THE NEUROPROTECTIVE EFFECTS OF REMACEMIDE HYDROCHLORIDE IN PATIENTS UNDERGOING ELECTIVE CORONARY ARTERY BYPASS SURGERY

by

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Abstract

Over the last forty years considerable evidence has been gathered in support of the hypothesis that amino acids are among the most important neurotransmitters within the central nervous system. The development of compounds that inhibit the actions of these recently described neurotransmitters led to the identification of several subtypes of amino acid receptor. Recognition of the neurotoxic effects mediated by excitatory amino acids (EAAs) has prompted investigation of the role of these naturally occurring substances in the processes that culminate in irreversible neuronal injury and death.

The observation that EAA receptor antagonists protect neurons from the toxic effects of hypoxia and potent EAA receptor agonists has stimulated interest in the potential therapeutic use of this new class of drug in neurodegenerative disorders. These include stroke, head injury, epilepsy, Parkinson's and Alzheimer's diseases, motoneurone disease, Huntington's Chorea and the neurological sequelae of the acquired immunodeficiency syndrome (AIDS).

Surgical procedures performed with the aid of cardiopulmonary bypass (CPB) represent a novel human model of diffuse neuronal injury. Advances in both technology and surgical technique have brought about a steady decline in the mortality and morbidity associated with such cardiac surgery. The fall in the incidence of major perioperative neurological sequelae (brain death, coma, stroke, seizures and altered conscious level) has paralleled that of other complications. Despite this apparent improvement in outcome, formal neuropsychological testing reveals that a significant proportion of patients sustain persistent deficits in cognitive function after otherwise successful surgery. Amongst the many factors implicated in the genesis of this phenomenon, the delivery of microemboli to the cerebral microcirculation during CPB, appears to be one of the most important.

This thesis reviews some of the historical landmarks in the evolution of coronary artery bypass surgery (CABS); discusses the neurological consequences of cardiac surgery and reviews the evidence for a role for amino acids in neurotransmission and neurotoxicity. The hypothesis that the incidence and severity of neuropsychological deficits after CPB can be reduced by Remacemide, a selective inhibitor of excitotoxic amino acids, is examined in a detailed study of patients undergoing CABS. Evidence for pharmacological neuroprotection is presented in this first reported use of an EAA antagonist in this clinical setting.
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Publications and presentations arising from this work


To my wife Sandra, my children; Sammy, Lulu and Beth

... and my (mostly) trusty computers ...

The ultimate arbiters of grammar and spelling.

Without whom nothing would have been possible - only sooner!
"Cardiac surgery has changed within living memory from desperate attempts to achieve miracles for a few to the present situation where there is high expectation of a good result for tens of thousands of patients each year. It is easy to recall the surgeons who performed the first heart operations, who used cardiopulmonary bypass while it was still in its infancy, or who started transplantation - all undertaken with a high initial mortality. They worked on doggedly, in the face of doubt, skepticism, and often widely publicised criticism. They are now remembered with respect as having had 'the courage to fail.' Many others, equally determined, did fail and are not remembered."

Prof. Tom Treasure

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Chapter 1

The Neurological Complications of Cardiac Surgery

"The brain is my second favourite organ"

Woody Allen
1.1. Introduction

Patient registries in both the UK and the USA show that, while the number of patients undergoing cardiac surgery for valvular, congenital and other types of heart disease has remained fairly constant, the number undergoing coronary revascularisation procedures is rising. [English, 1984] (Figures 1.1 and 1.2) Thanks to advances in many fields over the last four decades, there has been a steady fall in both the mortality and morbidity associated these procedures. Neurological injury now constitutes a leading cause of the residual postoperative morbidity [Mills, 1993] and is responsible for an increasing proportion of perioperative deaths. [Tuman, 1992; Gardner, 1985a] Advancing age and atherosclerosis makes the more than 800,000 patients a year that undergo cardiac surgical procedures worldwide particularly prone to neurological morbidity. [Roach, 1996] Since the introduction of cardiopulmonary bypass (CPB) in the early 1950s the neurological sequelae of cardiac surgery have been a fertile area of research with many hundreds of articles appearing in the medical literature. Wide variations in study design, an ever-changing surgical population and inevitable improvements in all aspects of medical care have produced markedly variable findings.

**Figure 1.1:** The Society of Cardiothoracic Surgeons (SCTS) Register 1977-1997. [Left] Summary of procedures carried out for ischaemic, valvular, congenital and miscellaneous acquired heart disease. [Right] Perioperative mortality. [Data from SCTS web site; http://www.scts.org/doc/2104]

**Figure 1.2:** The Society of Thoracic Surgeons (STS) Register 1987-1996. [Left] Summary of coronary artery bypass graft (CABG), valve and combined procedures. Data for 1996 is based on data collected during the first 6 months of 1996. [Right] Perioperative mortality following coronary artery bypass graft (CABG). [Data from STS web site; http://www.sts.org/outcomes/sts/ar97/ar97.html]

This chapter will first present some of the important historical milestones in the development of modern cardiac surgery; and secondly a review of research into the incidence, nature, aetiology and prevention of neurological injury associated with cardiac surgery.
1.2. Heart disease in history

For millennia the heart has been held in great reverence. The ancients believed that the heart was 'the seat of the soul, the emotions, and the spirit of life itself'. It was known over 6,000 years ago that the heart was essential to life and that its pumping action was responsible for pulsation in various parts of the body. References to the rapidly fatal effects of cardiac puncture wounds are to be found in the medical and military literature of the Romans, Greeks and Egyptians.

For centuries progress in medicine, as in all areas of science, has been subject to the close scrutiny of monarchs, politicians and religious leaders. All too often pioneers and their new ideas remained in obscurity for fear of ridicule, persecution or, worse, accusations of heresy or treason. Although much of the innovation in medicine is a product of the last one and a half centuries; religion, ignorance and prejudice, as will be demonstrated below, continue to play their part.

From early Christian times, and throughout the Middle Ages, for a period of over thirteen centuries, the ideas of the 2nd century Greek, Claudius Galen, physician to the gladiators in Pergamum, pervaded medicine and science without question. Galen believed that blood was formed in the liver from ingested food and that it ebbed and flowed through the interventricular septum. Little, if anything, new was learned about the heart during the time of Galen's influence. It was not until the Renaissance that meticulous dissections, documented by the early anatomists, provided the first insights into the true structure of the human body. Leonardo da Vinci was the first to accurately portray the human heart. In 1543, the Belgian Andreas Versalius, a graduate of Padua University and later its professor of surgery, published his De Humani Corporis Fabrica earning himself the title of the 'Father of Anatomy' - but not without a struggle. His critics, still faithful to the old authority of Galen, did not believe the evidence of their eyes. The condemnation of Versalius' work was such that he gave up scientific research, burned his notes, and became personal physician to the monarchs of Spain.

Nearly a century later, in 1628, four years before Rembrandt painted his celebrated Anatomy Lesson of Dr Nicolaas Tulp, the English physician William Harvey, in his De Motu Cordis, was the first to describe the circulation of blood. In doing so he laid the foundations of experimental physiology and finally put to rest many of the incorrect views still held by devotees of Galen.

It was suggested in 1648, by Jean Riolan, the Parisian professor of anatomy, that percutaneous drainage might be used to relieve cardiac tamponade caused by a large pericardial effusion. Riolan, however, did not dare to use this technique himself - progress in cardiac surgery remained static because of the widely held belief that the heart was surgically 'untouchable'.
Many prominent seventeenth century surgeons spoke out against any attempt to operate on the heart.

These prejudices prevailed and it was not until the early part of the nineteenth century that the Spaniard Francisco Romero reported the first use of Riolan's technique. Baron Dominique Jean Larrey, surgeon to Napoleon's elite Imperial Guard, performed a similar procedure in 1810. These appear to be the first known cardiac operations. Some authors regard the repair of a pericardial wounds by Georg Fisher, in 1868, and by Daniel Hale Williams, in 1891; and the repair of a myocardial stab wounds by Karl Victor Hall and Ansel Cappelen (unsuccessfully), in 1894, and by Ludwig Rehn (successfully), in 1896, as the true starting point of cardiac surgery.

It should be remembered that these early cardiac surgeons worked under impossible conditions. Anaesthesia and asepsis were in their infancy and there were no 'blood banks'. Patients were invariably in extremely poor physical condition due to massive haemorrhage. Filthy surgeons, using dirty instruments in dirty 'operating theatres', performed heroic surgery on conscious patients and bandaged them with dirty linen. Most patients died either from uncontrollable bleeding or post-operative infection. The medical student Charles Darwin, after witnessing two such operations in Edinburgh, changed his mind about becoming a doctor.

For reasons best known to themselves, the authors of many texts on the history of surgery pay little, if any, attention to the enormous contributions made by the early pioneers of antisepsis, anaesthesia, blood transfusion, physiology, chemistry, clinical pharmacology and microbiology. In the early 1840s, Crawford Long, and later Horace Wells, described the first clinical use of di-ethyl ether for surgical anaesthesia and in doing so gave birth to the new specialty of anaesthesia. Two decades later, following his observations of fermentation and putrefaction, Louis Pasteur described the role of germs in surgery and suggested an aseptic approach in the operating theatre. The institution of hand washing and the sterilization of surgical instruments by Ignatz Semmelweis practically eliminated puerperal sepsis from a Viennese obstetric ward. The intra-operative use of carbolic acid, promoted by Joseph Lister, became widely adopted. William Halsted introduced the use of rubber gloves to protect both the surgeon and the patient from contamination in 1898. The discovery of penicillin in 1929 earned Alexander Fleming both the Nobel Prize and a knighthood; and marked the beginning of the modern era of chemotherapy.

Despite these advances, the London surgeon Stephen Paget, in his book on thoracic surgery published in 1896, wrote that "Surgery of the heart has probably reached the limits set by Nature to all Surgery; no new method, no new discovery, can overcome the natural difficulties that attend a wound of the heart". Theodor Billroth, the eminent Viennese surgeon, is re-
ported to have said that anyone who attached importance to surgery of the heart deserved the scorn of his colleagues.

Before the end of the nineteenth century, when infant mortality was high and life expectancy short, accidents and infectious diseases (e.g. tuberculosis) were the most importance causes of chronic illness and death. Major congenital cardiac disease was invariably fatal in infancy, and the average adult simply did not live long enough to develop coronary artery disease.

Descriptive accounts of the symptoms, pathology and management of cardiac disease in pre-twentieth century medical literature are few and far between. In 1759, the British physician William Heberden accurately described the 'breast pain' - *angina pectoris* - experienced by his patients with ischaemic heart disease. Despite his insights and observations, Heberden was unaware of the cause of angina.

Around the middle of the nineteenth century, the Viennese pathologist Karl von Rokitansky described thickening of the walls of the coronary arteries. He correctly concluded that the deposits of fat, calcium, and fibrin that he found were derived from the bloodstream - in much the same way that mineral deposits accumulate in water pipes. It is noteworthy that Rokitansky himself died as a result of ischaemic heart disease (IHD) - his terminal illness, proceeded by angina pectoris and heart failure, was diagnosed neither by himself nor his physician.

In 1912, the Chicago surgeon James Herrick, reported the effects of acute occlusion of a coronary artery by a blood clot. His was the first precise clinical account of a heart attack. Despite the publication of Herrick's article, ignorance persisted. Textbooks on cardiology prior to the 1940's paid little if any attention to the aetiology, investigation and management of acute and chronic myocardial ischaemia.

In the years that followed the Second World War, the 'heart attack' came to be regarded by many as a form of divine judgment, which was being imposed with increasing frequency. It could strike anyone, especially men, without warning and often with fatal consequences. This new, inexplicable and seemingly untreatable disease even threatened young men. Veterans of the Korean War showed signs of atherosclerosis in their early twenties. Both Lyndon Johnson and Dwight Eisenhower suffered heart attacks in their mid fifties - no one, it seemed, was immune.

It was not long before the epidemiological experience gained in the study of tuberculosis was applied to the investigation of IHD. Although research has still yet to define the precise cause of the condition, the identification of strongly associated 'risk-factors', such as smoking, arterial hypertension, diabetes mellitus, and some hyperlipidaemias has lead, albeit gradually, to an increase in health awareness. The initial period of guilt has given way to an epidemic of atonement: the pursuit of health through diet, jogging, exercise, and abstinence. In
some parts of the world this has had some success in reducing the incidence of IHD. [Schumacher, 1992; Dunning, 1993]

1.3. Modern cardiac surgery

Modern cardiac surgery owes a great debt to a small group of gifted and tenacious individuals who had the courage to fail. Even in the modern era, prejudice and the fear of change continue to challenge advancement. Today's 'heresies' are principally ethical and moral - gene therapy, the clinical use of human fetal tissue and the development of transgenic species as a source of organs for transplantation.

Unfortunately, for the student of its history, the development of modern cardiac surgery did not occur in isolation from the other branches of surgery or, for that matter, from any other branch of medicine. It is impractical and, arguably, impossible to present a short, chronological review of the subject within the space permitted. For this reason, the most important milestones are summarised below;

The non-surgical advances that occurred at the turn of this century paved the way for the development of cardiac surgery. These early breakthroughs included the discovery X-rays by Roentgen in 1895, the description of ABO blood groups by Landsteiner in 1904, the use of endotracheal anaesthesia by Meltzer and Auer in 1911, the description of electrocardiographic patterns in heart disease by Einthoven in 1913 and by Wilson in 1930, and the discovery of heparin by McLean in 1916.

In 1929, the same year that Mark Lidwill invented the external cardiac pacemaker, Forsmann performed the first catheterisation of a human (his own!) heart and after telling his mentor, Ernst Ferdinand Sauerbruch, was fired. The use of X-ray contrast media to demonstrate the chambers of the heart and the great vessels (angiocardiography) was described by Robb and Steinberg in the mid 1930s. The accidental injection of contrast into a coronary artery during aortography by Mason Sones at the Cleveland Clinic in 1962 was the first description of a technique (coronary ciné-angiography) that is in widespread use today. The ability to visualise the coronary arterial tree in 'real time' gave surgeons precise information about the distribution and severity of coronary artery disease.

Soon after publication of reports of the surgical repair of pericardial and myocardial stab wounds, other 'closed heart' procedures were attempted. Théodore Tuffier reported performing a closed aortic valvotomy in 1912. The following year, Rehn and Sauerbruch reported pericardiectomy for the treatment of constrictive pericarditis. In 1925, a year after Friedrich Trendelenberg attempted the first pulmonary embolectomy, Henry Souttar's reported closed digital mitral valvotomy. When asked why he never again performed the procedure, Souttar said that his cynical and disapproving colleagues refused to refer him any more suitable pa-
tients. In 1931, Sauerbruch performed the first successful resection of a left ventricular aneu-
rysm. In 1938, Robert Gross and John Hubbard reported ligatation of a patent ductus arteriosus.
During the 1940s, Clarence Crafoord reported that the descending aorta could be safely Ross-
clamped for periods up to 2 hours and described the repair of aortic coarctation, Alfred Blal-
ock and Helen Taussig developed their systemic-pulmonary shunting procedure for the pal-
liation of Fallot’s tetralogy, and McQuiston began to use hypothermia during paediatric card-
diac procedures. In London, Russell Brock and Thomas Holmes Sellors performed the first
pulmonary valvotomies, and Souttar’s mitral commissurotomy was ‘rediscovered’ by Dwight
Harken and Brock.

The concept that the circulation might be taken over for short periods of time dates back to Le
Gallois in 1812. As far back as 1885 Von Frey and Gruber described an experimental extracor-
poreal blood oxygenating apparatus. In the early 1930s, after watching a young woman die
from massive pulmonary embolism, John Gibbon aided by his wife Mary Hopkins began ex-
periments with pump oxygenators. By the end of the War, the Gibbons had successfully used
 cardiopulmonary bypass in cats. On May 6th 1953, John Gibbon successfully closed an atrial
septal defect using a pump and screen-type oxygenator. In 1952, while other units were devel-
oping their own heart-lung machines, C. Walton Lilliehe was using an ingenious ‘cross-
circulation’ technique first described in animals by Charles Guthrie in 1908. Arterial and ve-
nous connections were made between the patient (usually a child) and a ‘donor’ (usually the
father) so that the donor’s lungs were used as the oxygenator. Although complex procedures
could be performed using this technique, it was quickly superceded by hypothermic cardio-
pulmonary bypass. Over the years the cardiopulmonary bypass machine has undergone con-
tinuous development so that today’s systems are efficient ‘off the shelf’ mass-produced, dis-
posable, all-in-one plastic units that can be assembled in a few tens of minutes.

Suggested by Charles François-Franck in 1899, and used clinically in the 1920s by Thomas Jon-
nesco, the first surgical approach to the treatment of coronary artery disease was cervical
sympathectomy. Chemical sclerosis of the cervical sympathetic plexus was developed in the
late 1930s by Mercier Fauteux. These deafferentation procedures were abandoned when it was
realised that complete denervation of the heart required bilateral ablation or removal of the
entire stellate ganglion and the first four thoracic ganglia. The observation that angina was
worse in patients with thyrotoxicosis lead Herman Blumgart to begin using thyroidectomy,
and later radioiodine ablation, as a treatment in the early 1930s. Although the procedure did
produce relief of angina it was not widely adopted.

At about the same time Claude Beck began a series of laboratory and clinical myocardial re-
vascularisation studies that spanned more than three decades. Beck employed a number of
methods (pericardial ‘talc’ or ‘asbestos’ poudrage, attachment of pectoral muscle flaps to
abraded epicardium, and omental-pericardial grafts) to produce anastamotic vascular adhe-
sions between the pericardium and the epicardium - 'cardiopericardiopexy'. Similar tech-
niques were developed simultaneously by Laurence O'Shaughnessy and William Rienhoff. 
By the mid 1940s Mercier Fauteux and Orvar Svenson began using coronary sinus ligation 
and pericoronary neurectomy to treat patients, with some limited success. By 1948 Beck had all 
but abandoned his early experiments and began using an autologous arterial graft between the 
aorta and the coronary sinus. The so-called Beck II procedure was complex and did not become 
widespread. In 1950, Arthur Vineberg began clinical use of a technique that enjoyed a remark-
able period of success. The 'Vineberg' operation was based on the assumption that an 
internal mammary artery implanted in a myocardial tunnel would sprout vessels that would 
make anastomotic connections with branches of the coronary arteries. Although these indi-
rect revascularisation techniques were abandoned after the introduction of coronary artery 
bypass it is curious to note that development as come 'full circle' with the introduction of 
transmyocardial laser revascularisation.

The technique for intima to intima anastomosis of blood vessels, using interrupted, everting 
mattress sutures, was introduced in 1896 by Jaboulay. In a series of reports published between 
1902 and 1912, Alexis Carrel described many refinements of these techniques. Many of the 
vascular and cardiac procedures he described are still in use today. Carrel's attempt to fash-
on an anastomosis between the aorta and a coronary artery using autologous carotid artery is 
the first recorded coronary artery bypass. In the early 1950s, Gordon Murray, using Carrel's 
techniques, began replacing segments of diseased coronary artery with interposition grafts. 
William Mustard's attempt at the first carotid-coronary anastomosis in 1953 ended in failure. 
Coronary endarterectomy without cardiopulmonary bypass was first used by Charles Bailey 
in 1956 and later by improved by William Longmire. At a meeting held in the early 1970s, 
Michael DeBakey reported that, in 1964, he had probably performed the first aorto-coronary 
graft using a segment of autologous saphenous vein. Towards the end of the 1960s, as the use of 
cardiopulmonary bypass and coronary angiography became more widespread, coronary artery 
bypass surgery with autologous saphenous vein was popularised by Rene Favaloro, and Dud-
ley Johnson. In 1967, Christian Barnard performed the first human heart transplant. Two 
years later Denton Cooley performed the first heart and lung transplant. [Schumacker, 1992; 
Brewer, 1981]

1.4. The current status of coronary artery bypass surgery

Since the late 1960s CABS has become an established method for treating CAD. During that 
time, a number of studies have compared outcome after CABS with outcome from conventional 
medical therapy. In specific subgroups of patients, particularly those with multivessel coro-
nary artery disease (CAD), left main stem CAD and impaired left ventricular function, surgi-
cal intervention results in longer survival and a better quality of life. [Chaitman, 1981; Mock, 1982; Killip, 1985; Chaitman, 1990; Emond, 1994]

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977, an increasing number of patients with multivessel CAD have undergone this procedure and avoided surgery. Recent developments in the field of interventional cardiology include plaque removal with rotational atherectomy and intraluminal coronary stenting. A number of large studies have attempted to compare the efficacy of PTCA to that of CABS. [Anonymous, 1990] To determine whether PTCA, as opposed to CABS, did not significantly compromise long-term survival the National Heart, Lung, and Blood Institute initiated a randomised study in 18 North American centres. The Bypass Angioplasty Revascularization Investigation (BARI), which studied 1829 patients, reported that 5 year survival after an initial strategy of PTCA was no different to that following CABS (86.3% versus 89.3%, p=0.19) although subsequent revascularisation was required more often (54% versus 8%). In a post hoc subgroup analysis of the 353 treated diabetic patients enrolled in the study, however, 5 year survival was significantly better following CABS (80.6% versus 65.5%, p=0.003). [BARI Investigators, 1996; 1997]

The implication of this investigation is that younger, non-diabetic patients with isolated proximal CAD and preserved left ventricular function are more likely to undergo PTCA and that patients undergoing CABS will be more likely to have risk factors for major complications and death.

1.5. Neurological injury following cardiac surgery

Advances in numerous fields, particularly in the area of critical care, and the introduction of more marginal indications for surgery has meant that patients previously thought inoperable a few years ago are now considered suitable for surgery. Over the past 20 years there has been a steady increase in the average age of patients undergoing cardiac surgery. Patients have more severe and disabling cardiac disease, and the incidence of re-operation, for recurrent disease, is rising. [Naunheim, 1988; Jones, 1991] In addition to these demographic pressures, increasingly stringent financial restraints and political constraints have reduced the amount of time that patients spend in hospital both before and after surgery. Nevertheless the likelihood of dying or sustaining a major complication after cardiac surgery in the late 1990s is significantly lower than in the 1950s. (see below) Not unreasonably, most patients expect to survive cardiac surgery intact, make a good functional recovery and, hopefully, live longer. Sadly a small, but not insignificant, number of patients undergoing modern cardiac surgery with CPB will suffer a major perioperative complication effecting one or more organ systems. Within each of these complications there is a spectrum of severity and, therefore, outcome-ranging from mild disability to death.
1.5.1. The Spectrum of neurological injury

Adverse neurological outcome from cardiac surgery covers a broad spectrum ranging from fatal brain injury (a 'cerebral catastrophe') to subtle changes in personality, behaviour and cognitive function. From the evidence presented later in this chapter it can be deduced that it is inevitable that most, if not all, patients will suffer some sort of cerebral injury during cardiac surgery and that outcome is related to the anatomical site(s) and severity of that injury. A major neurological complication following otherwise successful surgery is devastating for both the patient and his or her immediate family. The social and economic impact of unemployment and the requirement for long term domiciliary or institutional care may be enormous.

The prospective study of 312 patients conducted by Shaw [Shaw, 1985] in Newcastle upon Tyne provides a useful classification of the spectrum of the neurological sequelae of cardiac surgery as well as an indication of the incidence. (Table 1.1)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal brain injury</td>
<td>0.3%</td>
</tr>
<tr>
<td>Non fatal diffuse encephalopathy</td>
<td>Depressed conscious level</td>
</tr>
<tr>
<td></td>
<td>Behavioural changes</td>
</tr>
<tr>
<td></td>
<td>Intellectual dysfunction</td>
</tr>
<tr>
<td>Seizures</td>
<td>0.3%</td>
</tr>
<tr>
<td>Ophthalmological</td>
<td>Visually field defects</td>
</tr>
<tr>
<td></td>
<td>Reduced visual acuity</td>
</tr>
<tr>
<td>Stroke</td>
<td>5%</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>0%</td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td>39%</td>
</tr>
<tr>
<td>Peripheral nerve injury</td>
<td>Brachial plexopathy</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
</tbody>
</table>

Table 1.1: Types and incidence of neurological injury following cardiac surgery. From the Newcastle study reported by Shaw, 1985.

Major neurological complications are, fortunately, rare. Peripheral nerve injury, ophthalmological complications and cognitive dysfunction are, however, remarkably common. Fatal brain injury, manifested by failure to regain consciousness, is invariably the result of prolonged and/or profound cerebral hypoperfusion, macroembolism or some other intracranial catastrophe. Non fatal diffuse encephalopathy may manifest itself as depression of conscious level, intellectual dysfunction and behavioural changes ranging from frank psychosis to mild confusion. Seizures may occur in isolation or with other signs of neurological injury (e.g. stroke). Both early and late onset epilepsy have been described. Ophthalmological complications, such as a visual field defect and/or a deterioration in acuity, are remarkably common and are consistent with retinal ischaemia. Other reported injuries, not specifically mentioned in Shaw’s study, include hearing loss, tinnitus, and pituitary apoplexy. Details of this study are discussed later.
1.5.2. Measures of neurological outcome following cardiac surgery

As with most things in medicine, measuring neurological outcome in cardiac surgery has become increasingly complex and controversial. The adage "you can only find what you look for" is as true today as it was 50 years ago. The early retrospective studies could only detect what they set out to look for - neurological and psychiatric problems (e.g. coma, hemiparesis, seizures, blindness) that were sufficiently obvious to be noticed and recorded in the patient's chart. The real incidence of stroke following cardiac surgery is around 3-5%. (Table 1.2)

<table>
<thead>
<tr>
<th>Study design</th>
<th>References</th>
<th>Incidence</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>Bojar, 1983</td>
<td>32/3206</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Coffey, 1983</td>
<td>13/1669</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Gardner, 1985a</td>
<td>56/3279</td>
<td>1.7</td>
</tr>
<tr>
<td>Prospective</td>
<td>Tumispeed, 1980</td>
<td>8/170</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Breuer, 1983</td>
<td>21/400</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Shaw, 1985</td>
<td>15/320</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>Roach, 1996</td>
<td>66/2108</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Table 1.2: The incidence of focal neurological injury following coronary artery bypass surgery.

