0277eachus.html.
- Todorow S (1975) Recovery of children after severe head injury. Psychoreactive superimpositions. *Scandinavian Journal of Rehabilitation Medicine* 7: 93–96.
- Tommasino C, Grana C, Lucignani G et al (1995) Regional cerebral metabolism of glucose in comatose and vegetative state patients. *Journal of Neurosurgical Anesthesiology* 7: 109–16.
- Tresch DD, Sims FH, Duthie EH et al (1991) Clinical characteristics of patients in the persistent vegetative state. *Archives of Internal Medicine* 151: 930–32.
- Tsubokawa T, Yamamoto T et al (1990) Deep brain stimulation in a persistent vegetative state: follow-up results and criteria for selection of candidates. *Brain Injury* 4: 315–27.
- Tumani H, Windl O, Kretschmer HA et al (2002) Clinically atypical CJD: diagnostic relevance of cerebrospinal fluid markers and molecular genetic analysis? *Deutsche Medizinische Wochenschrift* 127: 318–320.
- Wade DT & Johnston C (1999) The permanent vegetative state: practical guidance on diagnosis and management. *British Medical Journal* 319: 841–44.
- Walker AE (1985) *Cerebral Death*. 3rd ed. Urban & Schwarzenberg, Baltimore.
- Werring DJ, Clark CA, Barker GJ et al (1998) The structure and functional mechanisms of motor recovery and complementary use of diffusion tensor and functional magnetic resonance imaging in a traumatic injury of the internal capsule. *Journal of Neurology, Neurosurgery & Psychiatry* 65: 863–69.
- Whyte J & Glenn MB (1986) The care and rehabilitation of the patient in a persistent vegetative state. *Journal of Head Trauma Rehabilitation* 1(1): 39–53.
- Wilson SL & McMillan TM (1993) A review of the evidence for the effectiveness of sensory stimulation treatment for coma and vegetative states. *Neuropsychological Rehabilitation* 3: 149–60.
- Wood RL (1991) Critical analysis of the concept of sensory stimulation for patients in vegetative states. *Brain Injury* 5: 401–9.
- Wood RL, Winkowski TB et al (1992) Evaluating sensory regulation as a method to promote recovery in patients with altered states of consciousness: a pilot study. *Brain Injury* 6: 411–18.
- World Medical Association (1989) *World Medical Association Statement on Persistent Vegetative State*. Adopted by the 41st World Medical Assembly. http://www.wma.net/e/policy/17-v_e.html
- Yamamoto T, Katayama Y, Oshima H et al (2002) Deep brain stimulation therapy for a persistent vegetative state. *Acta Neurochirurgica Supplement* 79: 79–82.
- Young B, Blume W et al (1989) Brain death and the persistent vegetative state: similarities and contrasts. *Canadian Journal of Neurological Science* 16: 388–93.
- Zandbergen EG, de Haan RJ, Hijdra A (2001) Systematic review of prediction of poor outcome in anoxic ischaemic coma with biochemical markers of brain damage. *Intensive Care Medicine* 27: 1661–67.
- Zandbergen EG, de Haan RJ, Stoutenbeek CP et al (1998) Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. *Lancet* 352: 1808–12.
- Zasler ND (1996) Nomenclature: evolving trends. *Neuro Rehabilitation* 6: 3–8.

ADDITIONAL READING

- Adams RD & Victor M (2001) *Principles of Neurology*. McGraw Hill. 7th edition, Ch 17.

The National Health and Medical Research Council

The National Health and Medical Research Council (NHMRC) is a statutory body within the portfolio of the Commonwealth Minister for Health and Ageing, established by the *National Health and Medical Research Council Act 1992*. The NHMRC advises the Australian community and Commonwealth; State and Territory Governments on standards of individual and public health, and supports research to improve those standards.

The NHMRC advises the Commonwealth Government on the funding of medical and public health research and training in Australia and supports many of the medical advances made by Australians.

The NHMRC also develops guidelines and standards for the ethical conduct of health and medical research.

The Council comprises nominees of Commonwealth, State and Territory health authorities, professional and scientific colleges and associations, unions, universities, business, consumer groups, welfare organisations, conservation groups and the Aboriginal and Torres Strait Islander Commission.

The Council meets up to four times a year to consider and make decisions on reports prepared by committees and working parties following wide consultation on the issue under consideration.

A regular publishing program ensures that Council's recommendations are widely available to governments, the community, scientific, industrial and educational groups.

The Council publishes extensively in the following areas:

- Aged care
- Child health
- Clinical practice guidelines
- Communicable diseases
- Dentistry
- Diabetes
- Drugs and poisons
- Drug and substance abuse
- Environmental health
- Ethics - Animal
- Ethics - Human
- Health procedures
- Health promotion
- Infection control
- Men's health
- Mental health
- NHMRC - National Health and Medical Research Council
- Nutrition
- Public health
- Research
- Sport/Injury
- Women's health
- Workforce

A list of current publications is available from:

The Publications Officer
NHMRC
MDP 100
GPO Box 9848
Canberra ACT 2601

Phone: (02) 6289 9520 (24-hour answering machine)

Toll-free: 1800 020 103

Fax: (02) 6289 9197

E-mail: nhmrc.publications@nhmrc.gov.au

Internet: <http://www.nhmrc.gov.au>