The introduction of cognitive or intellectual function testing broadened the scope and power of investigations. Prospective studies, such as the Newcastle study, not only demonstrate the value of a multimodal (i.e. neurological and cognitive) approach but highlighted the need for investigators to have the appropriate training and background. To date a wide variety of 'instruments' have been used by investigators in the study of adverse neurological outcomes after cardiac surgery. (Table 1.3)
<table>
<thead>
<tr>
<th>Pathological</th>
<th>Gross and microscopic postmortem examination [Björk, 1960; Brierley, 1963]</th>
</tr>
</thead>
</table>
| Clinical    | Retrospective chart review for mortality and gross neurological, psychiatric, cognitive complications [Ehrenhaft, 1961a; 1961b]  
Prospective neurological & psychiatric examination, Neuropsychological / cognitive function testing. Anxiety and Depression inventories [Shaw, 1985; Roach, 1996]  
Subjective (patient ± spouse) reports of cognitive function [Newman, 1989a] |
| Financial   | Duration of intensive care, Length of hospital stay, Patient charges [Roach, 1996] |
| Social      | Activities of daily living [Bunzel, 1989], Return to work [Westaby, 1979], Resumption of sexual activity |
Carotid [Stump, 1996] and transcranial Doppler [Padayachee, 1988; Pugsley, 1994] quantification of microemboli |
| Brain imaging | Brain computed tomography (CT), magnetic resonance imaging and spectroscopy [Harris, 1993; 1998], Positron emission tomography (PET) |
| Electrophysiological | Electroencephalography (EEG), Processed EEG (Cerebral Function Analysing Monitor - CFAM) [Prior, 1989; Nevin, 1989], Somatosensory evoked potentials (SSEPs) [Zeithofer, 1993] |
Blood glucose, Arterial pH and blood gases [Venn, 1995; Jonas, 1996] |
| Others      | Cerebral near infra-red spectroscopy (NIRS) [Brown, 1993]  
Jugular bulb oxygen saturation [Croughwell, 1994; 1995]  
Retinal fluorescein angiography [Blauth, 1986]  
Regional cerebral blood flow (rCBF) [Greeley, 1989; Venn, 1989; Rogers, 1992] |

Table 1.3: Perioperative methods used in the assessment of neurological outcome from cardiac surgery.

The low incidence of perioperative stroke dictates that investigators seeking to identify risk factors or measure the efficacy of interventions will require large study populations in order to be adequately powered to identify differences. When the background incidence of a complication is low (i.e. 5%) and the impact of an intervention is small (e.g. a 10-20% reduction in the complication rate) a large study sample will be required to reach statistically valid conclusions. (Table 1.4) On the other hand, neuropsychological dysfunction, which has an incidence at least one order of magnitude greater than stroke, offers the potential advantage of investigation with a smaller, more manageable sample size. Using neuropsychological testing as a measure of outcome, however, does have a number of problems.

<table>
<thead>
<tr>
<th>Base Rate (Outcome without treatment)</th>
<th>New Rate (Outcome after intervention)</th>
<th>Power = 80%</th>
<th>Power = 70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0%</td>
<td>5.0%</td>
<td>474</td>
<td>381</td>
</tr>
<tr>
<td>5.0%</td>
<td>2.5%</td>
<td>984</td>
<td>791</td>
</tr>
<tr>
<td>3.0%</td>
<td>1.5%</td>
<td>1664</td>
<td>1336</td>
</tr>
<tr>
<td>2.0%</td>
<td>1.0%</td>
<td>2517</td>
<td>2019</td>
</tr>
<tr>
<td>1.0%</td>
<td>0.5%</td>
<td>5066</td>
<td>4065</td>
</tr>
</tbody>
</table>

Table 1.4: The effect of base rate (background) incidence of stroke on the sample size per group required to show a 50% reduction in perioperative stroke rate. (Assumes two-sided α error of 0.05)
1.5.3. Problems with neuropsychological outcome measures

Neuropsychology is the applied science of behavioural expression of brain dysfunction. Neuropsychological testing typically includes measures of memory, attention, visuospatial or visuoconstructional ability, and motor and psychomotor speed. [Borowicz, 1996]

In recent years, more and more groups, including the Middlesex Hospital group, have used changes in neuropsychological test performance as a measure of both outcome and the success of interventions. A number of problems associated with perioperative neuropsychological testing continue to challenge the research community. Neuropsychological outcome may not correlate with the clinical outcome perceived by the patient and there is no definition of cognitive decline that has a reproducible clinical correlate. As yet, there is no ‘gold standard’ against which to compare new tests, and there is no agreement on which tests or groups of tests should be used, and the optimal time(s) for administration. [Stump, 1995] There is broad agreement that using a large number of tests is preferable to using only a few. The incidence of cognitive decline is reported to be higher in studies in which a large numbers of tests were used than in those where only a few tests were used. Using a larger number of tests, however, increases both the administration time and the likelihood that some patients will not be able to complete all tests. [Borowicz, 1996] The number of tests used and their timing, in relation to surgery will effect measured outcome. (Table 1.5) In addition, as might be expected, the incidence of both early and late postoperative cognitive dysfunction has fallen over the past 15 years.

There is no universally accepted method of analysing neuropsychological test results and therefore no standard for defining the incidence and severity of cognitive decline based on changes in test performance. [Blumenthal, 1995; Mahanna, 1996] A statistically significant cognitive decline in one patient may have little or no impact on activities of daily living, whereas a seemingly trivial decline in another may have an enormous impact. By focusing solely on a decline in cognitive function, most investigators have ignored the fact that, with repeated testing, normal volunteers tend to show an improvement in performance - a phenomenon known as the practice effect. [Newman, 1995a] Cognitive impairment should perhaps more properly be defined as decline as well as failure to improve. [Grieco, 1996; McKhann, 1997a]

The use of categorical or single-case definitions of cognitive dysfunction are strongly influenced by the phenomenon of regression toward the mean. [Browne, 1999] Extreme baseline test scores tend to become less extreme after repeated examination, even though a ‘true’ change in cognitive function has occurred. For this reason it has been suggested that group mean analysis with controls is potentially the most reliable method for detecting real changes in cognitive performance. [Browne, 1999]
If an age matched control group is not used in late follow-up studies it may be impossible to distinguish persisting neurological problems that developed in the perioperative period from the effects of normal aging processes, dementia or frank depression.

<table>
<thead>
<tr>
<th>References</th>
<th>Subjects</th>
<th># tests</th>
<th>Timing</th>
<th>Deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethune, 1982</td>
<td>8 CABS</td>
<td>1</td>
<td>8 days</td>
<td>12.5%</td>
</tr>
<tr>
<td></td>
<td>30 Valve</td>
<td>1</td>
<td>6 days</td>
<td>90%</td>
</tr>
<tr>
<td>Savageau, 1982a; 1982b</td>
<td>172 CABS</td>
<td>3</td>
<td>9 days</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>29 Valve</td>
<td>3</td>
<td>9 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 Mixed</td>
<td>3</td>
<td>9 days</td>
<td></td>
</tr>
<tr>
<td>Garvey, 1983</td>
<td>387 CABS</td>
<td>1</td>
<td>7 days</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>7 Valve</td>
<td>1</td>
<td>7 days</td>
<td></td>
</tr>
<tr>
<td>Shaw, 1987a</td>
<td>298 CABS</td>
<td>10</td>
<td>7 days</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>50 Vascular</td>
<td>10</td>
<td>7 days</td>
<td></td>
</tr>
<tr>
<td>Nevin, 1987</td>
<td>65 CABS</td>
<td>10</td>
<td>7 days</td>
<td>20%</td>
</tr>
<tr>
<td>Newman, 1987</td>
<td>67 CABS</td>
<td>10</td>
<td>8 days</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>31 Other</td>
<td>10</td>
<td>8 days</td>
<td>50%</td>
</tr>
<tr>
<td>Hammeke, 1988</td>
<td>46 CABS</td>
<td>12</td>
<td>10 days</td>
<td>54%</td>
</tr>
<tr>
<td>Pugsley, 1994</td>
<td>100 CABS</td>
<td>10</td>
<td>8 days</td>
<td>46-71%</td>
</tr>
<tr>
<td>Sotaniemi, 1981</td>
<td>49 Valve</td>
<td>7</td>
<td>2 months</td>
<td>27%</td>
</tr>
<tr>
<td>Newman, 1987</td>
<td>67 CABS</td>
<td>10</td>
<td>2 months</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td>31 Other</td>
<td>10</td>
<td>2 months</td>
<td>46%</td>
</tr>
<tr>
<td>Mattlar, 1988</td>
<td>64 CABS</td>
<td>7</td>
<td>2 months</td>
<td>0%</td>
</tr>
<tr>
<td>Savageau, 1982a; 1982b</td>
<td>245 Mixed</td>
<td>3</td>
<td>6 months</td>
<td>19%</td>
</tr>
<tr>
<td>Shaw, 1987b</td>
<td>259 CABS</td>
<td>10</td>
<td>6 months</td>
<td>22%</td>
</tr>
<tr>
<td>Venn, 1988</td>
<td>66 CABS</td>
<td>10</td>
<td>12 months</td>
<td>35%</td>
</tr>
<tr>
<td>Pugsley, 1994</td>
<td>100 CABS</td>
<td>10</td>
<td>8 months</td>
<td>8-27%</td>
</tr>
<tr>
<td>Murkin, 1995a</td>
<td>316 CPB</td>
<td>2 months</td>
<td>27-44%</td>
<td></td>
</tr>
<tr>
<td>Venn, 1995</td>
<td>70 CABS</td>
<td>2 months</td>
<td>20-49%</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.5: The incidence of neuropsychological deterioration after cardiac and non-cardiac surgery. Relation between patient group, and the timing and number of neuropsychological tests used.

Many confounding factors have made it difficult to make direct comparisons between studies that have employed differing methodologies. [Mahanna, 1996] Some investigators have attempted to rationalise neuropsychological assessments by choosing tests that either span a number of so-called ‘cognitive domains’ (thought to represent a spectrum of cortical and subcortical cerebral function) or that are believed to be specific for certain anatomical regions of the cerebral cortex. (Figure 1.3) Although a gross oversimplification, this method does allow the analysis of patterns of change in cognitive function.

Figure 1.3: Stylised representation of the anatomical basis of cognitive domains (After McKhann, 1999).
Within the last few years key members of the research community have sought to reach a consensus on the selection of core neuropsychological tests, procedures for test administration and the analysis of test scores. [Murkin, 1995b; 1997]

1.5.4. Markers of neuronal injury

Following cerebral hypoxia/ischaemia, numerous substances have been shown to be released from neurons, glia, endothelium, platelets, and leucocytes. (Table 1.6) As markers of cerebral injury, these substances offer the potential for rapid diagnosis and early intervention. Furthermore, if the degree of elaboration of a biochemical marker can be shown to correlate with clinical (neurological and cognitive) outcome, large intervention studies could be designed that do not rely on costly and time consuming neurological and neuropsychological testing.

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>MARKER(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glia</td>
<td>S100B, Myelin Basic Protein (MBP), Gial Fibrillary Acidic Protein (GFAP)</td>
</tr>
<tr>
<td>Neurons</td>
<td>Neuron Specific Enolase (NSE), Adenylate Kinase (AK), Creatine Phosphokinase brain isoform (CPK-BB), Guanine Nucleotide Binding Protein G0, Calbindin-D, Lactate Dehydrogenase (LDH), Glutamate</td>
</tr>
<tr>
<td>Inflammatory Cells</td>
<td>Interleukin-6, Transforming Growth Factor-β, Adhesion molecules (ICAM-1, E-selectin, Neural Cell Adhesion Molecule - NCAM)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Lactate, Cu-Zn Superoxide Dismutase (CuZn-SOD)</td>
</tr>
</tbody>
</table>

Table 1.6: Potential markers of brain injury. (by courtesy of Dr H.P.Grocott)

Although a marker of neuronal injury may provide an indication of the severity of a cerebral injury it cannot provide information about the anatomical distribution and clinical impact of that injury. A small infarct in the internal capsule may be associated with only a modest release of a marker substance and minimal cognitive decline yet cause disabling hemiplegia. Conversely, a considerably larger infarct in a frontal lobe, accompanied by a massive release of a marker, may produce few symptoms or physical signs.

In 1980, Taylor and colleagues evaluated cerebrospinal fluid (CSF) brain-specific creatine phosphokinase (CPK-BB) as a marker of neurological injury in a canine model of CPB. [Taylor, 1980] After 60 minutes of bypass with a bubble oxygenater there was a marked increase in CSF CPK-BB that persisted for 24 hours despite full clinical recovery. In a parallel study, the incorporation of a 40μm screen filter into the arterial line resulted in significantly lower CSF CPK-BB levels compared to those in unfiltered animals.

One of the earliest clinical reports of a biochemical marker of cerebral injury in cardiac surgery was that of Åberg and colleagues reported in 1982. [Åberg, 1982] Postoperative levels of CSF adenylate kinase (CSF-AK) were found to be elevated in 33/36 patients who had undergone open-heart surgery and 0/8 patient who had undergone pulmonary surgery without CPB. In 18 patients who had lumbar punctures both before and after cardiac surgery there was sig-
significant increase in CSF-AK. The authors suggested that the changes in CSF-AK levels in these patients were significantly associated with deteriorations in intellectual function, yet repeat analyses did not confirm this. [Wallemark, 1982; Treasure, 1982] In a larger study, published by the same group two years later, 87/94 patients had CSF-AK measured 24 hours after surgery. [Åberg, 1984] There was a statistically significant correlation between CSF-AK and performance in three psychometric tests. Interestingly there was no correlation between CSF-AK and duration of CPB.

In the Cleveland Clinic study reported by Breuer and colleagues, circulating levels CPK-BB were assessed as a measure of neurological injury. [Breuer, 1983] Although 98% of the 421 CABS patients studied had elevated levels of CPK-BB there was no correlation with the occurrence of encephalopathy or stroke.

Found in glial and Schwann cells, the S100β protein has numerous functions including promotion of axonal growth, glial proliferation, neuronal differentiation, and calcium homeostasis. Elevated levels of the protein in both blood and CSF have been found following acute stroke, transient ischaemic attacks, head injury, intracranial haemorrhage, post cardiac arrest coma, as well as Alzheimer's disease and Down's syndrome. In acute stroke the degree of S100β elevation correlates well with infarct volume and neurological outcome.

Several reports have shown elevation of S100β after cardiac surgery. Westaby and colleagues found a relationship between S100β levels and age, aortic cross-clamp time and duration of bypass. Patients with carotid artery stenosis had higher levels of S100β than those that did not and patients who had CABS without CPB showed no elevation in S100β. [Westaby, 1996]

Recently the Duke group has shown that there is a relationship between peak postoperative levels of S100β and intraoperative cerebral microemboli quantified with transcranial Doppler sonography. [Croughwell, 1997; Grocott, 1998]

The Oxford group have shown that, compared to controls, the use of an arterial line filter decreased the number of patients who had abnormal elevations in S100β after surgery. [Taggart, 1997a] The same group has also shown that intracardiac surgery (e.g. mitral or aortic valve procedures) is associated with a greater postoperative rise in S100β than CABS. [Taggart, 1997b]

The recent discovery that S100β is present in mediastinal tissue and that the use of cardiectomy suction is associated with elevations in serum S100β after cardiac surgery [Anderson, 2000] suggests that S100β may not, after all, be a reliable marker of cerebral injury. [Kuzumi, 2000; Grocott, 2001]

These methodological difficulties and the lack of a consistent correlation between biochemical marker release and neuropsychological outcome make it unlikely, therefore, that these substances will every replace clinical outcome measures.
1.6. The incidence and nature of neurological injury

It is, perhaps, ironic that the first reported coronary artery bypass resulted in a fatal neurological complication. [Carrel, 1902] Alexis Carrel's attempt to make an anastamosis between the ascending aorta and a coronary artery took longer than anticipated and the unfortunate subject of his study (a dog) died from cerebral ischaemia.

During the first half of the 20th century most cardiac operations were performed on the beating heart. Using venous inflow occlusion, surgeons were able to facilitate surgery by producing brief interruptions in the circulation by obstructing venous return to the heart. In 1925, Sir Henry Souttar reported the first successful closed mitral valvotomy. [Souttar, 1925] In the discussion section of his account Souttar clearly shows that he was aware that intraoperative hypoperfusion, resulting from both haemorrhage and inflow occlusion, placed the brain in extreme peril.

Of the investigations in this field carried out in the last fifty years the majority of objective data comes from the last 25 years. Early studies tended to be small and retrospective; focusing on clinical manifestations in survivors and neuropathological findings in non-survivors. These early investigators quickly recognised the importance of perioperative hypotension and cerebral embolism. In the late 1960s and early 1970s, as both mortality and the incidence of major neurological complications fell, larger retrospective studies began to appear in the literature. In addition to cerebral hypoperfusion and embolism, it became apparent that neurological complications were related to increasing patient age and duration of CPB. From the mid 1970s to the late 1980s, the focus of a large number of prospective investigations moved away from the stroke and coma (which were becoming increasingly uncommon) and focused, instead, on subtle neurological, psychological, cognitive and behavioural outcomes in survivors and sought to identify and quantify risk factors for these types of neurological injury. The last decade has been characterised by a search for objective biochemical markers of cerebral injury, risk stratification and intervention (neuroprotection) studies in which investigators have attempted to examine the influence of new drugs, equipment and techniques specifically designed to reduce the impact of these risk factors.

1.6.1. 1950-1980: We have a problem!

In 1954, the same year that John Gibbon published his account [Gibbon, 1939; 1954] of the first successful clinical use of CPB, a report appeared describing neurological and psychological dysfunction in a group of 32 patients following mitral valve surgery. [Fox, 1954] By the end of the 1950s other reports of postoperative impairment of neurological and psychological function in cardiac surgical patients began to appear in the literature. [Priest, 1957; Zaks, 1959; Torres, 1959; Rubinstein, 1959; Cohen, 1964] It was suggested that these findings were the
manifestation of pathological processes associated with cardiac disease and surgery. Evidence supporting this notion was soon provided by Björk who reported microscopic brain changes in ten of eleven children with congenital heart defects who died following cardiac surgery performed with deep hypothermia. [Björk, 1960] The findings included swelling, diffuse neuronal loss, gliosis, focal necrosis and evidence of macroembolisation variably distributed throughout the substance of the brain. These diffuse brain changes were divided into two groups based on their appearance and anatomical distribution. Changes localised to the cortex, hippocampus, cerebellum and thalamus were ascribed to diminished blood flow whilst those found predominantly in the globus pallidus were ascribed to ‘hypoxaemic hypoxia’. The authors speculated on the role of platelet and/or leucocyte aggregation in those cases where focal ischaemic lesions were found.

A retrospective analysis of 60 fatalities occurring in 250 patients (24% mortality) subjected to CPB at the University of Alberta Hospital between 1956 and 1961 revealed that in 7 (2.8%) cases death was caused by severe cerebral damage. [Callaghan, 1961] Air embolus was cited as the cause in 4 cases and calcium embolus in 2 cases. Micro air emboli from a bubble oxygenator were thought to be the cause of death in 1 patient who failed to regain consciousness after surgery.

In a retrospective study of 244 patients who underwent cardiac surgery with CPB, Ehrenhaft reported that 17 (7%) developed new neurological signs after surgery. [Ehrenhaft, 1961a; 1961b] Seizures occurred in 8 patients, hemiparesis in 8 patients and visual field defects in 3 patients. The mortality in this group was 3/17 (18%). Cerebral embolism (both gaseous and particulate) and hypoperfusion were thought to be significant aetiological factors.

Two years later Brierley reported neuropathological findings in 11 adolescent and adult patients who died from 6 hours to 11 days after open heart surgery. [Brierley, 1963] Surgery was performed with deep hypothermic cardiac arrest in two cases whilst a pump oxygenator and mild hypothermia was used in the remaining 9 cases. Intraoperative problems, included massive haemorrhage, profound and/or prolonged hypotension, resistant cardiac dysrhythmias, occurred in 8 cases. Postoperative signs of neurological injury included; unconsciousness (7 patients), hemiparesis, general irritability, generalised seizures, focal motor seizures, athetoid movements, mutism, and absent or extensor plantar reflexes. Microscopic findings included focal (perivascular) and diffuse areas of cell loss (9 cases), white matter infarction (1 case) and widespread pathology typical of global ischaemia following prolonged cardiac arrest (1 case). Brierley postulated that cerebral emboli of several types (air, fat, cellular aggregates and silicone antifoam), cerebral ischaemia/hypoxia and rapid rewarming of the brain all contributed to neurological injury. In a later study of 206 patients who died after open-heart surgery, Aguilar and coworkers found that 85% had neuropathological abnormalities. Em-
bolic occlusion of small vessels; acute petechial, perivascular and focal subarachnoid haemorrhages; and acute ischaemic neuronal necrosis were seen in most cases. [Aguilar, 1971]

In a small prospective study of 35 patients, reported by Gilman in 1965, twelve (34%) patients showed signs of cerebral injury after surgery. [Gilman, 1965] Five of these died whereas another 6 patients died without evidence of neurological injury or before an evaluation could be made. (Overall mortality 11/35, 31%) Of the surviving patients; two had hemiparesis, two had visual field defects and two had seizures. The author suggested that cerebral emboli were probably the cause of these complications whereas prolonged CPB time and protracted perioperative hypotension accounted for another 6 patients in whom an intellectual decline ('gnostic disorder') was noted.

In the early 1960s a number of reports described the frequent occurrence of 'delirium' (described as; distortion of perception, hallucinations, disorientation and/or paranoia developing after a lucid interval of 24-48 hours) and other psychiatric complications after cardiac surgery. [Egerton, 1964; Blachly, 1964] A group at Columbia University subsequently conducted two studies into the incidence, nature and aetiology of this phenomenon. In the first report of 119 unselected patients operated on between 1962 and 1964, the overall incidence of delirium in adult patients was 38% whereas none of the 20 children studied developed delirium. [Kornfeld, 1965] The incidence was highest (78%) in patients undergoing complex (double valve) surgery. In patients subjected to less than 3 hours of CPB the incidence of postoperative delirium was 34%. The incidence was significantly higher (53%) in patients subjected to more than 3 hours of CPB. In the second report of 100 unselected patients operated on between 1967 and 1969, the incidence of delirium had fallen to 24%. [Heller, 1970] Postoperative delirium was more common in patients with acquired heart disease (26% versus 8%) who were significantly older (54 versus 29 years), had longer mean bypass times (122 versus 81 minutes), and had higher severity of illness ratings than those with congenital heart disease.

One of the earliest reports of the effects of cardiac surgery on cognitive function was that of Giberstadt and Sako, who reported deteriorations in memory, attention and coordination in 53 patients examined three weeks after surgery. [Giberstadt, 1967] These findings were subsequently confirmed by Tufo and colleagues in a prospective study of 100 patients undergoing surgery with CPB for valvular or congenital heart disease. [Javid, 1969; Tufo, 1970] Neurological, visual field, mental state and psychometric evaluations were performed before and on several occasions after surgery. The mortality during the first 2 weeks after surgery was 15% - high by contemporary standards. At autopsy definite lesions were found in 9/10 of the brains examined. All patients had multiple small lesions diffusely distributed throughout the grey and white matter. Anoxic hippocampal damage was present in 7 cases. Of the survivors, 37(44%) had at least one new abnormal neurological sign after surgery. In 12 (15%) patients these new signs persisted until hospital discharge. Changes in mental state, classified as con-
fusion, disorientation and/or delirium, were frequently found in association with neurological signs. Adverse neurological outcome was associated with increasing age, CPB of more than 2 hours duration, the presence of symptoms of cardiac disease, increased pulmonary vascular resistance, a history suggestive of previous neurological deficit and profound and/or prolonged intraoperative hypotension.

The studies of Lee and colleagues [Lee, 1969; 1971] reached similar conclusions whereas late follow-up studies by the Columbia group [Frank, 1972] and others [Ellis, 1980] produced contradictory findings. Frank and coworkers reported that there was an improvement in all areas of intellectual function measured 6 months after cardiac surgery. [Frank, 1972] Of the 98 randomly selected patients studied 9 (9%) died within 6 months of surgery and only 49 (55%) of the survivors returned for psychological evaluation. Although the fate of the 40 survivors who did not attend for follow-up is unknown, current evidence suggests that it is patients with cognitive impairment who are more unlikely to comply with follow-up assessments. [Blumenthal, 1995] In a study of 30 patients undergoing CABS, Ellis showed that although the incidence of intellectual impairment was high at seven days (75%) and 4 weeks (70%) after surgery, the incidence fell to 0% at 6 months after surgery. [Ellis, 1980]

In 1972, Branthwaite reported neurological complications in a retrospective study of 417 patients who underwent cardiac surgery at the Brompton Hospital during 1970 and survived the immediate post-operative period. [Branthwaite, 1972] Neurological dysfunction, defined as impairment of consciousness, voluntary movement or vision, apparent within three days of surgery, was noted in 80(19%) patients. In 32(40%) an aetiology, such as hypotension, hypoxia, cardiac arrest, embolism, or superior vena caval obstruction was suspected. Of the 21(26%) fatalities in this group, neurological injury was thought to have contributed in 11 cases. An adverse neurological outcome was significantly associated with increasing patient age, duration of CPB and the presence of a history of neurological disorder.

The first definitive study of intellectual dysfunction after cardiac surgery was that of Torkel Åberg who compared 144 patients undergoing surgery with CPB for valvular or congenital heart disease with 46 patients undergoing thoracic surgery without CPB. [Åberg, 1975] Detailed neuropsychological assessments - made before and 1 week, 8 weeks and 12 months after surgery - demonstrated that patients who had undergone general surgical procedures had either unchanged or improved intellectual function, whereas those who had undergone operations involving extracorporeal circulation had impaired function. Tests of cognition, visuospatial perception and reaction speed were most frequently effected, whereas tests of verbal comprehension and reasoning were resistant to change.

In 1980, Sotaniemi reported that 37% of 100 consecutive valve surgery patients had evidence of neurological deficit one year after surgery. [Sotaniemi, 1980] In 1981, the same group reported the results of neuropsychological evaluation, using a battery of 24 neuropsychological
tests, in 60 patients undergoing cardiac valve surgery with CPB. [Juolasmaa, 1981] At follow-up, 5 months after surgery, 28% patients showed impaired test performance – defined as a postoperative test score half a standard deviation or more lower than the preoperative score. The authors concluded that the right cerebral hemisphere was more susceptible to damage than the left. In a long-term follow-up study of 49 valve patients the group reported a 27% incidence of neuropsychological changes 2 months after surgery. [Sotaniemi, 1981] Five-year follow-up of 44 of these patients showed that these neuropsychological changes were persistent. [Sotaniemi, 1986]

In 1981, Malone reported neuroelectrophysiological and neuropathological findings in 20 patients who died following cardiac surgery at the London Hospital between 1970 and 1977. [Malone, 1981] In 9 patients with evidence of brain damage, abnormalities in the intraoperative EEG (cerebral function analysing monitor; CFAM) correlated with the severity of postoperative neurological deficit. In contrast, 11 patients with normal or relatively normal CFAM recordings had macroscopically normal brains.

In 1982, Savageau reported early and late follow-up in 227 cardiac surgical patients of which 76% had undergone coronary artery bypass surgery. [Savageau, 1982a; 1982b] Patients underwent neuropsychological assessment before and after surgery. The 30% incidence of significant impairment found at 9 days fell to 19% at 6 months after surgery. It is noteworthy that some 14% of patients developed new impairment(s) after the first postoperative assessments.

The prospective study of 531 patients at the Cleveland Clinic revealed that 68 (16%) of the 418 patients that had undergone CABS had new central nervous system deficits by the fourth postoperative day. [Breuer, 1981] Focal deficits were present in 22/68 (37%), the remainder were described has having non-focal or diffuse encephalopathy. The overall mortality was 7/418 (1.7%), whereas 3 of the patients with neurological injury (4%) died. A later prospective study of 421 patients revealed a stroke incidence of approximately 5% following CABS. [Breuer, 1983; Furlan, 1984]

In 1983, Bojar and colleagues reported a retrospective study of 3206 patients undergoing CABS between 1976 and 1981. [Bojar, 1983] The mortality was 89/3206 (2.8%) and the incidence of major neurological complications was 32/3206 (1%). Of the latter, 10 patients remained comatose after operation, 10 patients had clinical evidence of stroke - 1 (10%) died, 6 patients sustained late neurological deficits and 6 patients had severe mental aberration without focal neurological deficit. Coma and stroke occurring without a lucid interval carried a poor prognosis; 5 (50%) of the comatose patients and 1 (10%) of the patients with perioperative stroke died. Causative factors were suspected in 14/20 (70%) of these patients, and included atheromatous embolism, perioperative hypotension, carotid artery occlusive disease and air embolism.
The study of 100 consecutive patients undergoing valve surgery reported by Sotaniemi highlighted the problems associated with retrospective studies. [Sotaniemi, 1983] Retrospective analysis revealed that the prevalence of cerebral abnormalities was 4% among survivors (6% overall) up to 10 days after surgery and 0% thereafter. This contrasted with the 37% (35% overall) and 5%, respectively, obtained by careful neurological, psychometric and electroencephalographic examination.

In the same year, the Cleveland Clinic reported a prospective investigation of neurological outcome in 421 consecutive CABS patients. [Breuer, 1983] The incidence of stroke was 22/421 (5.2%). There were no significant perioperative risk factors for stroke. The incidence of non-focal encephalopathy (characterised by confusion and disorientation) was 49/421 (11.6%). Significant risk factors appeared to be use of an intra aortic balloon pump (IABP) and use of vasopressors - both indicators of severe hypotension and/or hypoperfusion.

In many ways the study conducted in Newcastle by the neurologist Pamela Shaw, during the early 1980s marked a turning point in the field of neurological outcomes research in cardiac surgery. [Shaw, 1985; 1986a; 1986b; 1986c; 1986d; 1987a; 1987b; 1989] Her meticulous attention to detail set the standard for those that followed. In her prospective study of 312 cardiac surgical patients Shaw performed preoperative and daily postoperative neurological examinations, and administered a battery of 10 neuropsychological tests before, and 7 days and 6 months after surgery. [Shaw, 1985] One patient (0.3%) died from diffuse cerebral injury attributed to a prolonged period of profound hypotension at the end of CPB. Of the 10 patients (3%) who failed to regain consciousness within 24 hours of surgery most were alert by the 12th day. Fifteen patients (5%) developed perioperative stroke. The majority (12/15) of strokes were apparent on recovery from anaesthesia. One patient (0.3%) in this group developed seizures 3 months after surgery. A further 9 patients (3%) developed subtle neurological signs such as an extensor plantar response. Ophthalmological complications were common; occurring in 25% of patients. Areas of retinal infarction developed in 54 patients (17%) of whom half complained of visual disturbance. Eight patients (2.5%) developed visual field defects ranging from asymptomatic quadrantanopia to cortical blindness and a further eight patients (2.5%) had evidence of retinal macroembolism. New primitive (i.e. grasp, pout and/or pal-moment) reflexes developed in 123 patients (39%). Four patients (1%) developed frank psychosis requiring treatment with parenteral sedatives. In two of these there was a lucid interval of several days before the onset of psychosis. Brachial plexus injury developed in 21 patients (7%). In four this was associated with ipsilateral Horner's syndrome. A total of 17 patients (5%) developed other peripheral (e.g. ulnar, lateral cutaneous, peroneal, phrenic) nerve lesions. Of the 298 patients who completed psychometric testing 7 days after surgery 235 (79%) had a deterioration of more than one standard deviation in performance on one or more tests with short term memory, psychomotor speed, and attention being the areas most
commonly affected. Six months after surgery, clinically detectable neurological abnormalities were still present in 52% of the patients who had developed postoperative neurological complications. For most patients, however, these abnormalities were mild and had little or no impact on activities of daily living. Only 10 (4%) of the 260 patients reviewed 6 months after surgery were disabled by neurological problems. Neuropsychological impairment, as defined above, was present in 147 (57%) of the 259 patients who completed follow-up psychometric testing. This was considered moderate or severe in 18 (12%) patients and disabling in 3 (2%) patients.

1.6.2. 1985-1998: Aetiologies and interventions

From the mid 1980s onwards, while continuing to report the nature and incidence of adverse neurological outcomes after cardiac surgery, investigators began to examine the causes and mechanisms of neurological injury, develop indices of risk by defining predictive perioperative risk factors, and test beneficial effects of physical and pharmacological interventions. Unlike the previous section, in which published accounts have been discussed in chronological order, the research presented in the section that follows has been considered in terms of aetologies for the sake of clarity.

Arguably one of the most detailed and influential studies of recent years is that of the Multicenter Study of Perioperative Ischemia (McSPI) and Ischemia Research and Education Foundation (IREF), published in the New England Journal of Medicine at the end of 1996. [Roach, 1996] This prospective, observational study of 2417 patients at 24 U.S. medical institutions, sought to determine the incidence of neurological injury after CABS, identify independent predictors of these adverse outcomes, and assessment their impact on resource utilisation. Two categories of adverse neurological outcome were defined, type I: non-fatal stroke, transient ischaemic attack (TIA), stupor or coma at the time of discharge, or death due to stroke or hypoxic encephalopathy; and type II: new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or seizure without evidence of focal injury. Data from 2108/2417 (87%) patients was analysed.

Over 31.9% of patients were 70 years of age or older and there was a high prevalence of hypertension, unstable angina, cardiac failure and diabetes mellitus. In all 129/2108 (6.1%) patients had an adverse neurological outcome in the perioperative period. Type I outcomes occurred in 66/2108 (3.1%) and included 8 deaths due to cerebral injury, 55 non-fatal strokes, 2 TIAs and 1 case of stupor at the time of discharge. Type II outcomes occurred in 63/2108 (3.0%) patients and included 55 patients with intellectual dysfunction and 8 patients with seizures. There was a wide variation in institutional outcome rates for both Type I (1-13.8%) and Type II (0-9.3%) outcomes.
Univariate analysis identified eight statistically significant, independent predictors of Type I outcome. These were, in order of importance; proximal aortic atherosclerosis (detected by surgical palpation), a history of neurological disease, use of an intra aortic balloon pump (IABP), diabetes mellitus, a history of hypertension, a history of pulmonary disease, a history of unstable angina, and patient age. Seven statistically significant, independent predictors of Type II outcome were defined. These were, in order of importance; systolic hypertension at admission, a history of excessive alcohol consumption (requiring hospitalisation), a history of pulmonary disease, patient age, a history of previous CABS, cardiac dysrhythmia on the day of surgery, and antihypertensive therapy. Factors found not to be significant predictors were; perioperative hypotension (systolic blood pressure <40mmHg during CPB, or <80mmHg at other times for more than 10 minutes), intraoperative use of a ventricular vent, congestive cardiac failure on the day of surgery, and a history of peripheral vascular disease. (Table 1.7)

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>Type I Outcomes</th>
<th>Type II Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal aortic atherosclerosis</td>
<td>4.52 [2.52-8.09]</td>
<td></td>
</tr>
<tr>
<td>History of neurological disease</td>
<td>3.19 [1.65-6.15]</td>
<td></td>
</tr>
<tr>
<td>Use of IABP</td>
<td>2.60 [1.21-5.58]</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.59 [1.46-4.60]</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>2.31 [1.20-4.47]</td>
<td></td>
</tr>
<tr>
<td>History of pulmonary disease</td>
<td>2.09 [1.14-3.85]</td>
<td>2.37 [1.34-4.18]</td>
</tr>
<tr>
<td>History of unstable angina</td>
<td>1.83 [1.03-3.27]</td>
<td></td>
</tr>
<tr>
<td>Age (per additional decade)</td>
<td>1.75 [1.27-2.43]</td>
<td>2.20 [1.60-3.02]</td>
</tr>
<tr>
<td>Admission systolic BP &gt; 180mmHg</td>
<td></td>
<td>3.47 [1.41-8.55]</td>
</tr>
<tr>
<td>History of excessive alcohol intake</td>
<td>2.64 [1.27-5.47]</td>
<td></td>
</tr>
<tr>
<td>History of CABS</td>
<td>2.18 [1.14-4.17]</td>
<td></td>
</tr>
<tr>
<td>Dysrhythmia on day of surgery</td>
<td>1.97 [1.12-3.46]</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>1.78 [1.02-3.10]</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.7: Adjusted odds ratios [95% confidence intervals] for type I and type II cerebral outcomes associated with selected risk factors from the McSPI & IREF Study. BP = blood pressure. CABS = coronary artery bypass surgery. [Roach, 1996]

Although similar, the risk factors for focal (Type I) neurological injury are not the same as those for diffuse (Type II) neurological injury. Type I outcomes were associated with a 10-fold increase in in-hospital mortality, and Type II outcome with a 5-fold increase. The average duration of intensive care and the length of postoperative hospital stay were at least doubled in patients with adverse neurological outcomes. Using conservative estimates of hospital costs a Type I outcome added over $10,000 and Type II outcome over $6000 to patient in-hospital charges. Almost 90% (1773/1979) of those patients with no adverse neurological outcome were discharged home after surgery whereas only 32% (21/66) patients with Type I outcomes and 60% (38/63) patients with Type II outcomes could be discharged to their homes.
Patients not discharged home either died in hospital or were discharged to an intermediate or long-term care facility.

The authors recognised a number of limitations; the lack of standardised neurological examination, the lack of formal neuropsychological testing, the arbitrary use of two outcome categories, in an attempt to distinguish between focal and diffuse cerebral injury, the detection of aortic atherosclerosis by surgical palpation (see below), and the lack of a formal (i.e. duplex scanning) assessment of the prevalence and severity of carotid artery disease.

Using the same 2107 patient McSPI-IREF database, the Duke group developed a model to predict the development of postoperative stroke. [Newman, 1996a] The score is calculated from patient age and the presence or absence of a history of unstable angina, diabetes mellitus, prior CABS, neurological disease, vascular disease and/or pulmonary disease. (Table 1.8) A total score of 100 points predicts a 5% risk of central nervous system injury. (Figure 1.4) Although the McSPI CABS Stroke Risk Index (SRI) has not been validated in a prospective investigation it has been used recently in a retrospective analysis of 2804 patients undergoing CABS at Duke University. [van Wermeskerken, 2000] Patients experiencing adverse neurological outcome had a preoperative SRI more than twice the group without major neurological injury (mean ±SD; 0.077 ±0.067 versus 0.034 ±0.049; p=0.0001).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(Age - 25) x 10 / 7</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>14</td>
</tr>
<tr>
<td>Diabetes mellitus (history of either type I or type II diabetes or insulin use on admission or preoperatively)</td>
<td>17</td>
</tr>
<tr>
<td>History of neurological disease (previous stroke or transient ischaemic attack)</td>
<td>18</td>
</tr>
<tr>
<td>Prior coronary artery bypass surgery</td>
<td>15</td>
</tr>
<tr>
<td>History of vascular disease (peripheral vascular disease, known carotid vascular disease, claudication or vascular surgery)</td>
<td>18</td>
</tr>
<tr>
<td>History of pulmonary disease (emphysema, chronic bronchitis, asthma, restrictive lung disease)</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 1.8: Multicentre preoperative stroke risk index (SRI) for patients undergoing coronary artery bypass graft surgery. [Newman, 1996a]
Recently the same group has reported the results of a prospective, multicentre study of 273 patients undergoing intracardiac and coronary artery surgery. [Wolman, 1999] Adverse neurological outcome occurred in 43/273 (16%) patients indicating that this group of patients is an ‘extraordinary’ risk.

As mentioned above, the remainder of this section will focus on those factors thought to contribute to adverse neurological outcome following cardiac surgery. For the purposes of discussion they are divided into patients factors and operative factors.

1.6.2.1. Patient age

Of all the factors thought to be predictive of neurological injury in cardiac surgery, age is probably the least controversial. It is not surprising that older patients undergoing cardiac surgery have a higher mortality. [Ennabli, 1986] A large number of investigations have identified a significant association between increasing age and postoperative neurological or cognitive impairment. [Frank, 1972; Branthwaite, 1972; Barash, 1980; Cosgrove, 1984; Gardner, 1985b; Frye, 1992; Tuman, 1992; Newman, 1995b; Roach, 1996] (Figure 1.5)
Oestrogens appear to play an important and specific role in cognitive function in women. [Sherwin, 1994; 1996a; 1997; 1998] The finding that oestrogen administration reverses memory deficits in women rendered hypo-oestrogenic with leuprolide acetate (a gonadotrophin releasing hormone agonist) suggests that a study of oestrogen replacement in postmenopausal women undergoing cardiac surgery is warranted. [Sherwin, 1996b]

It is unclear, however, whether oestrogen/progesterone administered before or immediately after neurological injury (i.e. stroke) will be neuroprotective. Could any benefit observed be ascribed to cognitive enhancement or amelioration of neurological injury.

1.6.2.3. Severity of cardiac disease and cardiac function

Although an association between poor left ventricular function and increased risk of adverse neurological outcome makes sense; there is little objective evidence support this notion. The issue is further confounded by the observation that the severity of coronary artery disease frequently correlates with that of cerebrovascular disease.

An early study by Blachly suggested that the occurrence and severity of a postoperative brain syndrome or hallucinosis was related to low postoperative cardiac output. [Blachly, 1966] Lee and colleagues reported that patients who had symptoms of cardiac disease for more than 6 months were more likely to develop neurological damage following coronary artery surgery. [Lee, 1971; Javid, 1969; Tufo, 1970; Breuer, 1983] Poor preoperative left ventricular function and/or an episode of left ventricular failure has been reported to be associated with worse neurological outcome. [Savageau, 1982a; Shaw, 1987a] An analysis of the CASS registry revealed that the use of α-adrenergic drugs following CPB – presumably a marker of cardiac dysfunction, low cardiac output state and/or haemodynamic instability – was associated with increased stroke risk (p=0.00001). [Frye, 1992] The association between poor neurological outcome and diabetes, advanced coronary artery disease, aortic atheromatous disease and use of the IABP has been established. [Roach, 1996]

1.6.2.4. Cerebrovascular disease

In the non-surgical population carotid and vertebral artery disease causes about a quarter of ischaemic strokes. The likely mechanism of injury is embolisation from the surface of an atherosclerotic plaque. Asymptomatic carotid stenosis carries an annual stroke risk of around 2% whereas symptomatic disease is associated with a ten fold increase in risk of stroke within the first year.

In patients not undergoing cardiac or carotid surgery, the incidence of perioperative stroke is very low. In a study of over 24,000 patients undergoing general or vascular surgery over a 5 year period at a New York Hospital, the incidence of perioperative stroke was 0.08%. Mor-
The elderly are more likely to have impaired preoperative cognitive functioning, which together with perioperative decline, may significantly impinge on their autonomy. The reason may be that, although older patients appear to retain autoregulation (arterial pressure and metabolic coupling) of cerebral blood flow, there is undoubtedly an increase in the incidence of aortic atherosclerosis and occult cerebrovascular disease. [Blauth, 1992; Newman, 1995c] Objective evidence of an association between aortic disease and neuropsychological changes in the elderly is, however, notably absent.

1.6.2.2. Gender

Few studies have specifically examined the influence of gender on neurological outcome after cardiac surgery. [Gardner, 1985b] The principle reason for this is that men greatly outnumber women in the adult cardiac surgical population. The study of 100 valve patients in which mortality in females was 3/37 (8.1%) compared with 3/63 (4.8%) in males, appears to support the widely held view that women tend to have less favourable outcomes. [Sotaniemi, 1980] Data from the US Society of Thoracic Surgeons (http://www.sts.org/outcomes) for the years 1995 to 1996 suggests that operative mortality was significantly greater in females following both repeat and/or emergent CABG (4.30% versus 2.63%, p<0.0001) and primary elective CABG (2.9% versus 1.5%, p<0.0001). A recent report from the BARI group suggests that the higher mortality observed in women is a product of higher risk profiles rather than increased gender susceptibility. When risk factors are controlled for, female gender was an independent predictor of improved 5-year survival. [Jacobs, 1998] More recently published evidence from the University of Toronto [Abramov, 2000] supports this finding. Although perioperative complications and recurrent angina were more frequent in women, late (60 month, risk-adjusted) survival was increased.

Striking differences in gender susceptibility have been demonstrated in animal models of both traumatic and ischemic brain injury. [Roof, 2000] In humans, a similar gender difference has been observed following subarachnoid haemorrhage. [Kassel, 1996]

Laboratory evidence suggests that oestrogens have a vital role in neuronal growth, differentiation and survival. Pretreatment with 17β oestradiol protects primary cortical neurons from glutamate induced injury. [Singer, 1996] The majority of this neuroprotective effect does not appear, however, to be mediated via a receptor mechanism [Wise, 2001] that can be antagonised by the anti-oestrogen, tamoxifen. [Green, 1997] Mefepristone (RU486), a potent antagonist of progesterone and glucocorticoid receptors, has been shown to protect neuronal cultures from oxidative stress by preventing intracellular peroxide accumulation and cell death induced by amyloid β protein, hydrogen peroxide and glutamic acid. [Behl, 1997]
tality in these patients was 26%. Significant risk factors for stroke included; hypertension, smoking, a history of neurological disease, and cardiac dysrhythmia. Atrial fibrillation was the most common risk factor. The presence of a carotid bruit on preoperative examination was not predictive of postoperative stroke. [Parikh, 1993]

Patients with a history of stroke or TIA are more likely to sustain a perioperative stroke. [Turnipseed, 1980; Sotaniemi, 1980; Martin, 1982] Patients with significant but asymptomatic atheromatous disease in the extracranial (carotid and vertebral) cerebral arteries may too be at increased risk on the grounds that they will be more vulnerable to regional ischaemia during periods of hypoperfusion.

A number of studies have attempted to determine whether asymptomatic cerebrovascular disease is associated with increased risk of perioperative stroke. Of the 582 patients undergoing preoperative carotid artery ultrasound in the Veterans Administration Cooperative Study, 130 (22%) patients had >50% stenosis or occlusion of one or both internal carotid arteries (ICAs), and 70 (12%) patients had ≥80% stenosis or occlusion of one or both ICAs. The in-hospital stroke incidence was 2.1% (12/582) and 36 (6.2%) patients died. Of the seven patients with hemispheric stroke, five had ≥50% stenosis or occlusion of the ipsilateral ICA. The presence of ICA stenosis or occlusion was significantly associated with hemispheric stroke (no stenosis 0.34% versus stenosis 3.8%; p=0.0072). The authors concluded that carotid atherosclerosis is a risk factor for hemispheric stroke in patients undergoing CPB. [Schwartz, 1995a]

Although the preoperative detection of a carotid bruit is associated with a two-fold increase in absolute perioperative stroke risk after CABS it is a poor measure of the severity and has been shown not correlate well with angiographic findings. [David, 1973] In the presence of carotid disease detected by Doppler sonography, the risk of stroke is increased three-fold. [Breslau, 1981] As expected the risk of stroke increases with the severity of carotid disease. In a follow-up study of 4047 patients examined before CABS, Brener and colleagues demonstrated that in the presence of a >50% carotid stenosis the risk of stroke rose from 1.9% to 6.3%. In 32 patients with complete carotid occlusion, the stroke rate was 15.6%. [Brener, 1987] Because carotid disease is frequently found in association with proximal aortic atheroma, peripheral vascular disease and intracranial cerebrovascular disease, it is not clear whether carotid disease alone increases the risk of perioperative stroke.

A retrospective study at the Cleveland Clinic revealed that the incidence of new stroke after open-heart surgery was 13.4% in 126 patients with previous stroke. The likelihood of a new perioperative stroke was not related to the time interval between the previous stroke and surgery. Furthermore, the presence of extracranial occlusive disease appeared not to be a contributory factor. Patients with a recent stroke were more likely to have a worsening of a prior deficit whereas those with a remote stroke were more likely to have a stroke in a different
brain region. Intraoperative hypotension was more frequent in those patients recent preoperative stroke suggesting persistent vascular vulnerability. [Rorick, 1990]

In a study of 47 patients undergoing CABS at the Middlesex Hospital studied with intravenous digital subtraction carotid angiography; 51% had evidence of vessel wall disease and 17% had stenosis of at least one carotid artery in the neck. The incidence of neuropsychological deficit at 8 days and 8 weeks after surgery was not significantly greater among those patients with angiographically visible carotid artery disease. [Harrison, 1989]

In a recent Japanese study, the influence of craniocervical and aortic atherosclerosis on postoperative neuropsychological dysfunction and stroke was examined in 177 patients (age >60 years) undergoing CABS. [Goto, 2000] A composite measure of risk – an atherosclerotic score – was obtained using preoperative brain magnetic resonance imaging and carotid magnetic resonance angiography, and intraoperative epi-aortic ultrasound, and patients divided into three risk groups; low, intermediate and high. Despite alterations in surgical technique prompted by intraoperative findings in high-risk patients, the atherosclerotic score was highly predictive of neuropsychological dysfunction 7 days after surgery and postoperative stroke.

Current evidence suggests that asymptomatic extracranial cerebrovascular disease represents a modest increase in the risk of perioperative stroke and may not be very important in the genesis of neuropsychological deficits. Presumably other factors, such as embolism or profound hypotension, must be more important.

1.6.2.5. Diabetes mellitus and hyperglycaemia

For many years, the use of glucose containing priming solutions in the extracorporeal circuit was commonplace. Although there is evidence that outcome from stroke in human is worse in diabetics there are no data unequivocally implicating hyperglycaemia as the cause. [Sieber, 1997] The higher incidence of hypertension, renal impairment, and peripheral, coronary and cerebrovascular disease may partly explain a worse outcome in diabetic patients with stroke. In a recent study using $^{133}$Xe clearance, the Duke group demonstrated that insulin dependent diabetic patients have impaired autoregulation, characterised by increased oxygen extraction, during CPB. [Croughwell, 1990] This would theoretically increase their sensitivity to hypotension.

In recent years, there has been a re-evaluation of the use of glucose containing priming solutions in cardiac surgery. [Sieber, 1987] On the grounds that hyperglycaemia appears to worsen neurological outcome in animal models of focal cerebral ischaemia [Nakai, 1988; Li, 1996] some investigators maintain that hyperglycaemia during cardiac surgery is detrimental and should be avoided [Sieber, 1992] while others suggest that glucose administration may be beneficial. [Metz, 1991; 1995] More recently, however, a number of reports have suggested that
diabetes mellitus is a risk factor for poor neurological outcome. [Roach, 1996; Newman, 1996a; McKhann, 1997a] In a study of 70 patients conducted at the Middlesex Hospital randomly assigned to either electrolyte (Hartmanns solution) or dextrose prime, neuropsychological outcome was found worse in the dextrose prime group. [Newman, 1989b] In the author’s experience, few cardiac centres now use glucose containing priming solutions and treatment of hyperglycaemia with insulin is common.

1.6.2.6. Genetic susceptibility

The observation that patients with the similar demographic characteristics, identical medical histories and cardiac disease of equivalent severity could have markedly differing neurological and cognitive outcomes from otherwise uneventful cardiac surgery led investigators at Duke University to speculate that genetic factors may account for this variability. [Newman, 1994; 1995c] Concurrent laboratory studies at Duke, focusing on apolipoprotein E, prompted a clinical investigation.

Apolipoprotein E (APOE), a 34kD glycosylated lipid-binding protein, is expressed as three common isoforms in humans (e2, e3, or e4). Possession of the APOE e4 allele is now known to be a risk factor for the development of late-onset and sporadic forms of Alzheimer's disease. [Roses, 1994; Saunders, 1996] It may be associated with worsened outcome after subarachnoid haemorrhage, [Alberts, 1995] and with increased severity of chronic neurological deficits in boxers exposed to chronic head trauma (dementia pugilistica). [Jordan, 1997] Interestingly accelerated aortic atheromatous disease and early re-stenosis following coronary angioplasty, independent of serum cholesterol, may also be associated with APOE e4. [Hixson, 1991] APOE-deficient mice, subjected to focal cerebral ischaemia, have been shown to have a worse neurological outcome than wild-type mice. [Laskowitz, 1997] In transgenic mice constructed with the human APOE e4 gene, middle cerebral artery occlusion results in larger infarct volume and more severe hemiparesis than in mice with the APOE e3 gene. [Sheng, 1998]

In human stroke, however, the evidence linking APOE genotype with incidence and functional outcome is far from conclusive. While some studies have suggested that APOE e4 is associated with poorer outcomes [Pedro-Botet, 1992; McCarron, 1999], others suggest either no association [McCarron, 2000; MacLeod, 2001] or even superior outcomes. [Weir, 2001]

Based on this basic science research, APOE was evaluated as a predictor for postoperative cognitive dysfunction in 65 patients undergoing CABS. [Tardiff, 1997] A significant association was found between the APOE e4 allele and decline in 4/9 measures of cognitive function at discharge from hospital and 6 weeks after surgery. More recently, a study of 111 patients undergoing CABS has failed to confirm any association between APOE genotype and neuropsychological outcome. [Steed, 2001]
In a study of 560 patients undergoing primary CABS at Duke University, those with the APOE ε4 allele were significantly younger at presentation (p=0.032). [Newman, 2001] The effect was more pronounced in patients with two copies of the APOE ε4 allele (p=0.012). The authors hypothesised that patients with the APOE ε4 allele are predisposed to coronary artery disease and present earlier for CABS.

The notion that APOE isoforms may have a role in dictating the expression of early immediate genes following neuronal injury, and thus the balance between neuronal repair and neuronal death, is attractive but remains to be proven. (See next chapter)

1.6.2.7. Education level, socioeconomic status and mood

An interesting observation is that a higher number of years of formal education protects patients from cognitive decline. Level of educational achievement, however, appears to correlate poorly with baseline (preoperative) cognitive function test scores. [Newman, 1994] It has been speculated that this effect is similar to the protective effect of years of education seen in Alzheimer's disease, although the mechanism remains unclear. It has been speculated that reduced 'neuronal reserve' may play a role in the response to redo-cardiac surgery.

Depression is commonly reported after coronary artery bypass and other types of cardiac surgery. In a small study of 22 CABS patients, Folks and colleagues suggested that both low socioeconomic status and preoperative depression were associated with worse neuropsychological outcome. [Folks, 1988] The use of non-standard measures of depression, however, may have overestimated its frequency. A presumed association between postoperative depression and poor performance on neuropsychological tests has meant that mood assessment has become an integral component of many studies. In a recent study, the Center for Epidemiological Study of Depression (CES-D) depression measure and a battery of neuropsychological tests were used to assess outcome in 124 CABS patients one month and one year after surgery. [McKhann, 1997b] Depression was defined as a CES-D score of greater than 16. Only 12 (13%) of patients not depressed before surgery were depressed a month afterwards, whereas 18 (53%) of those who were depressed before surgery were depressed at a month (p=0.001). A year after surgery, 8 (9%) patients not depressed before surgery and 16 (47%) patients depressed before surgery were depressed (p=0.001). There was little or no correlation between depression and cognitive function changes. The suggestion is that cardiac surgery neither causes nor cures depression.

1.6.2.8. Cerebral embolisation

Emboli - which may be gaseous or particulate - can be conveniently divided into 'macro' and 'micro' according to size, the former occluding flow in arteries 200 µm or greater in diameter.
and the latter, in small arteries, arterioles, and capillaries. [Blauth, 1995] As early as 1913, it was suggested that air embolism occurring during surgery on the left heart represented a potential hazard. [Carrel, 1913] Other studies, conducted in the 1950s, suggested that polymethylsiloxane (Antifoam A), a de-foaming agent used in bubble oxygenators, was the source of cerebral emboli seen in humans and experimental animals. [Penry, 1959; Cassie, 1960] It is clear from the earliest clinical and neuropathological studies that cerebral embolism was considered to be an important aetiological factor in the spectrum of adverse neurological outcomes complicating cardiac surgery and that particulate matter, as well as bubbles, were implicated. [Brierley, 1963; Allardyce, 1966; Hill, 1969; Aguilar, 1971; Brennan, 1971; Orenstein, 1982] Today, few doubt this fact although it was not until the development of new histochemical techniques and modern ultrasound technology that qualitative and quantitative assessments of cerebral microemboli could be made.

Gaseous emboli consist of air or anaesthetic gases. [Butler, 1990] Air may directly reach the systemic circulation from the bypass circuit or as an inevitable consequence of left-heart surgery. [Spencer, 1965] Not surprisingly systemic embolisation is more common during valve surgery than CABS. [Kuroda, 1993] The size and fate of bubbles depends upon their size, the partial pressure of gases in solution, and temperature - which dictates the solubility of gases in liquids. Because of high surface tension forces, small bubbles are unstable and tend to collapse. Bubbles are more likely to grow in size during rewarming when solubility decreases. Although bubbles are known to traverse the cerebral vasculature, they may cause endothelial injury. [Blauth, 1995]

Particulate matter can be categorised according to composition and origin. Biological particles are formed from components of the circulation (aggregates of erythrocytes, leucocytes, platelets [Dutton, 1974; Solis, 1975a; 1975b], denatured protein and fibrin) and the operative site (thrombus, fat [Miller, 1962; Wright, 1963; Evans, 1964], calcium, cellular aggregates, atheroma, valve debris, muscle fragments, hair) whereas non-biological particles arise from the extracorporeal circuit and cardiotomy reservoir (polyvinyl chloride, silicone rubber, antifoam, priming solutions, cardioplegia solutions [Robinson, 1984]) [Reed, 1974] and from foreign material introduced into the operative field (fibres from swabs, glove talc, dust). [Blauth, 1988; Pugsley, 1989; Pearson, 1989; Blauth, 1995]

An early study of the ability of various heart-lung machines to remove microbubbles employed a transparent arterial line chamber and microscope to detect gaseous microemboli that were presumed to have originated in the oxygenator. [Selman, 1967]

The retina is the only cerebral microvascular bed amenable to direct examination and as such has potential as a 'window' on the cerebral microcirculation. The fundoscopic [Williams, 1971] and histopathological [Williams, 1975] studies of cardiac surgical patients, reported during the 1970s by Williams, supported the notion that cerebral microembolisation occurred
during CPB. In 1986, a report describing the use of fluorescein angiography to detect retinal microemboli during CPB, was published by a group at the Hammersmith Hospital. [Blauth, 1986] Arteriolar occlusion and capillary non-perfusion, consistent with microembolisation, was seen in all patients studied. In a later report, retinal vascular occlusion, at the termination of CPB, was seen in 21/21 patients studied. [Blauth, 1988] The appearances were categorised as either; arteriolar occlusion with an associated area of capillary non-perfusion, or capillary non-perfusion without occlusion of the feeding arteriole. Unexpectedly, the total number of retinal microemboli counted did not correlate with duration of bypass and was no different in the 10 patients in whom an arterial line filter was not used. Microembolic counts were, however, higher (p=0.075; Mann-Whitney) in those patients who had a deficit on psychometric testing.

In another study published by the same group two years later, retinal digital subtraction angiography and computerised image analysis was used to compare the impact of a bubble oxygenator and a flat sheet membrane oxygenator on retinal perfusion. [Blauth, 1990] All of the 30 patients supported with a bubble oxygenator had retinal perfusion deficits consistent with microemboli occlusion, whereas more than half of 34 patients supported with a flat sheet membrane oxygenator had normal retinal perfusion. As before, there was no correlation between retinal microemboli counts and duration of CPB.

Following initial reports of the use of ultrasound [Austen, 1965; Patterson, 1969] to detect gaseous and particulate matter in the arterial line during CPB, both continuous [Gallagher, 1973; Clark, 1978] and, subsequently, pulsed wave [Hatteland, 1985] Doppler ultrasound were used to detect emboli in the arterial line and the carotid arteries. The development of transcranial Doppler (TCD) sonography [Aaslid, 1982] provided investigators with a relatively simple and non-invasive means to monitor blood flow and cerebral microemboli in the basal cerebral arteries.

In 1987, Padayachee and colleagues studied 27 cardiac surgical patients at Guy's Hospital using intraoperative TCD. [Padayachee, 1987] Microembolic 'events' were detected in 22/27 (81%) during aortic cannulation. No events were subsequently detected in the 10 patients supported by a membrane oxygenator whereas events were detected in all 17 patients supported by a bubble oxygenator.

Although the use of arterial line filtration was apparently widespread in North America in the early 1980s, it took over a decade for them to be used routinely in Europe. [Gourlay, 1988; Treasure, 1989] An early report describing the influence of a 20µm filter on neurological outcomes could not demonstrate efficacy. [Aris, 1986] Another TCD study at Guy's Hospital demonstrated that both 25 µm and 40 µm arterial line filters could significantly reduce middle cerebral artery microemboli events during bypass. [Padayachee, 1988] The filter with the smaller pore size appeared to be more effective.
In 1989, Pugsley used TCD to determine the benefit of using a 40 μm arterial line filter with a bubble oxygenator in a randomised study of 40 patients. [Pugsley, 1989] There was no significant difference in the number of microembolic events detected during aortic cannulation and at the onset of bypass. Once CPB had been established, however, there was a major difference between the groups. (Table 1.9)

<table>
<thead>
<tr>
<th></th>
<th>Filtered</th>
<th>Non-filtered</th>
<th>p (Wilcoxon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannulation (MEE/1.5 min)</td>
<td>12 [1-25]</td>
<td>10 [2-20]</td>
<td>p &gt; 0.1</td>
</tr>
<tr>
<td>Inception of CPB (MEE/2.5 min)</td>
<td>36 [5-82]</td>
<td>45 [5-100]</td>
<td>p &gt; 0.1</td>
</tr>
<tr>
<td>During CPB (MEE/30 min)</td>
<td>6 [0-10]</td>
<td>243 [30-768]</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

Table 1.9: Transcranial Doppler quantification of cerebral microembolic events (MEE) in 20 patients with arterial line filters and 20 patients without filters. From Pugsley, 1989.

In order to assess the impact of microemboli on cognitive function, the Middlesex Hospital group went on to study 100 patients randomised to CPB with a bubble oxygenator either with or without an arterial line filter. [Pugsley, 1994] Patients underwent formal neurological examination before surgery and 1 day, 8 days, and 8 weeks after surgery. A battery of 10 neuropsychological tests was administered before surgery and 8 days and 8 weeks after surgery. Cerebral microembolic events were quantified with TCD. Although no patient sustained a focal neurological deficit, there was a significantly higher incidence of soft neurological signs (drowsiness, incoordination, nystagmus, and depressed tendon reflexes) in the unfiltered group on the day after surgery. Significantly, more patients in the unfiltered group had a decline in two or more neuropsychological tests at both 8 days (71% versus 46%) and 8 weeks (27% versus 8%) after surgery. The difference was particularly striking in a test of verbal memory. The incidence of neuropsychological deficit appeared to be related to microembolic events. At 8 weeks after surgery only 5 (8.6%, 95% C.I.; 5-12.2%) of the 58 patients with microembolic event counts less than 200 had a cognitive deficit, whereas 3 (43%, 95% C.I.; 25-61%) of the 7 patients with counts over 1000 had a deficit. A relationship between intraoperative cerebral microembolic events and adverse neurobehavioural outcome has since been confirmed by others. [Stump, 1996]

In a small study of patients undergoing mitral or aortic valve surgery with a flat membrane oxygenator and without arterial line filtration, van der Linden used TCD to determine when cerebral emboli occurred during open-heart surgery. [van der Linden, 1991a] Microemboli were detected during aortic cannulation in 9/10 patients, and at the start of bypass in 4/10 patients. Following the termination of bypass, subsequent filling of the left ventricle and ejection of blood into the aorta large numbers of microemboli were detected in all patients. The number of emboli was lower in two patients in whom extensive de-airing manoeuvres were employed.
In 1995, Clark and colleagues reported a neurological, neuropsychological and TCD study of 127 patients undergoing primary or secondary CABS. [Clark, 1995] Cerebral microembolic events were significantly associated with aortic cannulation, removal of the aortic cross-clamp, and during surgical manipulation of the heart. There was a significant correlation between a microembolic event count >60 and mortality and, neurological, cardiac and pulmonary complications. Deteriorations in memory, comprehension, attention and constructional ability were prominent and appeared to be related to microembolic event counts. These findings, however, should be taken cautiously as only 41 (32%) patients completed neuropsychological testing and only half of the patients monitored with TCD completed neuropsychological testing.

In 1990, a report from the Bowman Gray School of Medicine described the use of the alkaline phosphatase histochemical staining technique for thick celloidin sections [Bell, 1984] to examine the brains of dogs and humans. [Moody, 1990] (Non-specific alkaline phosphatase is native to arterial, arteriolar and capillary endothelium.) In six dogs and 4/5 patients, who had recently undergone CPB there were many focal dilatations or small aneurysms (10-40 µm in diameter) in terminal arterioles and capillaries. These elliptical or sausage-shaped lesions, which tended to have a predilection for bifurcation points, and were most numerous in dense vascular beds, were called small capillary and arteriolar dilatations (SCADs). A smaller number of SCADs, were observed in two patients who had undergone proximal aortography. No SCADs were seen in the brains of 6 dogs and 34 humans who had not undergone bypass. The endothelial walls of the SCADs appeared to be stretched and thin, rather than swollen, and no SCADs were detected in post-capillary venules. For these reasons, it was speculated that the lesions might represent the 'ghosts' of microemboli. This was supported by the discovery of birefringent particulate matter within a few SCADs. Based on a detailed study of one human brain it was estimated that the total number of SCADs was over 15 million! In a subsequent study of 29 patients, the numbers of SCADs were noted to be lower in those who had died several days or weeks after surgery. [Moody, 1995] If the number of SCADs seen in brain tissue reflect the total embolic 'load', it is clear that current methods (i.e. transoesophageal echocardiography, and carotid and transcranial Doppler) only detect a minute fraction of the total.

Using a canine model of CPB, the same group subsequently demonstrated that animals subjected to CPB without cardiotomy suction had fewer SCADs than animals subjected to cardiotomy suction. This finding suggests that anticoagulated blood, aspirated from the surgical field, is a potential source of microemboli. [Brooker, 1998]

The contribution of microemboli to neurological injury during CPB has been questioned in a recent T2* magnetic resonance imaging study in a piglet model of non-pulsatile, hypothermic CPB. [Mutch, 1997] During steady state hypothermic CPB a progressive, temperature inde-
pendent decrease in T2* signal intensity (suggestive of cerebral hypoxia) was observed despite adequate pump flow and arterial pressure. During rewarming the reduction in T2* signal intensity correlated with the decreases in $S_{O_2}$. No attempt was made to quantify cerebral microembolic load. The authors concluded that changes in autoregulation and the adverse effects of non-pulsatile CPB were more important than cerebral microemboli.

### 1.6.2.9. Aortic atheromatous disease

Although the possibility of atheromatous cerebral embolism during aortic surgery was recognised many years ago [Harris, 1967; McKibbin, 1976; Parker, 1985; Mills, 1991], it is only in recent years that this problem has been revisited. The severity of aortic atheromatous disease rises sharply with age. [Blauth, 1992] Postmortem studies indicate a prevalence of 20% in the fifth decade rising to 80% in the eighth decade. [Wareing, 1992] The prevalence of ulcerated atheromatous aortic plaques arch at autopsy has been shown to be higher (26% versus 5%) in patients with cerebrovascular disease but appears not to be correlated with the presence of extracranial internal carotid artery stenosis. [Amarenco, 1992] Surgical manipulations of the proximal aorta, cannulation through an atheromatous plaque or 'sandblasting' of the aortic wall during perfusion may cause atheroembolism. Evidence of atheroembolism was present in 4.5% of patients who died after CABG in 1982, but was detected in as many as 48% in 1989. [Wareing, 1992]

The advent of transoesophageal echocardiography (TOE) and intraoperative epiaortic ultrasound has allowed a more detailed view of the aorta during surgery and quantification of atheromatous plaques according to thickness and the presence of mobile components. The importance of aortic atheroembolism has been highlighted by Katz and associates [Katz, 1992] who found that the incidence of stroke was 25% in patients with mobile plaque of the aortic arch as opposed to 2% in patients with sessile plaque. A strong association between severe aortic atheroma and postoperative stroke or death has been confirmed by others. [Dávila-Román, 1991; Hosoda, 1991; Bar-El, 1992; Hartman, 1996; Roach, 1996] In a recent study of 84 patients undergoing CABG at Cornell University, the incidence of stroke was 2/74 (2.7%) in patients with non-mobile plaque and 3/9 (33%) in patients with mobile plaque as assessed with TOE. [Barbut, 1997] The presence of aortic atheroma was associated with a significantly longer period of postoperative hospitalisation. Although the numbers of cerebral microemboli detected (using TCD in 70/84 patients) during placement of the aortic clamp were higher in patients with severe atheroma the difference did not reach statistical significance.

show that the presence and severity of aortic atherosclerosis is underestimated by the transoesophageal technique. [Dávila-Román, 1996]

A number of centres are currently investigating the efficacy of alterations in surgical technique based on ultrasonic evaluation of the aorta. Such alterations include aortic cannulation at a different site, avoidance of aortic cannulation altogether, avoidance of aortic cross clamping and replacement of the ascending aorta and/or aortic arch.

1.6.2.10. Duration of cardiopulmonary bypass

The suggestion that CPB is associated with progressive cerebral microvascular obstruction suggests a relationship between duration of bypass and adverse neurological outcome. [Smith, 1986] Many investigators have either observed or suggested that neurological outcome is related to CPB duration. [Gilman, 1965; Javid, 1969; Tufo, 1970; Heller, 1970; Branthwaite, 1972; Savageau, 1982a; 1982b; Smith, 1986; Newman, 1987; Venn, 1988; Frye, 1992; McKhann, 1997c] Other reports have suggested otherwise. [Hammeke, 1988] The finding that progressive cerebral vasoconstriction leads to a gradual fall in cerebral blood flow during prolonged non-pulsatile hypothermic bypass [Rogers, 1988; Prough, 1991] may be an additional factor, but has not been substantiated by others. [Schell, 1993; Croughwell, 1998]

It is important to note that bypass time may be prolonged by a number of factors and circumstances which may, themselves, contribute to cerebral injury. A slow (meticulous) or ‘delayed’ surgeon may occasionally increase bypass time. It is more usual, however, that complicated surgical procedures (e.g. combined valve and CABS), complications or technical problems (e.g. haemorrhage, aortic dissection) and difficulty weaning from bypass are the main causes of prolonged bypass. From the foregoing discussion, it is clear that all of these factors may reflect a greater severity of cardiac disease in a population of surgical patients that have a higher incidence of adverse neurological outcomes.

1.6.2.11. Perfusion: pressure, flow and pulsation

Inadequate global perfusion of the brain has long been implicated as an important factor in the aetiology of neurological injury during cardiac surgery [Smith, 1986] (see above) and outcome from focal cerebral ischaemia depends, at least in part, on the adequacy of collateral circulation. There is little doubt that prolonged periods of profound hypotension and cerebral hypoperfusion is bad for the brain and that certain areas at the boundaries of anterior, middle and posterior cerebral artery territories (so-called ‘watersheds’) are particularly vulnerable. [Gilman, 1965] In recent years, however, there has been much debate as to relative importance of systemic (arterial or ‘pump’) blood flow, flow character, systemic arterial pres-
sure, and cerebral perfusion pressure during CPB in the genesis of neurological injury. Many of these issues are discussed in more detail in the next chapter.

Cerebral pressure flow autoregulation has been shown to remain intact at mean arterial pressures as low as 30 mmHg and that in α-stat managed patients CBF remains virtually constant within the range 30-100 mmHg. [Govier, 1984; Murkin, 1987] Children appear to tolerate pressures as low as 15 mmHg. [Greeley, 1989] Although it is usual practice to maintain a perfusion pressure of at least 50 mmHg during hypothermic CPB, Slogoff and colleagues found no association between postoperative neuropsychiatric complications and a perfusion pressure of less than 50 mmHg. [Slogoff, 1982] Although the maintenance of a perfusion pressure of 50 mmHg is tolerated by the vast majority of patients the safety of this practice has been the source of considerable debate. [Cartwright, 1998; Hartman, 1998]

An obvious question is whether the use of higher perfusion pressures (i.e. at least 80 mmHg) improves outcome. In an attempt to answer the question, Gold and associates prospectively compared cardiac and neurological outcome variables in 248 patients undergoing elective CABS randomly assigned to either lower (50-60 mmHg) or higher (80-100 mmHg) pressure perfusion. [Gold, 1995] Six months after surgery, the overall incidence of combined cardiac and neurological complications was significantly lower in the higher pressure group (4.8% versus 12.9%, p=0.026) as was the stroke rate (2.4% versus 7.2%). Cognitive and functional status outcomes, however, did not differ between the groups. The small study population (Table 1.4), unusually high baseline stroke rate and method of data analysis makes it hard to reach any definite conclusions. [Keats, 1996; Reves, 1996] The observed differences could have occurred purely by chance but may be accounted for by the greater number of patients with aortic atherosclerosis in the lower pressure group. [Hartman, 1996] A recent retrospective analysis of the Duke anesthesiology database, however, suggests that the maintenance of higher perfusion pressures during bypass may be associated with worse neurological outcomes (p=0.03). [Newman, 1998; van Wermeskerken, 2000]

It is customary to base systemic flow rate on body surface area and the degree of hypothermia (characteristically 1.6-2.4 l/min/m²) and to make adjustments based on indices of the adequacy of organ perfusion (e.g. arterial blood gases). In addition to those listed above, actual cerebral blood flow during CPB is determined by several other factors including acid-base management strategy (see below), temperature, depth of anaesthesia, haematocrit, and oxygen saturation. [Schell, 1993] In a study of 14 patients undergoing CABS, lowered regional CBF during coronary bypass surgery had an influence in performance on the Mini-Mental State Examination. [Freeman, 1985]

Although it is well established that low pump flow with concomitant arterial hypotension results in decreased CBF, the independent effects of low flow and low pressure are less well characterised. Using ¹³³Xe washout to measure CBF in a baboon model of non-pulsatile hypo-
thermic (28 °C) CPB, Schwartz and colleagues have shown that, regardless of pump flow, CBF is governed by mean arterial pressure (20-60 mmHg). Furthermore, when mean arterial pressure was maintained constant, changes in pump flow (0.75-2.25 l/min/m²) did not alter CBF. [Schwartz, 1995b] These findings are at odds with the results of several other studies of the determinants of CBF during CPB.

Govier and colleagues showed no correlation between CBF (measured by ¹³³Xe washout) and either mean arterial pressure (30-110 mmHg) or pump flow rate (1.0-2.2 l/min/m²) in 67 patients undergoing CABS. [Govier, 1984] In contrast, Soma and colleagues reported that cerebral perfusion (measured using argon in a modified Kety-Schmidt method) was directly dependent on pump flow rate (40-70 ml/kg/min). [Soma, 1989] Similarly, a TCD study concluded that CBF in children during deep hypothermic low-flow bypass correlated with pump flow rate but not cerebral perfusion pressure. [van der Linden, 1991b] In a series of experiments on patients undergoing CABS, the Bowman Gray group have reported the effects of arterial pressure alterations with sodium nitroprusside [Rogers, 1989] and phenylephrine [Rogers, 1988] administration on CBF (measured by ¹³³Xe clearance) at constant pump flow. In α-stat managed patients, changes in arterial pressure had no effect on CBF whereas in pH-stat managed patients, CBF was positively correlated with pressure. A subsequent study showed that modest changes in pump flow rate (1.75-2.25 l/min/m²) had no influence on arterial pressure or CBF. [Rogers, 1992] In a recent study of 215 patients undergoing CABS, moderate changes in mean arterial pressure (51-75 mmHg) during α-stat managed bypass at constant flow resulted in small proportional (0.086 ml/min/100g/mmHg) changes in CBF. [Newman, 1994; Newman, 1996b] These findings are in keeping with those of Grubhofer who showed that, at constant pump flow, jugular venous oxygen saturation (SjO₂) correlated with cerebral perfusion pressure in 20 patients undergoing hypothermic (29 °C) pulsatile bypass. [Grubhofer, 1998]

Non-pulsatile perfusion is associated with diminished endothelial shear stress and a reduction in endothelial nitric oxide production leading to increased vascular resistance and end-organ failure. [Macha, 1996] Furthermore, it is suggested that non-pulsatile flow may cause stasis of cerebral interstitial fluid [Wolbers, 1994] and may cause the cerebral swelling demonstrated by the Hammersmith group in humans after hypothermic [Harris, 1993] and normothermic [Harris, 1998] bypass. In a canine model of extracorporeal perfusion after 15 minutes of cardiac arrest, non-pulsatile perfusion was associated with worse cerebral hyperaemia and lower oxygen consumption compared with pulsatile perfusion. [Anstadt, 1993] In a prospective study of 316 patients undergoing CABS, however, Murkin and colleagues were unable to demonstrate any influence of mode of perfusion on neurobehavioural outcomes. [Murkin, 1995a]

Despite considerable research, the characteristics of 'optimal' CPB perfusion remain to be defined. [Arrowsmith, 2000] Within the bounds of usual CPB conduct, pressure, flow and flow
character appear to have little influence on CBF. [Schell, 1993] In the absence of unequivocal evidence suggesting otherwise, one could argue that there is little reason to alter perfusion practices that are tolerated by the vast majority of patients. [Arrowsmith, 2000] On the other hand, the abundance of anecdotal evidence, small observational studies and poorly designed intervention studies indicates the need for large, prospective, randomised comparative trials.

1.6.2.12. Temperature

Since the early days of cardiac surgery, largely due to the work of Bigelow [Bigelow, 1950] and Boreema, systemic and regional hypothermia has been the mainstay of organ protection during CPB. Hypothermia is unique among neuroprotective modalities in that it reduces energy consumption (about 7% per °C) associated with both electrophysiological function and the maintenance cellular integrity. In animal models of cerebral ischaemia, mild hypothermia reduces neuronal ATP depletion [Yager, 1996], and both delays the onset and reduces the rate of excitatory amino acid release. [Busto, 1987; 1989; Nakashima, 1996] In the teaching environment, the use of hypothermia allows trainees to refine their techniques and may 'buy' additional time during unforeseen events that threaten organ perfusion.

Hypothermia, however, does have a number of distinct disadvantages - not least the requirement for rewarming the patient at the end of the procedure. The observation that warming from moderate hypothermic CPB is associated with cerebrovenous oxygen desaturation (i.e. \( S_jO_2 < 50\% \)) suggests that cerebral oxygen extraction during this period exceeds supply. [Croughwell, 1992a; Cook, 1994] In a series of 255 patients studied at Duke, the cerebral arteriovenous oxygen difference (Ca-vO_2) on rewarming was significantly associated with overall cognitive decline (Figure 1.6; \( p=0.0013 \)). [Croughwell, 1994]

Rapid rates of warming, using temperatures \( >41 \^\circ C \), have long been considered a potential cause of neurological injury during CPB. [Brierley, 1963] Hyperthermia increases metabolic rate and may cause protein denaturation [Lee, 1961] and aeroembolism, as well as ischaemic areas within vital organs due to thermal gradients. [Cook, 1996] In a recent study, nasopharyngeal temperature monitoring was compared to continuous jugular venous temperature monitoring. [Grocott, 1997] Although there was a high degree of precision between the two monitoring sites, there was a marked difference in bias. This was most pronounced during rewarming when jugular venous temperature was 3.4 °C higher than nasopharyngeal temperature. The authors concluded that nasopharyngeal temperature monitoring underestimated brain temperature during rewarming and speculated that, as a result, the brain may be at increased risk of neurological injury. In a recently published, unrandomised and unblinded study of 28 CABS patients, however, von Knobelsdorff and colleagues suggested that the use of a slow rewarming regimen did not attenuate reductions in \( S_jO_2 \). [von Knobelsdorff, 1997] An ac-
companying editorial raised a number of methodological issues and advised caution in interpreting these findings. [Newman, 1997]

![Figure 1.6: Maximal cerebral arteriovenous oxygen content difference (C(a-v)O₂) during rewarming and cognitive deficits. The frequency of cognitive deficits at normothermia is divided into five groups according to maximal C(a-v)O₂ during rewarming. With increasing arterial-venous oxygen difference, the incidence of cognitive impairment increases. From Croughwell, 1994.](image)

The finding that even mild hyperthermia (38-39 °C) increases excitotoxic neurotransmitter release during cerebral hypoxia and delays recovery of energy-metabolism is clearly cause for concern. [Mora, 1996] The use of mild hypothermia (34 °C) after bypass and in the early postoperative period has been show not to be associated with increased bleeding, cardiac morbidity, or time to extubation. [Nathan, 1995] Any neuroprotective effect of this strategy remains to be established in prospective randomised trials.

In the brain, temperature is an important determinant of both cerebral metabolic rate (CMRO₂) and cerebral blood flow (CBF). During CPB, temperature is the single most important element influencing CBF. In the conscious adult at 37 °C, mean values for CMRO₂ and CBF are 3.5 and 50 ml/100g/min respectively whereas an anaesthetised adult at 35 °C (a modest degree of hypothermia) these values may be reduced by as much as 50%. At modest hypothermia, autoregulation of CBF is such that CBF is tightly coupled to CMRO₂. With decreasing temperature the CBF : CMRO₂ ratio increases resulting in 'luxury' brain blood flow. At temperatures of 15-20 °C (deep hypothermia), pressure-flow autoregulation is lost.
The relationship between nasopharyngeal (brain) temperature ($T_{np}$) and CMRO$_2$ if frequently expressed as the $Q_{io}$, or the degree of global cerebral metabolic rate reduction for each 10 °C reduction in body temperature. For adults undergoing cardiac surgery, the median $Q_{io}$ was 2.8. [Croughwell, 1992b] For children undergoing congenital heart surgery, the $Q_{io}$ was 3.65. [Greeley, 1991] The relationship between CMRO$_2$ and $T_{np}$ is given in the following mathematical expressions;

**ADULTS:** \[ \text{CMRO}_2 = T_{np} \times 0.021^{+1147} \]

**CHILDREN:** \[ \text{CMRO}_2 = T_{np} \times 0.019^{+1171} \]

In recent years, studies have suggested that normothermic cardioplegia might improve myocardial protection during heart operations. [Mora, 1996] As interest in these so-called 'warm-heart' techniques has increased, their use has become widespread. The immediate concern was that the abandonment of hypothermic perfusion during CPB would compromise cerebral protection and lead to a higher incidence of neurological morbidity.

To date, the studies that have examined the effect of normothermic cardioplegia and CPB on myocardial and neurological outcome have yielded conflicting results. Singh and colleagues [Singh, 1993; 1995], the Warm Heart Investigators from Toronto [Warm Heart Investigators, 1994] and McLean and colleagues [McLean, 1994] reported no increase in neuropsychological or neurological outcomes, whereas the Emory Warm Blood Cardioplegia Trial [Martin, 1994] demonstrated a marked increase in neurological injury in patients maintained at normothermia during CPB. Directly comparing these studies is difficult because actual brain temperature was not measured and because small variations or inconsistencies in CPB and operative technique may have had a crucial influence on temperature. This is further confounded by relatively low mean patient ages and the deliberate exclusion of patients with a predicted increased risk of perioperative stroke.

In an attempt to resolve this issue, Mora and colleagues [Mora, 1996] compared neurological and neuropsychological outcomes in 138 patients randomly assigned to receive either intermittent cold oxygenated crystalloid cardioplegia during hypothermic (less than 28 °C) bypass or continuous retrograde normothermic blood cardioplegia during normothermic (at least 35 °C) bypass. All of the seven patients found to have new focal neurological deficits came from the normothermic group. One patient died because of cerebral infarction having failed to regain consciousness after surgery. In contrast, there were no significant differences in neuropsychological test performance between the two groups.

These findings are consistent with the study conducted recently in Bristol. [Regragui, 1996] Regragui and colleagues prospectively investigated the effect of perfusion temperature (28 °C, 32 °C or 37 °C) on postoperative cognitive function in 96 adults undergoing elective CABG with CPB. Compared to patients perfused at 32 °C, the incidence of cognitive deficits was signifi-
cantly higher in patients perfused at 37 °C (p=0.021). Cooling to 28 °C appeared to offer no additional benefit.

Despite suggestions that normothermic bypass does not increase risk [McLean, 1996], it is interesting to note that at a meeting of researchers in the field, held in Oxford at the end of 1996, the majority indicated that they would rather undergo hypothermic (32 °C), rather than normothermic, bypass if they required cardiac surgery!

1.6.2.13. Acid base management

The solubility of gases in a liquid, including blood, increases as temperature falls. When arterial blood gases are analysed with a temperature correction during hypothermia, patients appear to have a respiratory alkalosis (decreased PaCO₂ and increased pH). The addition of CO₂ to 'normalise' the PaCO₂ and maintain a pH of 7.40 is known as 'pH-stat' acid-base management. The use of arterial blood gases without temperature correction is known as 'α-stat'. The physical principles of these differing approaches are discussed in more detail in the next chapter.

Nevin and colleagues highlighted the relevance of the maintenance of normocapnia prior to the onset of CPB in 1987. On the third postoperative day, patients who had been inadvertently hyperventilated (PaCO₂ <35 mmHg) had a higher incidence of neurological (46% versus 27%) and psychometric (71% versus 40%) deficits than patients who were normocapnic (PaCO₂ 35-45 mmHg) [Nevin, 1987]. It has since been suggested that the degree of neurological insult was, in fact, related to systemic hypotension, elevated central venous pressure and the magnitude of change in PaCO₂ at the onset of CPB. [Nevin, 2000]

During moderate hypothermic CPB, pressure-flow autoregulation of cerebral blood flow is maintained if α-stat blood gas management is used, but is lost when pH-stat management is used. The inability to autoregulate cerebral blood flow at low perfusions pressures, the possibility of 'steal' in patients with intracranial cerebrovascular disease, and the presence of 'acidosis' during rewarming associated with the pH-stat strategy increase the potential for brain injury. Furthermore, the excessive CBF associated with pH-stat may substantially increase the delivery of emboli to the brain. [Murkin, 1993]

The influence of pH management has been assessed by a number of groups. In a study of 86 patients undergoing CABS, Bashein and colleagues reported that pH management strategy had no influence on either cardiac or neuropsychological outcome. [Bashein, 1990] Stephan and colleagues in a prospective, randomised study of 65 patients undergoing CABS with hypothermic (26 °C) CPB. [Stephan, 1992] Use of the pH-stat strategy was associated with cerebral hyperaemia (+191% vs. -18%) and a higher incidence of neurological dysfunction 7 days after surgery (p=0.036). In a study of 316 patients undergoing CABS, cognitive dysfunction at 2
months was less prevalent after 90 minutes of CPB in patients managed with α-stat than with pH-stat strategy (27% versus 44%, p=0.047). Similar findings have been reported in a study of 70 patients undergoing CABS at St Thomas' Hospital (20% versus 48.6%, p<0.05) [Venn, 1995]

In patients [Jonas, 1996] and animals [Aoki, 1993; Kirshbom, 1996] undergoing deep hypothermic cardiac arrest (DHCA), however, pH-stat management prior to the onset of circulation arrest appears to improve neurological outcome. Using magnetic resonance spectroscopy in an immature piglet model of DHCA, Aoki and colleagues have shown that recovery of cerebral adenosine triphosphate and intracellular pH in the initial 30 minutes of reperfusion is faster in pH-stat managed animals. In α-stat managed animals, cerebral intracellular pH decreased during early reperfusion, whereas it showed continuous recovery in pH-stat managed animals. Postoperative brain water content (oedema) was also significantly lower in pH-stat managed animals. Possible reasons for these observations include improved brain cooling by increased blood flow to subcortical areas, improved oxygen delivery, and reduction of reperfusion injury, as well as an alkaline shift in intracellular pH with hypothermia in spite of a stable blood pH. [Aoki, 1993]

1.6.2.14. Haemodilution

The viscosity of blood, which is largely determined by the haematocrit, tends to increase as temperature falls. For this reason intentional haemodilution during CPB has been standard practice since the introduction of hypothermia. A haematocrit of 20% is widely considered an acceptable level of haemodilution during moderately hypothermic CPB. In the absence of objective evidence, this practice is likely based on the assumption that reduced oxygen carrying capacity is more than compensated for by a hypothermia-induced reduction in metabolic rate and more favourable rheology. Although most patients appear to tolerate a greater degree of haemodilution, there is a possibility that a low haematocrit during CPB might predispose or contribute to neurological dysfunction. [Chien, 1972]

During the last two decades, a trend towards greater haemodilution during CPB appears to coincide with growing concern about both the availability and safety of donor blood supplies. Although haemodilution to a haematocrit of less than 17% has been reported by a number of groups to be acceptable, the safety of this practice in elderly and 'high-risk' patients has been questioned. [Fang, 1997] In theory, the persistence of a low haematocrit during rewarming could expose the brain to a greater risk of hypoxic injury. Recent animal studies suggest that during CPB there is a temperature-dependent 'critical haematocrit' below which brain oxygenation and oxygen utilisation are decreased. [Cook, 1997] Critical haematocrit values for humans during hypothermic CPB have not been determined.
1.6.3. Neuroprotective interventions

Despite considerable efforts to define the optimal strategy for managing CPB (i.e. choice of PaCO₂, temperature, arterial pressure, flow rate and pattern, etc.), postoperative neurological and neuropsychological complications may still be evident. In many instances, investigations have raised more questions than they have answered.

The risk factors for adverse neurological outcome fall into two categories; (1) those that cannot be modified (i.e. age, gender, genotype, medical history, etc.) and (2) those that may be modified (i.e. cerebral embolism, aortic atheroma, CPB duration, cerebral perfusion, etc.). Interventions designed to reduce neurological injury during cardiac surgery can also be divided into two categories; (1) physical, and (2) pharmacological. Table 1.9 summarises some of the physical interventions that have been used or advocated.

<table>
<thead>
<tr>
<th>General considerations</th>
<th>Expeditious surgery. Attention to myocardial preservation and haemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintaining cerebral perfusion</td>
<td>Avoid prolonged/profound arterial hypotension. Avoid prolonged systemic hypoperfusion. Avoid prolonged superior vena caval obstruction. Consider retrograde cerebral perfusion during DHCA.</td>
</tr>
<tr>
<td>Temperature management</td>
<td>Moderate hypothermia (i.e. 32°C). Avoid rapid / excessive rewarming.</td>
</tr>
<tr>
<td>Acid-base management</td>
<td>Alpha-stat regimen. (pH-stat during cooling prior to DHCA and in patients with significant aorto-pulmonary anastomoses) Avoid hypocapnia.</td>
</tr>
<tr>
<td>Other</td>
<td>Avoid/treat hyperglycaemia. Direct cooling of the spinal cord during aortic surgery.</td>
</tr>
</tbody>
</table>

Table 1.10: Potentially neuroprotective physical interventions. [Arrowsmith, 2000]

1.6.3.1. Advanced neurological monitoring

A number of the ‘neuro-monitoring’ devices used in clinical research have yet to reach the mainstream of cardiac anaesthesia or surgical practice. (Table 1.9) There is no reproducible evidence that any neurological monitoring device can be used to predict or alter neurological outcome. The frequently high capital equipment and disposables costs and a number of practical factors limit their utility. Physical and electromagnetic interference render the operating theatre a ‘hostile’ environment in which to conduct electrophysiological assessments. Posi-
tioning of monitors such as TCD probes may be time consuming and the maintenance adequate signals may be difficult.

1.6.3.2. Neuroprotective interventions

For a small number of patients, pharmacological neuroprotection may offer the only form of salvation. At present, however, there is no agreement on the need for prophylactic neuroprotectants much less on the choice of agent. [Roach, 1997; Rogers, 1997] A growing understanding of the pathophysiology of cerebral injury has revealed a large number of potential therapeutic opportunities and lead to the development of several classes of neuroprotective agents. These are discussed in more detail in the following chapter.

With the exception of some of the anaesthetic agents, most of the prototype neuroprotective agents studied in cardiac surgery were originally developed for the treatment of stroke. In some ways, cardiac surgery could be thought of as a convenient model with which to test these agents - a large number of patients sustaining an ischaemic cerebral injury at a predictable time. Unfortunately, disagreement over the precise nature of the brain injury seen after cardiac surgery (focal versus diffuse micro-focal versus diffuse), the confounding influences of other 'standard' neuroprotective strategies (hypothermia, blood gas management, arterial line filtration etc.) and the lack of a gold standard for the assessment of neurological and cognitive outcomes, reduces its utility as an experimental model.

The observation that certain barbiturates could reduce cerebral metabolic rate led to extensive research into their potential therapeutic use as neuroprotective agents. In 1986, Nussmeier and colleagues reported the first demonstration of barbiturate-neuroprotection in humans. [Nussmeier, 1986] One hundred and eighty two patients undergoing open-ventricle procedures were randomised to either thiopentone (mean dose 39.5 mg/kg), sufficient to maintain electroencephalographic silence throughout the period from before atrial cannulation to termination of bypass (n=89), or fentanyl (n=93). On the first postoperative day, clinical neuropsychiatric abnormalities were more common in the control group (8.6% versus 5.6%). By the tenth postoperative day, all neuropsychiatric dysfunction had resolved in the thiopentone group but persisted in seven (7.5%) control patients (p<0.025). The incidence of complications was significantly related to calcification of replaced valves, aortic valve replacement, advanced age, and prolonged bypass, but not to hypotension during perfusion. It is curious to note, that in a later publications by the same group, the incidence of new neurological deficit was much lower [Slogoff, 1990; Metz, 1990] In a similar study of patients undergoing CABS, however, no protective effect by barbiturates could be demonstrated. [Zaidan, 1991] Mortality in the thiopentone group was, however, lower than in controls (0.7% versus 2.6%, p=0.018) More recently, a retrospective evaluation of 227 open-heart surgery patients revealed that high-dose thio-
pentone (mean dose 38.1mg/kg) had no beneficial effect on neurological outcome although mortality was significantly lower in the thiopentone group (1.2% versus 9.6%, p=0.034).

The short acting anaesthetic agent, propofol (2,6-diisopropylphenol) has similar effects to thiopentone on cerebral metabolism and blood flow. [Cheng, 1997] Although evidence from animal studies suggests a direct neuroprotective action, perhaps via GABA_\text{A} receptors [Hollrigel, 1996], it is also proposed that a propofol-induced reduction in cerebral blood flow reduces the delivery of microemboli to the cerebral circulation. [Newman, 1995d]

The observation that elevated levels of intracellular calcium appear to play an important role in the death of neurons [Choi, 1987; 1988], has stimulated considerable interest in the use of calcium channel antagonists. Of these, nimodipine, an L-type calcium channel blocker, has shown considerable promise as a neuroprotectant in the management of subarachnoid haemorrhage [Pickard, 1989] but not acute head injury. [The European Study Group on Nimodipine in Severe Head Injury, 1994] As a prelude to a neuroprotective study, subsequent investigations evaluated its safety and tolerability in cardiac surgical patients. [Forsman, 1990; Hynynen, 1995] A prospective double-blind randomised study of nimodipine in 400 patients was terminated after 150 patients had been studied because of lack of efficacy and significant adverse events. [Legault, 1996] The incidence of new neurological deficits observed was no different to placebo (72% versus 77%, p=0.55). In the 6-month follow-up period mortality was significantly higher in the nimodipine group (10.7% versus 1.3%, p=0.02). Major haemorrhage was also significantly more common in the nimodipine group (13.3% versus 4.1%, p=0.04).

Prostacyclin (epoprostenol) has been used in addition to, or as a replacement for, heparin during CPB. It is known to reduce platelet aggregation during extracorporeal circulation and, therefore, may be neuroprotective. [Fish, 1986] In 1987, Fish and colleagues reported the results of a randomised, double-blind study designed to evaluate the effect of prostacyclin on the incidence and severity of postoperative neuropsychological dysfunction in 100 patients undergoing CABS. [Fish, 1987] Of the 96 patients who completed the psychological and neurological evaluations 1 week after surgery; 74 were evaluated psychologically 2 months after surgery. There were no differences in neurological outcome or psychological test performance.

Grieco and colleagues have recently reported the results of a small double-blind placebo-controlled pilot study of GM_1 ganglioside, an inhibitor of protein kinase C, in patients undergoing cardiac surgery. [Grieco, 1996] Neurological and neuropsychological outcomes were superior in the GM_1 ganglioside group (n=18) than in the placebo group (n=11) although the differences were not statistically significant.

The systemic inflammatory response associated with CPB, characterised by the release of cytokines in response to activation of the coagulation, fibrinolytic and complement cascades, has been the subject of recent discussion. [Hill, 1996] The bovine serine protease inhibitor
aprotinin has been shown to significantly reduce intraoperative bleeding and transfusion requirements in a variety of settings including cardiac surgery with CPB. Despite an early study report suggesting an increased incidence in perioperative myocardial infarction [Cosgrove, 1992] there is now a suggestion, from a meta-analysis of several studies, that high-dose aprotinin may reduce the incidence of perioperative stroke. [Smith, 1996] Whether or not this action is due to the non-specific anti-inflammatory properties of anti-proteases remains unclear. Nafamostat mesilate (FUT-175), a synthetic serine protease inhibitor, is currently under investigation in cardiac surgery. It is known that glucocorticoids can suppress some of the inflammatory cytokines liberated during CPB. [Hill, 1995] A retrospective evaluation of the effect of glucocorticoids administration in 262 comatose cardiac arrest survivors, however, revealed no benefit. [Jastremski, 1989] Furthermore, recent laboratory evidence suggests that glucocorticoids may actual worsen neurological outcome. [McIntosh, 1996]

Indications that free radical free production increases during CPB [Barsacchi, 1992; Inal, 1994] and in cerebral ischaemia [Chow, 1994] suggests a possible neuroprotective role for free radical scavengers such as vitamins A and E. [Cavarocchi, 1986] The iron chelator deferoxamine (desferrioxamine) has been evaluated in 24 adult patients (12 controls, 12 treated) undergoing CPB for various cardiac operations. [Menasche, 1988] Deferoxamine was given both intravenously and as an additive to the cardioplegic solution. Polymorphonuclear neutrophils (PMNs) harvested from deferoxamine-treated patients produced significantly fewer superoxide radicals than those of control patients. It was concluded that deferoxamine-exposed PMNs had a decreased oxidative responsiveness, and that these results were consistent with the hypothesis that deferoxamine, by inhibiting iron-catalysed free radical production, may limit the free radical-mediated amplification of the inflammatory response to bypass and as such could be effective in reducing the harmful effects of extracorporeal circulation. To date no evaluation of any neuroprotective effect has been reported.

In light of experimental evidence indicating a role for excitatory amino acid neurotransmission in the pathogenesis of brain injury occurring during cardiac surgery with CPB and number of compounds have reached phase II clinical trials. Prior to the initial reports of the investigation presented in this thesis [Arrowsmith, 1996; 1997a], no other study of the use of glutamate antagonists in cardiac surgery had been published. A recently published report described the effects of dextromethorphan, a noncompetitive N-methyl-D-aspartate receptor antagonist, in 13 infants undergoing cardiac surgery. [Schmitt, 1997] Mild hemiparesis developed after operation in one child of each group, and severe encephalopathy in one of the placebo group. Sharp waves were recorded in postoperative continuous electroencephalography in all placebo (n=7) but only in 2/6 dextromethorphan treated children (p=0.02). Although children with dextromethorphan showed fewer abnormalities in electroencephalography
and MRI, dissimilarities of the treatment groups by chance diminished conclusions to possible protective effects of dextromethorphan.

Numerous agents are currently being evaluated in stroke, epilepsy, head injury, subarachnoid haemorrhage, and cardiac arrest. Agents currently under investigation in cardiac surgery include; chlormethiazole, lignocaine, nicorandil and magnesium sulphate.

1.7. Summary

Neurological complications are now the leading cause of mortality and significant morbidity after cardiac surgery. The use of new techniques, the introduction of more marginal indications for surgery, and increased public expectation has lead to an increase in the average age of cardiac surgical patients and an increased incidence of repeat procedures. With these changes have come an increased risk of neurological complications. The likelihood of perioperative stroke varies between one and 5% in most published series and is dependent on a multitude of risk factors. Of these factors, patient age, aortic atheroma, symptomatic cerebrovascular disease, diabetes mellitus and the type of surgery appear to be most important. In contrast, cognitive or neuropsychological deterioration after cardiac surgery is far more common affecting as many as 80% of patients a few days after surgery and persisting in a third of patients. Recent studies, however, suggest that the incidence of both early and late cognitive dysfunction has decreased.

The recognition that certain equipment and practices, as well as patient factors, contribute to neurological morbidity has prompted 'neuroprotective' interventions many of which have been shown to improve outcome. Although it is undoubtedly true that prevention is better than cure, a small number of patients will inevitably sustain a cerebral injury during otherwise successful cardiac surgery. Pharmacological neuroprotection may offer some of these unfortunate patients an improved outcome.
The heart of darkness

Russian President Boris Yeltsin’s delayed operation (Medical Team Decides On Yeltsin Surgery Later This Fall - Sept. 26) highlights a dire dilemma: If he does not undergo heart surgery, he will remain physically incapacitated, and if he does, he may become mentally incapacitated.

More than half the patients undergoing cardiac surgery develop problems of concentration, memory and mental speed, which remain for a year in up to a third of the cases.

A frightening thought is a mentally impaired Mr. Yeltsin with renewed energy to act out his impulses.

We hope for the best, for his sake and Russia’s.

Vladimir Hachinski, MD
Richard and Beryl Ivey Professor,
Chairman, Department of Clinical Neurological Sciences
University of Western Ontario, London
Chapter 2

The pathophysiology of cerebral ischaemia during cardiopulmonary bypass

"One digs one's grave with a fork and a cigarette"

A. J. Dunning, 1993
2.1. Introduction

This chapter will review the normal control of cerebral blood flow (CBF) and its perturbations under the influence of pharmacological agents and during cardiac surgery. It will then present modern ideas about the biochemical mechanisms of neuronal death due to ischaemia, as a prelude to a review of possible neuroprotective medication that might be applied to the clinical situation.

2.2. Cerebral blood flow

This section will review human cerebrovascular anatomy, and describe the physiological factors that control cerebral blood flow, methods of measuring cerebral blood flow, and the effects of common anaesthetics and vasoactive agents on CBF. The section concludes with a discussion about CBF during CPB.

2.2.1. Cerebrovascular anatomy

Blood flow to the normal human brain is supplied by the paired internal carotid and vertebral arteries. The common carotid artery arises directly from the aortic arch on the left and from the innominate branch of the aorta on the right. After ascending within the neck, to the level of the upper border of the thyroid cartilage, the vessel divides into the internal and external carotid arteries. The internal carotid arteries then ascend to the base of the skull entering the cranial cavity through the carotid canal in the petrous temporal bone. The vertebral arteries are branches of the first parts of subclavian arteries, ascending through the foramina of the transverse processes of the upper six cervical vertebrae before entering the skull through the foramen magnum. After entering the cranial cavity, the four arteries anastomose on the inferior surface of the brain to form the circulus arteriosus - better known as the circle of Willis. (Figure 2.1)

The intracranial internal carotid artery has five branches; (i) The anterior cerebral artery (ACA); supplying all of the medial surface of the cerebral cortex as far back as the parieto-occipital sulcus, the "leg area" of the pre-central gyrus, and a strip of cerebral cortex on the adjoining lateral surface. The ACAs are joined to one another, across the midline, by the anterior communicating artery (ACoA) (ii) The middle cerebral artery (MCA); supplying the entire lateral surface of the cerebral hemisphere with the exception of the part supplied by the ACA, and the occipital pole and inferolateral surface of the hemisphere, which are supplied by the posterior cerebral artery (PCA). (iii) The choroidal artery; supplying the choroidal plexus. (iv) The ophthalmic artery; supplying the contents of the orbit. (v) The posterior communicating artery (PCoA); which anastomoses with the ipsilateral PCA.
The vertebral arteries ascend medially on the surface of the medulla oblongata giving off the posterior inferior cerebral arteries as well as branches to the meninges, spinal cord, and medulla oblongata. At the lower border of the pons, the vertebral arteries join to form the basilar artery. This gives off branches to the pons and the anterior, inferior and superior cerebellar arteries before dividing into the two PCAs at the upper border of the pons. The PCA supplies the inferolateral surface of the temporal lobe and the lateral and medial surfaces of the occipital lobe.

In the absence of occlusive cerebrovascular disease, little, if any, blood flows through the communicating arteries. If, however, blood flow through one, or more, of the supplying vessels is reduced or interrupted (typically by atheromatous disease) the anterior and/or posterior communicating arteries may act as a conduit for collateral circulation. Anastomotic channels also exist between the external carotid and vertebral arteries (via the occipital artery) and the external and internal carotid arteries (via the superficial temporal and ophthalmic arteries).

It should be borne in mind that this ‘textbook’ description of the cerebral circulation, particularly that of the circle of Willis, is subject to enormous anatomical variation (e.g. congenital absence of one or more of the communicating arteries). Until recently, these variations could only be demonstrated at autopsy or by using angiography. The introduction of transcranial Doppler (TCD) ultrasonography has provided, for the first time, a simple, safe and non-invasive means of assessing the cerebral circulation and its capacity for collateral circulation.

Figure 2.1: The basal cerebral arteries and the circle and Willis. ACA=anterior cerebral artery, ACoA=anterior communicating artery, MCA=middle cerebral artery, ICA=internal carotid artery, BA=basilar artery, PCA=posterior cerebral artery, PCoA=posterior communicating artery, VA=vertebral arteries.
2.2.2. Regulation of cerebral blood flow

Under normal conditions, the carotid arteries supply the majority of cerebral blood flow (CBF). Cerebral perfusion pressure (CPP), defined as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP), is an important factor contributing to perfusion of the brain.

Since normal ICP, in the supine position, varies very little (10-15 mmHg / 1.3-2.0 kPa), MAP is the major factor affecting CPP. CBF, however, is maintained at a relatively constant level over a wide range of perfusion pressures (50-150 mmHg / 6.6-19.7 kPa) by a homeostatic mechanism termed autoregulation. In the conscious, normotensive, and normothermic adult human, a fall in MAP to below 50 mmHg is associated with a fall in CBF and the potential for cerebral ischaemia. (Table 2.1) Under such conditions those areas of the brain that lie on the boundary zones of the major cerebral arteries, are particularly vulnerable to ischaemia and hypoxia. Of these so-called ‘watershed’ areas, the parieto-occipital cortex, which lies at the boundary of the territories supplied by all three cerebral arteries, is the most vulnerable. [Taylor, 1993]

<table>
<thead>
<tr>
<th>CBF (ml/100g/min)</th>
<th>Consequence(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Normal perfusion</td>
</tr>
<tr>
<td>20</td>
<td>EEG: slowing, reduced frequency, increased amplitude</td>
</tr>
<tr>
<td>15</td>
<td>EEG: flat. Threshold of electrical failure</td>
</tr>
<tr>
<td>10</td>
<td>Lactic acidosis, failure of ionic pumps. Threshold of irreversible tissue damage</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Increased extracellular potassium and calcium. ECG: Anoxic depolarisation</td>
</tr>
</tbody>
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Table 2.1: Threshold values of cerebral blood flow (CBF) [O’Sullivan; 1989]

Autoregulation is the ability of a vascular bed to alter its impedance in response changes in perfusion pressure such that flow remains relatively constant. (Figure 2.2) The blood flow to many organs, including the brain, heart, and kidneys, is controlled by autoregulation. In the conscious, normotensive and normothermic adult human, CBF remains at about 50 ml/100g/min when perfusion pressures are in the range of 50-150 mmHg. The precise mechanisms of autoregulation are not fully understood. Although both adrenergic and cholinergic nerves innervate intracranial and extracranial blood vessels, it is not thought that the autonomic nervous system exerts any significant control of CBF. It is, however, known that autoregulation may be impaired by certain pathological conditions (such as trauma, cerebrovascular disease, hypertension, hypoxia and tumours) and because of pharmacological intervention, particularly with inhalational and intravenous anaesthetic agents. Whether or not autonomic neuronal control becomes important in these circumstances remains controversial. When autoregulation is impaired, CBF is passively dependent upon CPP.
Figure 2.2: Idealised relationship of cerebral blood flow (CBF) to varying mean arterial pressure and the arterial partial pressure of carbon dioxide (PaCO₂) and oxygen (PaO₂). When one variable is altered, the other two remain stable at normal values.

Although subject to regional variability, the brain, as a whole, has a high rate of aerobic metabolism. The absence of any significant oxygen reserve and a minimal capacity for anaerobic metabolism leaves the brain reliant on a continuous supply of oxygen and metabolic substrates for normal function. The local release of vasodilatory metabolites, particularly H⁺, is believed to be responsible for the normally close relationship between cerebral metabolic rate for oxygen (CMRO₂) and CBF. With increasing hypothermia, there is an exponential fall in the rate of all energy dependent cellular processes. The fall in CMRO₂ that occurs in hypothermia is mirrored by a fall in CBF.

Extrinsic chemical control of CBF is mediated by the arterial partial pressures of oxygen (PaO₂) and carbon dioxide (PaCO₂). Of these, PaCO₂ is the most potent determinant of CBF. The relationship between PaCO₂ and CBF is almost linear for PaCO₂ between 20 and 80 mmHg (2.6-10.5 kPa) with a 4% rise in CBF for each 1mmHg increase in PaCO₂. At 80 mmHg maximal cerebral vasodilation is thought to occur and further increases in PaCO₂ cause little further increase in CBF. Small changes in PaO₂ do not influence CBF to any significant degree. CBF, however, does increase in the presence of severe arterial hypoxia (PaO₂ <50 mmHg). [Govier, 1988]

2.2.3. Methods for the measurement of cerebral blood flow

The anatomical complexity and inaccessibility of the cerebral vasculature hampers all attempts to measure CBF. It is not possible to use conventional methods such as flow meters and timed venous outflow. Consequently, most methods for measuring CBF are invasive. The prob-
lem is further compounded by the uncertain contribution to CBF made by the extracranial circulation and the regulation of that contribution. As already mentioned, there is a wide variation in regional cerebral blood flow (rCBF) so that measurements of global CBF may fail to detect local changes in flow.

At first sight, the simplest way to monitor CBF would be to use the Fick principle. Theoretically, under conditions of constant arterial oxygen saturation ($S_{aO_2}$) and CMRO$_2$, the jugular venous oxygen saturation ($S_02$) should reflect global CBF because:

$$\text{CBF} = \frac{\text{CMRO}_2}{(S_{aO_2} - S_02)}$$

Unfortunately, $S_02$ values have been found not correlate with measurements of CBF or carotid arterial pressure. [Perry, 1970] Furthermore, neurological damage has been reported with $S_02 >60\%$. [Larsen, 1967]

The first clinically applicable method for measuring CBF, based on the Fick principle, employed nitrous oxide ($N_2O$) as an inert, diffusible tracer gas. [Kety, 1945] Multiple arterial and jugular bulb blood samples are required to follow the uptake and release (after saturation) of the tracer gas from brain tissue. The technique gives an average blood flow for the brain as a whole and the cerebral metabolic rates for oxygen (CMRO$_2$) and glucose (CMRG Gl) can be calculated from the arteriovenous oxygen and glucose differences. Typical normal values for CBF and CMRO$_2$ given by this technique are 45-55 ml/100g/min and 3-3.5 ml/100g/min respectively.

The rate of washout of a radioactive tracer gas (either $^{133}$Xenon or $^{55}$Krypton) injected into the carotid artery was an important modification to the Kety-Schmidt method. Using the technique CBF is calculated from the rate of isotope clearance detected with extracranial scintillation (gamma ray) counters. Isotope washout follows a dual compartment, exponential pattern reflecting differences in white and grey matter metabolic rate and blood flow. Values for CBF produced by this method have been found to correlate well with the inhaled $N_2O$ method but unlike the $N_2O$ method, isotope washout provides information about rCBF. The inability to sample regional venous blood, however, makes it impossible to calculate regional CMRO$_2$ and CMRG Gl. $^{133}$Xe, unlike $^{55}$Kr, undergoes rapid first past elimination through the lungs. This reduces its effective (biological) half-life from 5.3 days to 5 minutes, reducing patient exposure to gamma radiation and permitting repeated CBF measurements. Typical normal values for white and grey matter rCBF given by this technique are 20 and 80 ml/100g/min respectively.

The isotope washout technique, unfortunately, does have limitations. Firstly, areas of brain with no blood flow tend to be 'looked through' so that the gamma counter 'sees' only surrounding areas that have normal blood flow. Secondly, extracranial sources of gamma rays (e.g. the scalp and skull) tend to produce a 5-7% overestimate of CBF. Thirdly, the most accurate
measurement of CBF (so-called CBF\(_{15}\)) requires a relatively constant flow for at least 15 minutes. Measurements, therefore, do not reflect rapidly changing CBF. An alternate method; using the initial slope index (ISI), is more suited to situations where CBF is subject to medium term fluctuations. Fortunately, there is a near linear relationship between ISI and CBF\(_{15}\). Finally, both temperature and haematocrit effect the partition coefficient of xenon. This must be taken into account when calculating CBF during CPB. [Venn, 1988; 1989]

Despite many practical and methodological problems, the measurement of CBF using the \(^{133}\)Xe-clearance method remains the 'gold standard' with which newer methods are compared.

2.2.4. Pharmacological influences on cerebral blood flow

Many drugs are known to influence both CBF and CMRO\(_2\). It is appropriate, therefore, to review those agents commonly prescribed to the cardiac surgical population and agents used during CABS.

All of the inhalational anaesthetics share the ability to produce cerebral vasodilatation and impair cerebral autoregulation in a dose-related fashion. There is a non-linear relationship between anaesthetic concentration and the associated increase in CBF and reduction in CMRO\(_2\). The increase in cerebral blood volume (CBV) that accompanies the increase in CBF causes an increase in ICP. Even at quite modest concentrations (i.e. 1 x minimal alveolar concentration; MAC = 0.8% halothane, 1.2% isoflurane, 1.6% enflurane) CBF may become entirely pressure dependent. In this respect, halothane is more potent than either enflurane or isoflurane. Enflurane, however, has the greatest influence on CMRO\(_2\); an end expiratory concentration of 1 MAC (1.6%) producing a 25-35% reduction. At very much higher concentrations, enflurane may induce seizures, which markedly increase CMRO\(_2\). The observation that the increases in CBF and ICP produced by isoflurane may be reversed by a moderate degree of hypocapnia has lead to widespread use of the agent in neuroanaesthesia. Nitrous oxide probably acts in a similar way, albeit to a lesser extent. At present, there are limited data on the effects of the recently introduced agents, sevoflurane and desflurane. It is likely, however, that both will share the properties of the established agents.

The actions of intravenous anaesthetics differ markedly from those of the inhalational agents. By reducing neurophysiological function, the barbiturates (e.g. thiopentone sodium) are the most potent depressants of CMRO\(_2\). The reduction in CMRO\(_2\) is mirrored by reductions in both CBF and ICP. In addition, global cerebral depression produces a profound, centrally mediated fall in MAP.

At normocapnia, the opioid fentanyl citrate produces little change in either CBF or CMRO\(_2\). In combination with droperidol (so-called neurolept anaesthesia), fentanyl produces a 40% reduction in CBF and a 15-20% reduction in CMRO\(_2\). Droperidol alone appears to reduce CBF
to the same extent but has little effect on CMRO₂. Morphine in combination with N₂O, however, does produce a decrease in both parameters. Despite having minimal effects on MAP and CPP, etomidate, at induction doses (0.1-0.3 mg/kg), reduces CBF whilst increasing both ICP and CMRO₂. The benzodiazepines (e.g. lorazepam, midazolam and diazepam) produce a coupled fall in both CBF and CMRO₂. Midazolam is reported to increase cerebrovascular resistance.

As an anaesthetic induction agent, ketamine is unique. Its actions as chronotrope, inotrope and peripheral vasodilator induce marked (>25%) increases in heart rate, cardiac output and MAP. This is accompanied by a 50% increase in CBF, a 20% increase in CMRO₂ and a rise in ICP that reduces CPP despite the increase in MAP.

The non-depolarising, neuromuscular blocking drugs (e.g. curare, pancuronium bromide, and atracurium besylate) have little direct effect on the cerebral circulation. The rise in ICP that transiently follows administration of curare may be related to the release of histamine.

The effects of α and β adrenergic agonists and antagonists, and ganglion blockers (e.g. trimetaphan) are not fully understood. It is likely that they have little or no direct effect on the cerebral circulation unless changes in MAP exceed the capacity of autoregulation. In the presence of severe hypotension, however, the administration of adrenaline, noradrenaline or isoprenaline can restore CPP and thus increase CBF.

The potent vascular smooth muscle relaxants sodium nitroprusside and glyceryl trinitrate increase CBF and ICP if MAP is maintained. [Turner, 1977]

2.3. Cerebral blood flow during cardiopulmonary bypass

In recent years, researchers have repeatedly attempted to answer a number of fundamental questions regarding the conduct of CPB and its effect on cerebral blood flow, cerebral metabolism and neurological morbidity. For a considerable time, many issues remained unresolved; does cerebral autoregulation take place during CPB? What is the lowest arterial pressure that can be safely tolerated by the brain during CPB? Does the perfusion flow pattern (i.e. pulsatile vs. non-pulsatile) influence CBF? Does the acid-base management strategy employed during hypothermic CPB influence the cerebral circulation? What other factors, operating during CPB, adversely influence cerebral outcome?

Early studies indicated that low arterial pressures during CPB were associated with a higher incidence of cerebral complications [Branthwaite, 1973; Javid, 1969] Based on the not unreasonable assumption that postoperative cerebral dysfunction was secondary to inadequate CBF it was concluded that mean arterial pressure should be maintained at levels above 50 mmHg during CPB. [Tufo, 1970; Stockard, 1973] Subsequent prospective studies, however, failed to show a correlation between perfusion pressure and adverse neurological outcome. Moreover,
perfusion pressures of less than 50mmHg were found to be neither a determinant nor reliable predictor of post-operative cerebral dysfunction. [Kolkka, 1980; Slogoff, 1982]

When comparing studies of CBF measured during cardiac surgery seemingly minor differences in methodology may make useful interpretation and comparison of studies very difficult. Henriksen and associates, using the $^{133}$Xe-clearance technique, measured CBF in 29 patients before, during and after hypothermic CPB. [Henriksen, 1983] An initial fall in CBF at the onset of CPB, which correlated with a fall in MAP to below 50 mmHg, was demonstrated in 9 patients. During steady state, hypothermic extracorporeal circulation however, mean CBF unexpectedly increased by 67% from a pre-CPB level of 38 ml/100g/min to 64ml/100g/min. After rewarming, mean CBF fell to 42 ml/100g/min. The investigators stated that “reactive hyperemia certainly indicates that something is or was wrong” suggesting that hyperaemic border zones around embolic cerebral microinfarcts were the reason for the observed brain hyperperfusion.

Govier and associates studied the influence of MAP, systemic blood flow, PaCO$_2$, temperature and haemoglobin concentration on regional CBF ($^{133}$Xe) during non-pulsatile CPB in patients undergoing CABS. [Govier, 1984] There was a significant (55%) decrease in rCBF during CPB and of the factors examined, only temperature and PaCO$_2$ had any significant influence on CBF. Variations in MAP and systemic flow rate during CPB were not associated with any clinical affects. It was concluded that cerebral autoregulation, during CPB with moderate hypothermia, was preserved at mean perfusion pressures as low as 30 mmHg.

Lundar and associates, using electromagnetic probes, measured internal carotid artery (ICA) blood flow in five patients undergoing CPB. [Lundar, 1985] After an initial fall at the inception of CPB, a sustained increase (50-100% above pre-bypass level) in ICA blood flow was demonstrated throughout the rest of CPB. ICA blood flow displayed a pressure-passive flow pattern. The investigators concluded that either cerebral autoregulation was impaired or that the cerebral perfusion pressure was below the lower limit of the autoregulatory range.

Johnsson and associates, using the $^{133}$Xe-clearance technique, measured CBF in 10 men during CABS. [Johnsson, 1987] During CPB mean CBF remained unchanged compared with pre-bypass levels without evidence of cerebral hyperaemia or impaired autoregulation.

The apparent discrepancy between the findings of these studies is, on first reading, rather difficult to explain. If cerebral autoregulation is preserved during hypothermic CPB, it would seem reasonable that the expected fall in CMRO$_2$ would be mirrored by a fall in CBF. Cerebral hyperperfusion, on the other hand, would suggest that some disruption of cerebral autoregulation has taken place. Two factors, however, explain the disparity. Firstly, patients in Henriksen’s study population were given enflurane (a potent cerebral vasodilator) prior to CPB. Secondly, in both Henriksen’s and Lundar’s studies blood gas measurements were
corrected to estimated brain temperature whereas no such correction was made in the studies of Govier and Johnsson. The reason for this effect and the continuing controversy surrounding acid-base management during CPB is further discussed below.

The dissociation of water into $H^+$ and $OH^-$ ions is profoundly affected by temperature. At 25°C, the pH of neutral water is 7.0, whereas neutrality at 0°C is pH 7.425 and at 37°C is pH 6.796. (i.e. $\Delta pH/°C = -0.017$) Not surprisingly when a sample of whole blood is held in a gastight syringe (i.e. at constant $CO_2$ content), there is a predictable relationship between temperature and pH. (ApH/°C = -0.0147) The increase in pH that occurs as temperature falls is due, in part, to the increased solubility of gases (PaO$_2$ and PaCO$_2$ therefore fall) but also, to alterations in the dissociation constant (pK) of the bicarbonate and protein-bound imidazole buffer systems. [Rahn, 1975]

When temperature corrected blood gas measurements are used, hypothermic patients appear hypocapnic and alkalotic. For over 25 years anaesthetists induced 'normocapnia' (pH=7.42) during CPB ('pH-stat' management) on the grounds that hypothermia-induced alkalosis (hypocapnia) increased cardiac irritability and reduced cerebral blood flow. The practice persisted despite a report suggesting that the incidence of spontaneous ventricular fibrillation was increased. [Virtue, 1955] The suggestion that hypocapnia during hypothermia was a 'normal' physiological response prompted a rethink of this strategy. [White, 1981]

In the normal human, as in other endotherms, the pH of arterial blood is a spectrum rather than a sharply defined value. [White, 1981] Arterial pH represents heterogeneity of pHs depending on the temperature of the tissue perfused. For example, blood perfusing the skin may cool from an average core temperature of 37°C (pH 7.4) to below 25°C (pH 7.58), whereas blood perfusing exercising skeletal muscle may be warmed to 41°C (pH 7.34). In hibernating mammals, however, arterial pH is maintained near the typical normothermic value of 7.4 while body temperature falls to around 5°C. By contrast, in organisms whose body temperature is a function of environmental temperature (ectotherms) there is a direct relationship between body temperature and pH. The slope of this relationship is similar to both the in vitro behaviour of blood and the neutral pH of water. [Rahn, 1975] Across a great spectrum of temperatures there is near constancy of $[OH^-]/[H^+]$ such that there is constant blood alkalinity relative to the pH of neutrality of water.

The discovery that the charge state and thus buffering capacity of proteins is highly dependent on the degree of dissociation of peptide-linked α-histidine-imidazole groups gave credibility to the idea that the true reference value is not any fixed pH but rather the point of electrochemical neutrality (i.e. pH=pOH) [Reeves, 1969; 1972; Rahn, 1975; Reeves, 1976a; Malan, 1976; Reeves, 1976b; 1977; 1978] The use of 'a-stat' management results in preservation of cerebral autoregulation and several other metabolic advantages and has become virtually universal in hypothermic CPB.
2.4. Cerebral ischaemia, excitotoxicity and neurprotection

In recent years, detailed investigation of the pathophysiological processes that culminate in neuronal death has revealed a number of potential therapeutic opportunities. Central to our understanding of these processes and our ability to manipulate them has been the wide acceptance that (i) amino acids are important neurotransmitters within the central nervous system (CNS) of both vertebrates and invertebrates, and (ii) the excessive release of excitatory amino acids (EAAs) in response to brain injury is neurotoxic. It is now apparent that EAAs play an important role in the natural history of neuronal death secondary to hypoxia/ischaemia, hypoglycaemia and trauma. In addition there is evidence emerging for a role in several other neuropathological conditions including seizure disorders, Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, Huntington's chorea and the acquired immunodeficiency syndrome (AIDS).

Considerable interest has been focused on pharmacological interventions in two areas; (1) the reduction of the toxic effects of EAAs and the associated rise in levels of intracellular calcium, and (2) the reduction of the cytotoxic effects of secondary mediators of inflammation liberated in sustained cerebral ischaemia.

The following section will present some of the historical aspects of the discovery of amino acid neurotransmission - focusing in detail on glutamate, glutamate receptors, and the concept of excitatory amino acid neurotoxicity - and, finally, evidence for the efficacy of pharmacological modification of this transmitter system in models of neuronal ischaemia.

2.4.1. Global versus focal ischaemia

In the study of cerebral blood flow and ischaemia, we must first make a distinction between global and focal ischaemia. Broadly speaking the extent and severity of the resulting tissue damage is dependent upon; the degree and duration of ischaemia, the degree of mismatch between substrate delivery and neuronal metabolic requirements, and the innate vulnerability of the affected cell populations.

In global ischaemia (for example during cardiac arrest) blood flow to the entire brain is either markedly reduced or absent. In contrast, focal ischaemia effects only tissues supplied by a particular cerebral artery whilst blood flow to areas in other vascular territories remains virtually intact. The resulting 'stroke' lesion can be thought of as consisting of a densely ischaemic core or focus surrounded by less densely ischaemia perifocal areas - the 'penumbra'. Cells within the core are ultimately fated because of inadequate blood supply whereas collateral vessels may perfuse tissues in the penumbra and remain viable for several hours after the onset of ischaemia. Penumbral tissues, however, are 'at risk' as in time the ischaemic focus invariably grows in size as perifocal tissues are recruited to the infarction process.
The observation that this recruitment process takes place over a period of hours and possibly days implies that there should exist some sort of 'window' for therapeutic intervention. In theory it should be possible to protect or rescue penumbral tissues by the timely restoration of blood flow and/or the pharmacological inhibition of their recruitment into the infarction process. [Siesjo, 1984; 1992a; 1992b]

### 2.4.2. Amino acids as neurotransmitters?

The CNS contains high concentrations of amino acids, in particular glutamate, glycine and gamma aminobutyrate (GABA). Despite early reluctance to accept the concept that these simple precursors of protein synthesis could act as neurotransmitters, current evidence overwhelmingly suggests that these, and probably other amino acids, do indeed have this function. The fact that amino acids are ubiquitous - being involved in many metabolic pathways - made it very difficult to make a convincing distinction between a pool of putative neurotransmitters and other metabolic pools. (Figure 2.3) Furthermore, the enzymes associated with amino acid metabolism are found in most cell lines and are by no means specific to transmitter-synthesising neurons. Direct measurements of neuronal amino acid release were further hampered by the fact that these compounds are both taken up and released by glial cells as well as neurons.

![Figure 2.3: The metabolism of transmitter amino acids in the brain. GS=glutamine synthetase, AST=aspartate transaminase, GAD=glutamate decarboxylase, ABT=aminobutyrate transaminase, SSD=succinate semialdehyde dehydrogenase, GD=glutamate dehydrogenase, CoA=coenzyme A.](image-url)
The finding that glutamate and GABA function as excitatory and inhibitory transmitters respectively at the neuromuscular junction of various insects and crustacea lent support to the idea that they might have similar functions in the mammalian brain. Experimental support has been gained principally through the study of the action of antagonists of these amino acids at certain well-defined synapses. The dicarboxylic acids (e.g. glutamate and aspartate) are excitatory whereas the mono carboxylic \( \alpha \)-amino acids (e.g. GABA, glycine, \( \beta \)-alanine and taurine) are inhibitory.

![Chemical structures of amino acids](image)

**Figure 2.4:** The chemical structures of gamma amino butyric acid (GABA), glycine, glutamate, aspartate and N-methyl-D-aspartate (NMDA).

### 2.4.2.1. Gamma (\( \gamma \)) aminobutyric acid (GABA)

Formed by the decarboxylation of glutamate (Figure 2.4), GABA was first identified as a unique chemical constituent of brain tissue in 1950. It is found in particularly high concentrations (10 mmol/g tissue) in the nigrostriatal system and at lower concentrations (2-5 mmol/g) throughout the grey matter. Only trace amounts are found in other mammalian tissues.

GABA-ergic neurons have an active GABA uptake system, and it is this, rather than GABA transaminase, which removes GABA from the synaptic cleft after it has been released. GABA is thought to act as an inhibitory transmitter in many different CNS pathways including the cerebellum, cerebral cortex, olfactory bulb, cuneate nucleus, hippocampus and striatum. In most situations GABA is found in short interneurons, the only long GABA-ergic tracts being those running to the cerebellum and striatum. The widespread distribution of GABA, and the fact that virtually all neurons are sensitive to its inhibitory effect, suggests that its function is ubiquitous in the brain.

Two distinct types of receptors for GABA have been postulated in vertebrates. The GABA\(_A\) receptor resembles, but is not identical to, the inhibitory GABA receptor of invertebrates. Electrophysiological studies of GABA on CNS neurons have shown that its post-synaptic inhibitory effect depends on an increase in the chloride permeability of the post-synaptic membrane, which has the effect of reducing the depolarisation produced by excitatory transmitter action. The action of GABA at post-synaptic GABA\(_A\) receptors is mimicked by muscimol, com-
petitively inhibited by the convulsant bicuculline and potentiated by benzodiazepines, barbiturates and certain steroids. It is believed that benzodiazepines exert their powerful sedative and anxiolytic effects via a high affinity accessory GABA\(_A\) site, which facilitates GABA binding and enhances its pharmacological effects. Interestingly GABA\(_A\) receptors are found in a variety of peripheral neurons (e.g. autonomic ganglia) where GABA has no transmitter role. At these sites, however, there is no potentiating effect of benzodiazepines. To date useful therapeutic effects have not been obtained from the use of GABA\(_A\) agonists, inhibitors of GABA reuptake or agents that interfere with GABA synthesis or degradation.

The observation that GABA exerts a modest inhibitory effect on pre-synaptic nerve terminals at many sites in the brain and peripheral nervous system (e.g. dopamine releasing terminals in the striatum, peripheral sympathetic nervous system, etc.) led to the conclusion that a GABA-like substance might prove to be affective in controlling epilepsy and other convulsive disorders. Since GABA itself fails to penetrate the blood brain barrier (BBB), a search was begun for more lipophilic GABA analogues. One such substance is the p-chlorophenyl derivative of GABA (baclofen) which was introduced in 1972. Detailed comparisons of the actions of GABA and baclofen, however, revealed important differences. Baclofen, like GABA, inhibits the release of transmitter from many types of nerve terminal but, unlike GABA, has little post-synaptic inhibitory effect. Furthermore, the actions of baclofen are not antagonised by bicuculline. Other GABA-like substances (e.g. muscimol) produce the post-synaptic, bicuculline-sensitive effects of GABA, but not the pre-synaptic, bicuculline-resistant effects. These latter findings are characteristic of GABA\(_B\) receptors. The ionic mechanism underlying the GABA\(_B\) effects is still uncertain although recent studies have shown that these receptors, in some neurons, act to inhibit pre-synaptic voltage-sensitive calcium channels (VSCC) - which may account for the reduction in transmitter release - and to activate post-synaptic potassium channels. Evidence of a physiological role of GABA\(_B\) receptors in the brain is likely to remain lacking until selective GABA\(_B\) antagonists are developed. [Rang, 1987]

### 2.4.2.2. Glycine

This amino acid is present in particularly high concentration (5 mmol/g tissue) in the ventral-quadrant grey matter of the mammalian spinal cord. Applied iontophoretically to motor neurons or interneurons it produces an inhibitory hyperpolarisation that is indistinguishable from the inhibitory synapse response. Most significantly, the convulsant strychnine blocks both the synaptic inhibitory response and the response to glycine. This, together with direct measurements of glycine release in response to nerve stimulation, provides strong evidence for its physiological role as a transmitter. [Rang, 1987] With the exception of experiments with strychnine and strychnine-like antagonists, there has been little pharmacological manipulation of neuronal glycine release in the spinal cord. The discovery that glycine acts as a facili-
tative agonist at one type of glutamate receptor has, however, offered therapeutic possibilities. (See below)

2.4.2.3. Glutamate

Glutamic acid is a natural component of proteins. Some 15% of most food is protein of which 20% is glutamic acid. Of the 40 g of protein, ingested daily by the average adult, 1-10% is in the form of free glutamate. Foods such as mushrooms and tomatoes have a high endogenous free glutamate concentration. It has long been known that monosodium glutamate (MSG) possesses a unique flavour enhancing property, probably due to its ability to directly excite neurons. In 1908, it was shown that MSG was the active ingredient in the seaweed *Laminaria Japonica* that had been used for centuries as a flavour enhancer in oriental cooking. Although regarded as safe by the US Food and Drug Administration, MSG has been implicated in the so-called Chinese Restaurant Syndrome, first described in 1968. [Reif-Lehrer, 1983]

Glutamic acid is the most abundant amino acid in the adult CNS, with the highest concentrations being found in the nucleus accumbens, cerebral cortex, cerebellum, globus pallidus, diencephalon and hippocampus. Observations that amino acids could produce excitation were first made over four decades ago. When injected directly into the brain, both aspartate and glutamate produce seizures. [Hayashi, 1954] The introduction of microiontophoretic techniques in the late 1950s allowed the demonstration that both amino acids had a non-specific excitatory action upon single spinal interneurons and motoneurons in the cat. [Curtis, 1959; 1960] The subsequent discovery of amino acid containing vesicles, several uptake mechanisms for amino acids in both neurons and glia [Balcar, 1972; Henn, 1974] and membrane binding sites for amino acids added to the weight of evidence supporting a central neurotransmitter role for glutamate and other amino acids.

2.4.3. Glutamate receptors

Three glutamate receptor subtypes were originally described, each being named after a specific agonist to which it is differentially sensitive, N-methyl-D-aspartic acid (NMDA - a synthetic analogue of aspartic acid), quisqualic acid (QUIS) and kainic acid (KAIN - an antihelminthic agent). [Watkins, 1981; 1987] More recently these receptors have been further classified into five heterogeneous categories depending on the agonist that most effectively activates them; high- and low-affinity KAIN, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), NMDA and QUIS. (Table 2.2)
The first four subtypes are 'ionotropic', acting as ion channel gates whereas the QUIS subtype, termed the 'metabotropic glutamate receptor' (mGluR), is linked via G-proteins to either adenosine or phosphoinositide metabolism. At least eight mGluR subtypes have been described. In addition, it appears that there is a receptor that mediates the synaptic depressant actions of L-2-amino-4-phosphonobutyrate (AP4 or APB) a phosphono-amino acid analogue of glutamate. It is likely, therefore, that the classification will require further modification.

The first glutamate receptor subunits were cloned in 1989 [Hollmann, 1989] and since that time ionotropic receptor subunits have been cloned faster than they can be definitively named. Genes for all EAA receptors have now been identified. [Gasic, 1992; Hollmann, 1994] The GluR1, GluR2, GluR3 and GluR4 subunits exhibit properties akin to those of the native AMPA receptor; the GluR5, GluR6, GluR7, KA-1 and KA-2 subunits may be components of the high affinity KAIN receptors; and the NMDAR1, NMDAR2A, NMDAR2B, NMDAR2C and NMDARD subunits are probably components of the NMDA receptors. [Choi, 1992]

2.4.3.1. N-methyl-D-aspartate (NMDA) receptors

Until quite recently the NMDA, ionotropic receptor has been the most actively studied of the EAA receptors. NMDA receptors are expressed widely throughout the vertebrate CNS and are believed to participate in the majority (over 80%) of excitatory synapses in the brain and spinal cord. [Sakurai, 1991] The receptor appears to be responsible for mediating slow synaptic potentials with long time courses mediating synaptic plasticity in the hippocampus, neocortex, optic tectum and cerebellum. The phenomenon, characterised by the induction of sustained enhancement of synaptic responses following brief high frequency trains of stimuli, is referred as long term potentiation (LTP) and is thought to be involved in learning and memory. [Collingridge, 1989] The involvement of NMDA receptors in synaptic transmission has been characterised in detail in a number of brain systems. (Table 2.3)
Table 2.3: Distribution and functional importance of NMDA receptors in the central nervous system.

<table>
<thead>
<tr>
<th>Anatomical Site</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>Locomotion</td>
<td>Smith, 1988</td>
</tr>
<tr>
<td>Ventrobasal thalamus</td>
<td>Somatosensory evoked responses</td>
<td>Salt, 1989</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>High frequency stimulation</td>
<td>Collingridge, 1989</td>
</tr>
<tr>
<td>Dorsal lateral geniculate nucleus</td>
<td>Visual responses in geniculate relay neurons</td>
<td>Silito, 1990</td>
</tr>
<tr>
<td>Vestibular nuclei</td>
<td>Vestibular reflexes</td>
<td>de Waele, 1990</td>
</tr>
</tbody>
</table>

Composed of several subunits and recognition sites, the normal function of this remarkable receptor complex depends on a dynamic equilibrium between several facilitatory and inhibitory factors. (Figure 2.5) Both NMDA and quinolinic acid are selective agonists whilst ibotenic acid is a potent, but non-selective, agonist.

![The NMDA receptor ionophore complex.](image)

Figure 2.5: The NMDA receptor ionophore complex. PCP = phencyclidine, NMDA = N methyl D aspartate, ATP = adenosine triphosphate.

The action of agonists at the NMDA receptor is competitively antagonised by a plethora of substances. Although early antagonists, such as 3-amino-1-hydroxy-2-pyrrolidine (HA-966) and DL-α-aminoadipate (DLAA), were not particularly potent they were selective and did help to demonstrate the existence of multiple types of EAA receptor and their role in the mediation of synaptic excitation. They were soon superseded by more potent and highly selective antagonists, including the α-phosphono α-carboxylic amino acids, notably the D(-) enantiomers of 2-amino-5-phosphono-pentanoate (D-AP5) and 2-amino-5-phosphonoheptanoate (D-AP7). [Evans, 1982] Structurally more rigid forms of AP7 and AP5, namely 3-((±)2-carboxypiperazin-4-yl) propyl-1-phosphic acid (CPP) and 4-phosphono-methyl-2-piperidine carboxylic acid (CGS19755) respectively, are also potent competitive antagonists.

A variety of substances, with diverse chemical structures, share the ability to block responses to NMDA in a non-competitive manner. (Table 2.4) They are only selective in terms of their actions at EAA receptors as many have effects on other transmitter systems or ions channels.
Among these are the dissociative anaesthetics, phencyclidine (N-(1-phenylcyclohexyl) piperidine (PCP) and ketamine, and (±)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate (dizocilpine or MK801) which bind to a recognition site (the PCP site) inside the ion channel which is distinct from the Mg\(^{2+}\) binding site. Once bound the ligand may be trapped within the channel. Both Mg\(^{2+}\) and PCP block the passage of Na\(^+\) and Ca\(^{2+}\).

In the spinal cord, low concentrations of Mg\(^{2+}\) have been shown to block depolarisation induced by NMDA, but not KAIN or QUIS. [Ault, 1980] The ion channel associated with the receptor is gated by magnesium (Mg\(^{2+}\)) ions in a voltage-dependent fashion. This blockade is relieved when the membrane is depolarised. Further modulation of the NMDA receptor complex is mediated by other divalent cations (Co\(^{2+}\) and Zn\(^{2+}\), but not Ba\(^{2+}\), Cd\(^{2+}\) or Sr\(^{2+}\)), [Koh, 1996] polyamines (such as spermidine and ifenprodil) and glycine acting at separate recognition sites.

<table>
<thead>
<tr>
<th>Group</th>
<th>Agent(s)</th>
<th>Site of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino-phosphonic acids</td>
<td>APS, AP7, CPP, CPPene, CGS19755</td>
<td>Glutamate site</td>
</tr>
<tr>
<td>Arylcyclohexylamines</td>
<td>Ketamine, PCP, Tiletamine</td>
<td>PCP site</td>
</tr>
<tr>
<td>σ 'opioid' benzomorphans</td>
<td>Cyclazocine</td>
<td>PCP site</td>
</tr>
<tr>
<td></td>
<td>N-allylnormetazocine (SKP10047)</td>
<td></td>
</tr>
<tr>
<td>Dioxolanes</td>
<td>Etoxadrol, Dexoxadrol</td>
<td></td>
</tr>
<tr>
<td>Benz(f)isoquinolone</td>
<td>LY154045</td>
<td></td>
</tr>
<tr>
<td>Morphinans</td>
<td>Dextrophan, Dextromethorphan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Levorphanol</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Mecamylamine, Polymyxin B</td>
<td>PCP site</td>
</tr>
<tr>
<td></td>
<td>2-methyl-3,3-diphenyl-3-propanolamine (2MDP)</td>
<td>Glycine site</td>
</tr>
<tr>
<td></td>
<td>Dizocilpine (MK801)</td>
<td>Polyamine site</td>
</tr>
<tr>
<td></td>
<td>HA-966, Kynurenate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ifenprodil, SL82.0715</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.4: Antagonists acting at the NMDA receptor complex.

The discovery that the presence of glycine is mandatory for NMDA mediated channel activation and potentiates responses to NMDA agonists [Johnson, 1987; Johnson, 1993] gave way to the search for agents acting specifically on this receptor system. The pharmacology of the glycine modulatory site is quite different from that of the strychnine-sensitive inhibitory receptor found in the brain stem and spinal cord. The first compound, suggested on the basis of binding studies, to antagonise the actions of glycine at this site was kynurenic acid. Other antagonists include HA-966, the quinolinediones (CNQX and DNQX), 7-chlorokynurenic acid and 5,7-dichlorokynurenic acid.

### 2.4.3.2. Kainate receptors

Prior to cloning of the genes for these receptors there was doubt as to the existence of unique KAIN receptors. Kainate binding is most dense in the inner layers of the cerebral cortex. Al-
though the first AMPA receptor unit to be cloned was found responsive to kainate, a number of subsequently isolated non-NMDA subunit genes (KA-1 and KA-2) were found to have a unique sensitivity to kainate. When expressed with GluR5 and GluR6, these subunits form functional ion channels.

In the hippocampus, kainate binding is most dense in the stratum lucidum of CA3, in CA4 and the dentate gyrus. In the basal ganglia binding is most dense in the striatum. [Young, 1995] Agonists acting specifically at KAIN receptors include kainic, domoic and acromelic acids. These excitatory KAIN agonist effects are resistant to both NMDA and QUIS receptor antagonists whereas the majority of AMPA receptor antagonists reduce kainate induced excitation. (See below) Until the recent demonstration that 5-nitro-6,7,8,9-tetrahydro[g]indole-2,3-dione-3-oxime (NS-102) interacts selectively at low-affinity KAIN receptors, no specific KAIN antagonists had been available.

2.4.3.3. AMPA receptors

In contrast to NMDA receptor, AMPA receptors appear to be predominantly involved in fast synaptic transmission in the mammalian CNS and have been found in all EAA mediated pathways studied to date. Activation of the AMPA receptor allows the passage of Na+ and K+ through the associated ion channel. Unlike the NMDA receptor, the AMPA ionophore is neither significantly permeable to Ca2+ nor voltage-dependent. In terms of temporal characteristics of activation and the ionic specificity of the ion channel, the function of AMPA receptors is very similar to that of nicotinic cholinergic receptors at the neuromuscular junction.

Autoradiographic studies have shown that the highest densities of AMPA sites are in the outer layers of the cerebral cortex and the dentate gyrus and striatum radiatum of the CA1 region of the hippocampus. In the basal ganglia, AMPA binding is dense in the striatum, globus pallidus and subthalamic nucleus. [Young, 1995; Monaghan, 1984]

The development of potent non-NMDA receptor antagonists allowed the differentiation between NMDA and AMPA mediated responses. Early compounds, such as the quinoxalinediones (CNQX and NBQX) lacked specificity (presumably because KAIN and AMPA receptors share subunits) whereas more recently, (S)-2-amino-3-[3-(carboxymethoxy)-5-methylisoxazol-4-yl] propionic acid (S-AMOA) has been shown to antagonise AMPA induced excitation with less effect on KAIN induced excitations.

2.4.3.4. Quisqualate (metabotropic) receptors

The metabotropic receptors (mGluRs) are coupled to different effector systems through G-proteins and have not been as well characterised pharmacologically as the ionotropic (NMDA, AMPA and KAIN) receptors. [Pin, 1995] Both quisqualate and ibotenate are agonists
at both ionotropic EAA receptors and mGluRs whilst (1S,3R)-amino-1,3-cyclopentanedicarboxylate (ACPD) shows some selective affinity for certain mGluRs. Some texts refer to a separate ACPD receptor that is linked to inositol trisphosphate formation. [Teichberg, 1992] In recent years, a series of phenylglycine derivatives with differing actions at mGluRs have been described. Among these compounds, (S)-4-carboxy-3-hydrophenylglycine (4C3HPG) and (S)-α-methyl-4-carboxyphenyl-glycine (MCPG) are the most potent antagonists.

2.4.3.5. AP4 receptors

The 2-amino-4-phosphonobutyrate (AP4) receptor is very poorly characterised pharmacologically and, other than AP4 itself, few agonists have been described. The existence of the receptor was inferred from the observation that AP4 depresses certain excitatory pathways in both the brain and spinal cord. It is thought that activation of these pre-synaptic glutamate receptors (possibly a member of the mGluR family) blocks synaptic transmission although post-synaptic AP4 receptors have been described. The action of AP4 is blocked by the broad spectrum EAA antagonists, γ-D-glutamylglycine and cis-2,3-piperidinedicarboxylate.

2.4.4. Excitotoxicity

The first hint that amino acids were neurotoxic was provided by Lucas and Newhouse who described the destruction of neurons in the developing retina of infant mice following subcutaneous administration of glutamic acid [Lucas, 1957] In retrospect, an earlier observation that intravenous injection of glutamate and aspartate caused vomiting in dogs was probably an early indication that these two amino acids may mediate a central action. [Madden, 1945] More than a decade after Lucas' report, Olney discovered that newborn mice given an intraperitoneal injection of sodium glutamate grew to be extremely obese adults. [Olney, 1969] It was speculated that glutamate entered the brain in the posterior hypothalamus, where the blood brain barrier is absent, leading to swelling and death of cells in the arcuate nucleus. Destruction of the arcuate nucleus is associated with overeating.

The following year the potent excitatory properties of the antihelminth, kainic acid, applied electropherically to single neurons, were described. [Shinozaki, 1970] Kainic acid subsequently proved to be an extremely useful tool in the study EAA toxicity. Both systemic [Olney, 1974a; 1974b] and intracerebral [Schwarcz, 1977] administration of low doses of kainic acid were shown to be powerfully cytotoxic, acting against dendrites and neural somata whilst leaving axons and nerve terminals intact. This differential action, characteristic of EAA neurotoxicity, suggested a post-synaptic site of kainate action. Later work showed that kainate-like lesions could be produced with both ibotenic and quinolinic acids.
Neurodegeneration is known to follow ingestion of several naturally occurring environmental agents including the chickpea toxin, \( \beta \)-N-oxalylamino-L-alanine (causing neurolathyrism) and the false sago palm seed toxin, \( \beta \)-N-methyl-amino-L-alanine. [Olney, 1976] In 1987, more than 150 people presented with severe gastrointestinal and neurological symptoms after eating blue mussels cultivated in eastern Prince Edward Island, Canada. Domoic acid, an excitatory amino acid with kainate-like properties, was isolated from the mussels and identified as the responsible toxin. [Perl, 1990; Teitelbaum, 1990] Both contaminated mussel extract and domoic acid produced similar signs of toxicity when administered to rodents. [Iverson, 1989]

The wide distribution of EAAs in the CNS and the apparent ability of both endogenous and exogenous EAA agonists to attack and destroy neurons lead Olney to speculate on the possible role of EAAs in human neuropathological processes. Thus emerged the so-called 'excitotoxic' hypothesis.

The demonstration of distant dendrosomatic and axon sparing (excitotoxic) neuronal damage following KAIN induced seizures posed the question - is seizure related brain damage an excitotoxic process? That is; does sustained, repetitive depolarisation and repolarisation of axonal membranes interfere with cellular energy metabolism to the point that homeostatic EAA reuptake mechanisms are compromised? It has, therefore, been speculated that excitotoxicity may play a role in status epilepticus [Ben-Ari, 1979], Huntington's disease [Coyle, 1976; Beal, 1986] and Parkinson's disease. [Dawson, 1995]

More recently, considerable evidence has been accumulated for the role of excitotoxicity in neural injury following cerebral ischaemia/hypoxia. Using microdialysis measurements, Benveniste demonstrated that extracellular levels of glutamate were markedly (800%) increased in the rat hippocampus following 10 minutes of transient cerebral ischaemia [Benveniste, 1984] These findings were reproduced in a rat model of percussion-induced subdural haematoma. [Bullock, 1991] The observation that denervation of the vulnerable CA1 pyramidal layer of the hippocampus by lesioning glutamatergic afferents resulted in little or no ischaemic glutamate release suggested that glutamatergic input was essential for the development of ischaemia neuronal damage. [Benveniste, 1989]

Glutamate release during cerebral ischaemia has been demonstrated in several different species and brain regions: cortex (rat, cat, human), striatum (rat), hippocampus (rat, gerbil, rabbit), and thalamus (rat). What can be concluded from these studies is that;

- total glutamate release is dependent upon the duration of ischaemia,
- total glutamate release is dependent upon the severity of ischaemia,
- extracellular glutamate reaches a plateau level during irreversible ischaemia,
- glutamate release during ischaemia occurs in all species and brain regions examined,

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• hypothermia attenuates ischaemia-induced glutamate release,
• glutamate release is dependent upon cerebral blood flow, and
• brain regions tolerant to 20 minutes of transient ischaemia also release glutamate.

Although evidence for excitotoxicity in humans is sparse, there is little doubt that a variety of insults give rise to a rise in extracellular glutamate. Glutamate release in epilepsy was reported as long ago as 1985. [Olney, 1985] In a patient undergoing electrocortical mapping during tumour resection a microdialysis probe was implanted in a defined epileptic focus. [Carlson, 1992] During a spontaneous seizure, there were abrupt increases in aspartate, glutamate, glycine and serine, which returned to normal 4 minutes after the termination of the seizure. Sustained elevation in glutamate have been observed after head injury [Palmer, 1994] and aneurysmal subarachnoid haemorrhage (SAH). [Säveland, 1996] In the case of SAH a correlation between glutamate levels, focal neurological deterioration and eventual outcome has been observed.

2.4.5. Cellular mechanisms underlying neuronal ischaemia

Our current understanding of the mechanisms underlying neuronal damage can be summarised under three headings as follows.

- **Induction** - the combination of cellular energy failure and activation of receptor operated ion channels leads to an influx of calcium (Ca$$^{2+}$$), sodium (Na$$^{+}$$) and water that cannot be balanced by extrusion and sequestration mechanisms.

- **Amplification** - the rise in free cytosolic Ca$$^{2+}$$ leads to the activation of phospholipases and protein kinases and a cascade of reactions that liberate compounds with lipolytic, chemotactic, vasoactive and other properties.

- **Expression** - in terminal hypoxia the development of worsening acidosis further inhibits recovery mechanisms and the expression of arachidonic acid metabolites and free radicals results in loss of membrane integrity and irreversible damage to the cytoskeleton. In hypoxia that is not immediately fatal, the rise in intracellular Ca$$^{2+}$$ may lead to the induction of certain genes and expression of certain protective neurotrophic and growth factors.

Under normal circumstances there is an unequal distribution of physiological ions across membranes such that a potential difference in the order of -60 mV, with respect to the inside of the cell, is present. This potential difference is maintained by a series of energy dependent active mechanisms, which transport ions 'uphill' against their electrochemical gradients. (Figure 2.6) Energy derived from adenosine triphosphate (ATP) directly drives the exchange of 3Na$$^{+}$$ for 2K$$^{+}$$ and of Ca$$^{2+}$$ for 2H$$^{+}$$ maintaining extracellular : intracellular concentration ratios for Na$$^{+}$$, Ca$$^{2+}$$ and K$$^{+}$$ of 10, 10000 and 0.025 respectively. (Fig. 3.5) The Na$$^{+}$$ gradient de-
Developed by the ATP dependent mechanism provides a source of energy that is used to drive Na⁺ back into the cell either passively, via a Na⁺ conductance channel, or in exchange for other ions, such as H⁺ and Ca²⁺ or substances such as amino acids.

![Diagram of ion fluxes across polarised membranes]

**Figure 2.6:** Schematic illustration of the major ion fluxes across polarised membranes. Electrochemical gradients drive passive fluxes. Active fluxes are directly or indirectly dependent on adenosine triphosphate (ATP). From Siesjo, 1984 & 1992a.

Over a wide range of arterial blood pressures cerebral blood flow (CBF) is maintained by autoregulatory mechanisms. As CBF falls below a certain level ischaemia develops. (Table 2.1) As ischaemia becomes increasingly severe two so-called ischaemic thresholds are traversed. Firstly, at CBF below 16 to 18 ml/100g/min spontaneous and evoked neuronal activity ceases and, secondly, at CBF below 10 to 12 ml/100g/min cellular ion homeostasis is lost. Loss of ionic homeostasis is associated with potassium (K⁺) efflux and uptake of Ca²⁺, Na⁺, chloride (Cl⁻) and water. [Siesjo, 1992a; 1992b; O'Sullivan, 1989]

The observation that derangement of intracellular K⁺ and Ca²⁺ homeostasis occurs in hypoglycaemic coma lent support to the conclusion that the loss of ionic homeostasis in ischaemia/hypoxia is secondary to cellular energy failure. In hypoglycaemic coma, however, the fluxes of K⁺ and Ca²⁺ appear to precede and precipitate energy failure. The reason for this appears to be that the metabolic demands imposed by increases in ion conductances depletes intracellular ATP. The events that occur in complete ischaemia are illustrated in Figure 2.7.

![Graphs of labile nucleotides and extracellular potassium in relation to ischaemic time]

**Figure 2.7:** Changes in [Left graph] adenosine triphosphate (ATP), adenosine diphosphate (ADP) and phosphocreatine (PCr) and [Right graph] extracellular potassium in relation to time or total ischaemia. (Ischaemia induced at time = zero).
The sequence of events is believed to be as follows: Instantaneous anoxia arrests mitochondrial synthesis of ATP and other nucleotide triphosphates. The continuing activity of ATPase results in hydrolysis of the remaining ATP to produce adenosine diphosphate (ADP). The rise in ADP causes a shift in the equilibrium for creatine kinase (CK) activity in favour of the conversion of ADP and phosphocreatine (PCr) to creatine and ATP. This maintains ATP levels close to normal values until PCr levels approach zero. (Figure 2.8) The absence of an adequate energy source has three significant effects; the stimulation of anaerobic glycolysis leading to intra- and extracellular acidosis, the perturbation of ion homeostasis leading to \(\text{Ca}^{2+}\) influx and cell swelling, and the derangement of mechanisms that maintain the cytoskeleton, organelles and cell membrane. [Ginsberg, 1992]

During an initial period (phase I), while ATP levels are above 90% of control, \(\text{K}^+\) slowly leaks out of cells and \([\text{K}^+]_e\) (the extracellular \(\text{K}^+\) concentration) slowly rises from a normal level of about 3 mM to around 10-15 mM. Extracellular pH falls, due in part to \(\text{H}^+\) leakage and non-ionic lactate diffusion. At this point, as the ATP:ADP ratio begins to fall, the \(\text{Na}^+/-\text{K}^+\text{ATPase}\) ion exchange mechanism rapidly fails and \(\text{K}^+\) efflux accelerates (phase II). The simultaneous \(\text{Na}^+\) influx, via voltage sensitive \(\text{Na}^+\) channels, depolarises the presynaptic terminals leading to \(\text{Ca}^{2+}\) influx via N-type voltage sensitive calcium channels (VSCCs). The extracellular concentrations of calcium \([\text{Ca}^{2+}]_o\), sodium \([\text{Na}^+]_e\) and chloride \([\text{Cl}^-]_e\) rapidly fall while \([\text{K}^+]_e\) rises to values of 50-70 mM. The changes reflect passive equilibrium of all ions across depolarised membranes. As a consequence of rising intracellular calcium concentration \([\text{Ca}^{2+}]_i\), excitatory amino acids, including glutamate, are released into the synaptic cleft triggering post-synaptic ion fluxes. [Ekholm, 1992]

The glutamate released acts as a mixed agonist at a series of both ionotropic and metabotropic receptors. At AMPA receptors glutamate triggers opening of an ion channel permeable to monovalent cations (\(\text{Na}^+, \text{K}^+\) and probably \(\text{H}^+\) and \(\text{NH}_4^+\)) with the net effect of producing \(\text{Na}^+\) influx, depolarisation and cell swelling. The NMDA receptor ion channel, which is permeable to \(\text{Na}^+, \text{K}^+\) and \(\text{Ca}^{2+}\), is normally blocked by physiological concentrations of \(\text{Mg}^{2+}\) whilst the membrane is hyperpolarised. As depolarisation relieves this block AMPA receptor acti-
vation appears to 'prime' the NMDA receptor to catalyse Ca\(^{2+}\) influx as well as allowing Ca\(^{2+}\) influx via L- and T-type VSCCs.

In addition to membrane ion transport system failure, the rise in intracellular Ca\(^{2+}\) is contributed to by a number of other mechanisms. The release of Ca\(^{2+}\) from intracellular stores (mitochondria and endoplasmic reticulum) may be triggered by the rise in [Ca\(^{2+}\)] itself. The release of Ca\(^{2+}\) from intracellular sites follows failure of ATP dependent intracellular sequestration mechanisms. The rise in [Ca\(^{2+}\)], is further enhanced by rising [H\(^{+}\)], which may impair Ca\(^{2+}\) binding at cytosolic buffer sites such as calmodulin either by altering binding affinity or by direct competition.

The activation of surface receptors, including those of the metabotropic (mGluR) quisqualate type, leads to the hydrolysis of phospholipids and, ultimately, to Ca\(^{2+}\) release from the endoplasmic reticulum. Phospholipase C (PLC) catalyses the conversion of phosphatidyl inositol biphosphate (PIP\(_{2}\)) to diacylglycerate (DAG; a source of arachidonic acid) and inositol triphosphate (IP\(_{3}\)). Phospholipase A\(_{2}\) (PLA\(_{2}\)) gives rise to free fatty acids (including arachidonic acid) and lysophospholipids which are believed to act as membrane detergents. It is now also clear that the oxygenated metabolites of arachidonic acid, produced by cyclooxygenase and lipoxygenase, have a number of secondary functions including chemotaxis, modulation of synaptic events and the mediation of changes in vascular permeability.

The sequelae of pathological activation of PLC and PLA\(_{2}\) can be considered in detail under four separate headings; the cyclo-oxygenase pathway, the lipoxygenase pathway, protein kinase (PK) activation and platelet activating factor (PAF) production.

The accumulation of arachidonic acid associated with ischaemia provides substrate for the production of the eicosanoids. Although oxygenase activity is oxygen dependent - suggesting activation during re-perfusion - oxidative arachidonic acid metabolites are probably formed during incomplete ischaemia. The principle product of the 5-lipoxygenase pathway is 5-hydroperoxy-eicosatetraenoic acid (5-HPETE) which gives rise to 5-hydroxy-eicosatetraenoic acid (5-HETE) and the leukotrienes (LT). Both 5-HETE and LTB\(_{4}\) are potent chemotactic agents for neutrophils, whilst LTD\(_{4}\), LTE\(_{4}\) and LTE\(_{4}\) mediate vasoconstriction and increased vascular permeability. The principle products of the cyclo-oxygenase pathway are the thromboxanes, prostaglandins and prostacyclin (PGI\(_{2}\)). Thromboxane A\(_{2}\) (TXA\(_{2}\)) mediates platelet aggregation and vasoconstriction whereas prostacyclin is anti-aggregatory and a vasodilator. It has been shown that the administration of inhibitors of thromboxane synthetase [Pettigrew, 1989] and cyclo-oxygenase [Nakagomi, 1989] are associated with favourable improvements in blood flow and neuronal survival.

The lipolysis of alkyl-2-acyl-sn-glycerophosphocholine (a component of phosphatidylcholine) by PLA\(_{2}\) yields arachidonic acid and, ultimately, PAF, which triggers platelet degranu-
lation as well as the activation and endothelial adhesion of white blood cells. The observation that PAF antagonists reduce free fatty acid accumulation in ischaemia suggests that binding sites for PAF exist in the brain and that PAF activity may itself trigger PLA₂ activity. [Braquet, 1987]

The rise in \([\text{Ca}^{2+}]_i\) produced by the mechanisms described above leads to the activation and membrane translocation of protein kinase C (PKC) which may cause membrane changes by phosphorylation of receptors and/or ionophores. Antagonists of PKC, such as gangliosides and staurosporine, appear to have neuroprotective properties. [Vaccarino, 1987; Hara, 1990]

It is known that neurological outcome after transient cerebral ischaemia is worsened in the presence of hyperglycaemia. [Siemkowicz, 1985] The degree of oedema, the incidence and severity of seizures and the progression and extent of infarction are all exaggerated in the presence of hyperglycaemia probably due to increased lactate production and more pronounced damage to glial and endothelial cells. Intracellular acidosis has a number of putative deleterious effects. The extrusion of \(\text{H}^+\) and \(\text{HCO}_3^-\) in exchange for \(\text{Na}^+\) and \(\text{Cl}^-\) leads to cell swelling. Rising \([\text{H}^+]_e\) may inhibit \(\text{H}^+\) extrusion by competing with the \(\text{Na}^+/\text{H}^+\) exchanger. Mitochondrial oxidative phosphorylation, in vitro, is retarded by acidosis suggesting a possible mechanism for reduced ATP synthesis. Low pH may lead to lactate accumulation by blocking the enzymatic conversion of lactate to pyruvate.

Free radicals superoxide (''O₂'), peroxide ('H₂O₂') and hydroxyl ('OH) are short-lived toxic species that are formed in all aerobic cells. Free radicals damage DNA, proteins, membrane lipids and carbohydrates. [del Zoppo, 1997] A number of mechanisms, both enzymatic (e.g. superoxide dysmutase and glutathione peroxidase) and non-enzymatic (vitamins C and D), exist to protect cells from their damaging effects. Left unchecked these species can cause indiscriminate damage to lipids and proteins. Several conditions, including hyperoxia and the shift from anaerobic to aerobic metabolism, are associated with increased free radical production. It has long been suggested that free radicals contribute to cell death in a multitude of situations including ischaemia, hyperoxic stress, aging and malignancy. Agents known to scavenge free radicals or reduce their production have been shown to reduce neurological injury following transient ischaemia with reperfusion. [Patt, 1988]

Recent evidence suggests that the raised intracellular levels of \([\text{Ca}^{2+}]\), DAG and IP₃ lead to the induction of certain immediate early genes (IEGs) and phenotypic alteration in cell function. These IEGs, which include the c-fos, c-jun, jun B, zif/268 and nur 77 proto-oncogenes, are known to express transiently in response to a variety of stimuli. Levels of c-fos messenger ribonucleic acid (mRNA) rise in the spinal cord after peripheral sensory stimulation and in the brain after phentyltetrazol (PTZ), kindling or lesion induced seizures. It is believed that many IEGs regulate expression of neurotrophic genes such as those that transcribe nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophins 3 and 4 (NT-3 and
NT-4). Neurotrophins, which promote the differentiation and survival of specific types of neuron, are known to be expressed after neural injury. [Hsu, 1993; Akins, 1996]

Figure 2.9: Cellular mechanisms in neuronal ischaemia and potential sites of neuroprotective interventions. VDSC= voltage dependent sodium channel, A1= Adenosine 1 receptor, AMPA=alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate, mGluR= metabotropic glutamate receptor, NMDA=N-methyl-D-aspartate receptor, VSCC= voltage sensitive calcium channel, GPC= , FFA= free fatty acids, PLA2= phospholipase A2, PIP2= phosphatidyl inositol diphasphate, IP3= inositol triphosphate, DAG= diacylglycerate , PLC= phospholipase C, PKC= protein kinase C, ER= endoplasmic reticulum , PAF= platelet activating factor, IEG= immediate gene.

2.4.6. Pharmacological neuroprotection

In four decades of excitatory amino acid receptor research, a huge pharmacopoeia of agents, both agonistic and antagonistic have been developed. Although many of these compounds have been used as tools for examining the validity of excitotoxicity as a mechanism for injury, the principle reason for the development of these agents has been the search for drugs for use in CNS injury. In theory, if a drug can be given early enough after an insult and reach the cerebral extracellular space in sufficient quantity there should be a neuroprotective effect. Success in the laboratory, however, has not been translated into successful clinical trials. From the foregoing description it is clear that the pathophysiological processes that are triggered by ischaemia can be attenuated in several ways: reduction of glutamate release, prevention of cation influx via receptor and voltage operated channels, intracellular enzyme inhibition, etc. It is, therefore, unlikely that a single agent will prevent ischaemic injury. Broadly speaking neuroprotective strategies fall into 3 groups; revascularisation (i.e. with thrombolytics), anti-inflammatory agents, and neuroprotectants. (Table 2.5) Agents that have undergone trials or that are in development are discussed below.
Type Agent(s)
1 Glutamate receptor antagonists Dizocilpine (MK801), Magnesium, Aptiganel (CNS1102; Cerestarot), Dextrorphan Selrotel (CGS19755), Remacemide, Eliprodil
2 Glutamate release inhibitors Lubeluzole, Acadesine, Fosphenytoin
3 GABA receptor agonists Muscimol, Loreclezole, Chlormethiazole
4 Calcium channel antagonists Nimodipine
5 Free radical inhibition Vitamin E, Tirilazad
6 Cyclo-/Lipoxygenase inhibitors NSAIDs
7 Modification of the inflammatory response Antileucocyte antibody, Immunosuppressants, Corticosteroids, Tacrolimus, Cyclosporin
Thrombolytics Streptokinase, tPA
8 Others Citicoline, Gangliosides, Tacrine, Donepezil, AIT-082

Table 2.5: Types of potentially neuroprotective drugs and examples of agents studied.

Of the numerous agents studied, tissue plasminogen activator (t-PA) is currently the only agent licensed for use in acute ischaemic stroke. [NINDS rt-PA Stroke Study Group, 1995] In this pivotal, two-part study, patients treated with t-PA were at least 30% more likely to have minimal or no disability 3 months after treatment. This improvement in clinical outcome was observed despite an increased incidence of t-PA associated intracerebral haemorrhage within 36 hours (6.4% versus 0.6%, p <0.001).

Sadly the majority of patients with ischaemic stroke do not meet the accepted criteria for thrombolytic therapy. As many as half of these patients are excluded on the basis of the time interval from the onset of symptoms to eligibility for thrombolytic therapy exceeding 3 hours. [O'Connor, 1999]

Disappointingly, neither the second European-Australasian Cooperative Stroke Study (ECASS II) [Hacke, 1998] nor the Alteplase Thrombolysis of Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study [Clark, 1999] have confirmed the results of the NINDS Stroke Study Group.

2.4.6.1. Glutamate receptor antagonists
The NMDA antagonists, which inhibit Ca\(^{2+}\) influx, were the earliest compounds to receive attention. Psychotomimetic side effects, similar to those seen with ketamine, limit their clinical application. High doses may cause changes in blood pressure, respiratory depression, sedation, agitation, confusion, ataxia, nystagmus and dysphoria including hallucinations, psychosis and memory dysfunction. [del Zoppo, 1997] Many of these agents have specific affinity from the PCP site and their actions are, therefore, use-dependent.

Among the first to be tested was the non-competitive agent dizocilpine (MK801) which was found to be effective in preventing NMDA (but not kainate or AMPA) induced damage. [Wong,
In animal models of focal ischaemia, MK801 produced significant reductions of infarct in several species [Park, 1988a; 1988b] but was ineffective in global ischaemia.

Magnesium, which inhibits ionic conductance through the NMDA ionophore, has been shown, like MK801, to be neuroprotective in focal ischaemia. [Izumi, 1991] Magnesium penetrates the blood brain barrier poorly and associated hypotension and inhibition of pancreatic insulin secretion may be detrimental. Clinical trials of magnesium have been conducted in acute stroke without obvious adverse effects. In a pilot study of 60 patients, early mortality was lower in patients treated with magnesium within 12 hours of stroke (p=0.066) although there was no significant difference in death or functional impairment at 3 months (p=0.42). [Muir, 1995a] A larger trial (Intravenous Magnesium Efficacy in Stroke; IMAGES) is currently in progress.

Non-competitive NMDA antagonists studied in human trials include; aptiganel and dextrophan. Aptiganel hydrochloride (CNS1102, Cerestat™), is currently in phase III trials. [Muir, 1995b; McBurney, 1997; Lees, 1997; Dyker, 1999] Despite encouraging phase II trials, a phase III study of dextrophan was terminated because of adverse CNS side effects. [Albers, 1995]

Of the competitive NMDA antagonists, selfotel (CGS19755) showed promise in phase II studies [Grotta, 1990; 1995] but two phase III studies were halted after the enrollment of 567 patients because of side effects and lack of efficacy. [Davis, 1997] Early (30 day) mortality from CNS-related causes was significantly higher in the selfotel group (19% versus 13%, p=0.05). In a later publication the investigators suggested that the agent might have neurotoxic effects. [Davis, 2000]

Remacemide hydrochloride [Muir, 1995c; Dyker 1999] and a related analogue (FPL-15896AR) have been demonstrated to be well tolerated in stroke patients, as has the NMDA glycine-site antagonist ACEA-1021. [del Zoppo, 1997] It is not clear whether or not further investigation of remacemide in acute ischaemic stroke is planned.

The observation, in preclinical studies, that gavestinel (GV150526) reduced cerebral infarct volumes prompted its clinical evaluation. In a subsequent randomised, controlled clinical trial the drug was administered intravenously within 6 hours of acute ischaemic stroke. In the 721 gavestinel-treated patients who were analysed for the primary (functional) endpoint at 3 months, the outcome was good in 246 (34.1%), moderate in 136 (18.8%), and poor in 339 (47.0%), compared with 256 (34.9%), 133 (18.1%), and 345 (47.0%), respectively, of 734 patients who received placebo (p>0.8). Mortality at 3 months was 147 (20.4%) in the gavestinel group and 138 (18.8%) in the placebo group.
Eliprodil [Lees, 1997], an antagonist at the NMDA polyamine site, has been shown to prolong the QTc interval in a dose-dependent fashion. [del Zoppo, 1997] A trial in acute stroke was terminated because of lack of efficacy.

The AMPA receptor antagonists have been shown to be effective in models of both focal and global ischaemia and have fewer psychotropic side effects than many of the NMDA antagonists. [Bullock, 1994] Of the many compounds found to be protective in animal models, those currently in clinical trials include YM-90K, LY-293558 and LY-300164. [del Zoppo, 1997]

### 2.4.6.2. Glutamate release inhibitors

Considerable interest has been focused on both pre- and postsynaptic voltage dependent Na+ channels and their role in glutamate release. [Taylor, 1997] Compounds such as BW-619C89 and BW-1003C87 have been shown to inhibit glutamate release and reduce infarct volume in experimental ischaemia. [del Zoppo, 1997]

Another agent, lubeluzole (Prosynap®, Janssen), has entered clinical trials. The phase II European multicentre, double-blind, placebo-controlled clinical trial of lubeluzole of 232 patients with ischaemic stroke, confirmed the agent's safety and efficacy. [Diener, 1996] Compared to placebo, 28 day mortality was lower in patients treated with low-dose lubeluzole (6% versus 18%, p=0.019) but higher in patients treated with high-dose lubeluzole (35% versus 18%). There were no statistically significant differences in neurological outcomes in survivors at 28 days. Phase III studies were subsequently conducted in Europe and North America. In North America, 721 patients were enrolled at 83 centres in the USA and Canada. Mortality at 3 months was lower in lubeluzole treated patients (21% versus 26%, p=0.069). Significantly more lubeluzole treated survivors had superior neurological outcomes (47% versus 40%, p=0.035). [Grotta, 1997] In contrast, the European-Australian trial suggested no impact on mortality or clinical outcome. [Morgenstern, 1997; Diener, 1998]

Adenosine is known to inhibit excitatory amino acid release by acting at presynaptic adenosine (A_1) receptors to reduce Ca^{2+} influx. Compounds such as acadesine and GP-668 have been reported to be neuroprotective in experimental models of cerebral ischaemia [del Zoppo, 1997] and marginally neuroprotective in CABS. [Mangano, 1997]

Phase III trials of the anticonvulsant fosphenytoin are currently in progress.

### 2.4.6.3. GABA receptor agonists

The observations that GABAergic neurons are particularly resistant to ischaemia and that GABA inhibits voltage-gated Ca^{2+} influx following glutamate release, suggests that GABA agonists may be neuroprotective. GABA_A receptors agonists, such as muscimol, loreclezole and
chlormethiazole, have been shown to be neuroprotective. [Zhong, 1997] A European phase II trial of chlormethiazole in 1360 patients has suggested benefit (defined as return to functional independence) in patients with large strokes (40.8% versus 29.8%, p=0.008). Overall, however, chlormethiazole did not show improved functional outcome compared to placebo at 3 months (56.1% versus 54.8%, p=0.649). [Wahlgren, 1999; Lutsep, 1999]

2.4.6.4. Calcium channel antagonists

There are at least six subtypes of voltage sensitive calcium channels (VSCCs). Neuroprotection has been demonstrated following blockade of L-, N- and T-type VSCCs. The association between P- and Q-type VSCCs and neurotransmitter release may indicate additional therapeutic targets. Several L-type VSCC modulators, including nifedipine, diltiazem, and nicardipine, have undergone preclinical testing in experimental ischaemia. Despite an encouraging start [Gelmers, 1988], several clinical trials involving nimodipine in acute stroke have had negative results. [del Zoppo, 1997] A recent meta-analysis of 9 major nimodipine trials involving 3719 patients suggests that mortality and neurological outcome is improved if the drug is administered within 12 hours of the onset of ischaemia. [Gelmers, 1990; Mohr, 1994; del Zoppo, 1997] A study of nimodipine in cardiac surgical patients was halted because of increased haemorrhagic complications. [Legault, 1996]

2.4.6.5. Free radical inhibition

As described, reperfusion following ischaemia may exacerbate vascular and parenchymal injury by producing cytotoxic oxygen free radicals. Free radical scavenging agents or antioxidants that have been shown to be effective in vitro include a-tocopherol, superoxide dismutase (SOD), pegylated-SOD, and lazaroids (21-aminosteroids such as tirilazad mesylate). Although some improvement in outcome was seen in a clinical trial of tirilazad in subarachnoid haemorrhage [Haley, 1997], a recent stroke trial was halted because of lack of efficacy. [Johnston, 1998] The recently published systematic review of 6 trials of tirilazad in 1757 patients with presumed acute ischaemic stroke [Tirilazad International Steering Group, 2001] concluded that tirilazad treatment was associated with a 20% increase in the combined endpoint of death and disability, and that further trials were unwarranted.

2.4.6.6. Modification of the inflammatory response

Prevention or attenuation of the activation of the humoral and cellular components of the inflammatory response may be neuroprotective. Activation of leucocytes after ischaemia leads to the expression of surface adhesion molecules (selectins, integrins and immunoglobulin-related receptors). Leucocytes accumulate in the microvasculature and may cause obstruction
further worsening ischaemia. Attenuation of leucocyte activation can be achieved by reducing
the number of circulating leucocytes (leucocyte filters in CPB) or by administration of a mono­
clonal (MoAb) anti-leucocyte antibody. The results of a phase III study of enlimomab, a mono­
clonal anti-intracellular adhesion molecule (ICAM) antibody, involving 625 patients in 62
North American cities, were recently reported. [The Enlimomab Acute Stroke Investigators,
1997] Although neurological outcome three months after stroke onset was better in the treat­
ment group (7% versus 14%, p=0.004), mortality (22% versus 16%, p=0.05) and the incidence of
fever (51% versus 27%) were significantly lower in the placebo group, reiterating the fact
that hyperthermia is dangerous following cerebral ischaemia. The observation that
aprotinin reduces the inflammatory response to CPB and septic shock suggests a neuroprotec­
tive action.

As mentioned above, interfering with eicosanoid metabolism may have neuroprotective ef­
fects. Inhibitors of thromboxane synthetase (such as 1-benzylimidazole) may alleviate
ischaemic brain damage by reducing cerebral TXA₂ concentrations and elevating cerebral blood
flow. [Pettigrew, 1989] Inhibitors of cyclo-oxygenase (e.g. piroxicam, flurbiprofen, and indo­
methacin) have been shown to be neuroprotective. [Sasaki, 1988; Nakagomi, 1989] Lipoxy­
genase inhibitors (e.g. AA-861, BW-755C), however, have not been shown to be neuroprotec­
tive. [Nakagomi, 1989]

2.4.6.7. Immunomodulators

A recent Cochrane Review [Qizilbash, 2001] assessed the effect of corticosteroids in acute pre­
sumed ischamic stroke. Of the 22 published trials identified only 7 (involving 453 patients)
were considered to be of adequate quality. There was no difference in the odds of death
within one year and treatment did not appear to improve functional outcome in survivors. It
was concluded that there was insufficient evidence to evaluate corticosteroid treatment for
people with acute ischameic stroke. The authors went on to suggest that the present data do
not hold enough promise of clinically worthwhile benefits to advocate a large scale trial.

The immunosuppressive agent tacrolimus (FK-506) has been shown to significantly reduce cor­
tical damage following middle cerebral artery occlusion in the rat. Cyclosporin has been re­
ported to reduce cerebral oedema after focal ischaemia in the gerbil. [del Zoppo, 1997]

2.4.6.8. Cholinergic agents

Loss of cholinergic function, a consistent feature of Alzheimer's disease, has prompted inves­
tigation of cholinergic agents and anticholinesterases. The anticholinesterase tacrine
(1,2,3,4-tetrahydroaminoacridine monochloride; Cognex®) was approved by the U.S. Food and
recently, other ‘cognitive enhancers’, such as donepezil (Aricept®) and the purine analogue AIT-082 (4-[[3-(1,6-dihydro-6-oxo-9-purin-9-yl)-1-oxopropyl]amino] benzoic acid) [Middlemiss, 1995] have been shown to improve so-called primary or working memory. Their use remains controversial. [Howell, 1996; Gray, 1997]

The Cochrane Collaboration has recently published reviews of the use of donepezil, galantamine, and rivastigmine in mild to moderate Alzheimer’s disease. In eight placebo-controlled trials, involving 2664 participants, donepezil treatment was associated with modest, but statistically significant, cognitive improvement but no improvement in patient self-assessed quality of life. [Birks, 2001a] In seven small placebo-controlled trials, galantamine at doses greater than 8 mg/day were associated with significant improvement in cognitive function and measures of activities of daily living and behavioural symptoms. [Olin, 2001] In seven placebo-controlled trials, involving 3370 participants, high-dose rivastigmine treatment (6-12 mg/day) was associated with a significant improvement in cognitive function. [Birks, 2001b] Information concerning the long-term use of these agents is, as yet unavailable, as the majority of the studies reviewed by the Cochrane group involve relatively short treatment duration. To date there have been no studies conducted to assess the neuroprotective effects of these agents and the cost-effectiveness of these agents in Alzheimer’s disease remains unsure. [Clegg, 2001]

2.4.6.9. Other agents

The systemic administration of choline and cytidine (cytidine-5-diphosphocholine, CDP-choline; Citicoline®) is believed to promote cellular membrane repair by stimulating phosphatidylcholine synthesis. [del Zoppo, 1997] Others have suggested that it acts as a free radical scavenger. [Morgenstern, 1997] A U.S. phase IIb trial showed efficacy in stroke at the lowest of the 3 doses studied. [Clark, 1996] More recently the agent has been evaluated in a multicentre, randomised, placebo-controlled trial in 394 patients with acute ischaemic stroke. There was no difference in primary or secondary outcome measures – mortality or disability at 90 days. However, a post hoc subgroup analysis revealed that patients with more severe stroke treated with CDP-choline were more likely to make a full recovery (33% versus 21%, p=0.05). [Clark, 1999]

Siagoside (monosialoganglioside, GM1) has neuroprotective and neurotrophic actions. Despite promising preclinical studies [Vaccarino, 1987; Hara, 1990], several large phase III trials have produced contradictory results. [SASS Investigators, 1994; Argentino, 1989]

Further elucidation of the role of early immediate genes in cerebral ischaemia and the development of new transmission vectors may reveal produce potential opportunities for gene therapy in the treatment of cerebrovascular disease and cerebral ischaemia. [Heistad, 1996]
2.4.7. Summary

Studies of the physiology, pharmacology and pathophysiology of the cerebral circulation, and the complex mechanisms that operate during cerebral ischaemia have provided new tools with which to improve outcome from neurological injury. Although it is clear that excitatory amino acid neurotransmission and excitotoxicity lie close to the 'heart' of cerebral ischaemia many other mechanisms are involved.

After more than 40 years of active research, hundreds of preclinical studies and a few dozen clinical trials, only one drug has been approved for use in acute ischaemic stroke. How is it then that striking success in the laboratory cannot be translated to the bedside? Why does apparent safety and efficacy in phase II trials not persist into phase III trials? Neuroprotection, or strategies that reduce the intrinsic vulnerability of neurones to ischaemic injury and the metabolic consequences of the ischaemic cascade, remains an elusive goal. It is clear that the pathophysiology of neuronal ischaemia comprises innumerable parallel and sequential processes, some lasting several days. For a single neuroprotective agent to be effective it must target a critical step in the cascade. Without reperfusion of an ischaemia brain region, a neuroprotective agent may not reach its intended site of action in sufficient time and concentration to be of use. Perversely, any neuroprotective benefit may be subsequently lost as a result of reperfusion injury. Although combinations of neuroprotective agents represent a further logical step in drug development, most regulatory bodies – the FDA included – preclude this approach.

Despite many obstacles, a small number of promising compounds have been shown to be safe and efficacious and are gaining approval for use in stroke and subarachnoid haemorrhage. In the near future, studies of individual neuroprotective agents will give way to the next generation of trials involving multiple agents from different classes.
Chapter 3

Remacemide
3.1. Introduction

In the search for new anti-epileptic agents over 140 related glycinate compounds have been synthesised and tested for anticonvulsant activity. Discovered by Dr R Griffith and synthesised by Chris Becker, remacemide is a product of this screening program. Pharmacological evaluation of remacemide has been undertaken independently by Astra Arcus USA and Astra Charnwood Pharmaceuticals (formerly Fisons) plc and by the Anti-epileptic Drug Development (ADD) program of the Epilepsy Branch of the National Institutes of Neurological Disorders and Strokes (NINDS), National Institutes of Health, in the USA. [Swinyard, 1969; Krall, 1978a; 1978b; Swinyard, 1980; 1985]

The safety and tolerability of remacemide in both animal and phase II clinical studies of refractory epilepsy and stroke prompted us to further investigate the neuroprotective properties of the agent in patients undergoing CABS.

3.2. Chemistry and pharmaceutics

Remacemide hydrochloride (APL12924AA) formerly designated PR934-423A and FPL12924AA is the US approved name for the compound (±)-2-amino-N-(methyl-1,2-diphenylethyl)-acetamide monohydrochloride - chemical formula: C_{17}H_{20}N_{2}O.HCl, molecular weight: 304.82 daltons. Hydrochloride salts are designated ‘AA’, fumarate salts ‘AJ’, maleate salts ‘AE’ and the respective free bases ‘XX’.

![Chemical structures of Remacemide Hydrochloride (APL12924AA) and its desglycine metabolite 1,2-diphenyl-2-propylamine monohydrochloride (APL12495AA).](image)

Figure 3.1: Chemical structures of Remacemide Hydrochloride (APL12924AA) and its desglycine metabolite 1,2-diphenyl-2-propylamine monohydrochloride (APL12495AA).
3.2.1. Enantiomers

The structure of remacemide includes one asymmetric carbon atom and remacemide hydrochloride is a racemate. (Figure 3.1) Fumarate salts of the two enantiomers APL14144AJ(R+) and APL14145AJ(S-) have been synthesised for use in pre-clinical testing. Doses of remacemide are expressed in terms of the free base equivalent of the salt form administered; i.e. 1.136mg of the hydrochloride salt is equivalent to 1.0mg free base.

3.2.2. Physical properties

Remacemide monohydrochloride anhydrous is a white crystalline powder which is soluble (pK 8.0) in most aqueous media; water - 40 g/l over the pH range 2-8; normal saline - 22 g/l; dilute hydrochloric acid - 26 g/l and sparingly soluble in ethanol - 24 g/l at room temperature. For the majority of pre-clinical studies remacemide hydrochloride for oral (po), intravenous (iv) and intraperitoneal (ip) administration was dissolved in distilled water (Astra), or 30% polyethylene glycol (PEG-400) or 0.5% methylcellulose (ADD Program). For studies comparing the racemate with its separate enantiomers, the fumarate salt (APL12494AJ) was used. [Muir, 1991]

3.2.3. Clinical formulations

For the purposes of clinical trials the remacemide is presented as either an opaque, white, hard gelatin capsule or a white, film-coated, capsule-shaped tablet. The capsule excipients are; dibasic calcium phosphate dihydrate PhEur/USP, microcrystalline cellulose PhEur/NF, pregelatinised starch BP/NF, anhydrous colloidal silicon dioxide PhEur/NF and magnesium stearate PhEur/NF. The tablet base excipients are; microcrystalline cellulose PhEur/NF, croscarmellose sodium NF, lactose PhEur/NF, and magnesium stearate PhEur/NF. The film coating consists of hydroxpropyl-methyl cellulose PhEur/NF, PEG 400 NF, and titanium dioxide BP.

3.2.4. Bioavailability of clinical formulations

Following oral administration as the hydrochloride, both the tablet and capsule formulations of remacemide undergo extensive dissolution with more than 80% of the content being dissolved within 30 minutes.

3.3. Pre-clinical pharmacology

Several methods are established for the pre-clinical evaluation of anticonvulsant agents. The majority of procedures described follow the guidelines established by the ADD program.
Those used in the investigation of remacemide include; protection against maximal electroshock (MES) induced, chemically induced, kindling and audiogenic seizures; protection against N-methyl-DL-aspartate (NMDLA) - induced seizures; in vitro studies of the mechanism of action of remacemide; neuroprotective effects; general pharmacology and drug interactions. These are discussed below.

3.3.1. Protection against maximal electroshock seizures (MES)

Remacemide was identified as the most active in a series of diphenylethylacetamide derivatives in the selective suppression of MES in mice. [Porter, 1984] The (+) enantiomer of remacemide (APL14144AJ) is less potent than the racemate and the (-) enantiomer (APL14145AJ) is more potent than the racemate when evaluated in the MES test. The ED\textsubscript{50} dose maintained protection against MES at 50% for 4 hours. This was longer than phenytoin, phenobarbitone, carbamazepine or valproate at their respective ED\textsubscript{50} doses. Eighty per cent protection against MES was maintained for 8 hours after 3 times ED\textsubscript{50} doses of remacemide. APL12495AA, a desglycinated metabolite of remacemide, is more potent than the parent compound against MES but produces neural impairment at lower doses. (Table 3.1)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Doses in mg/kg</th>
<th>po ED\textsubscript{50} MES</th>
<th>TD\textsubscript{50}</th>
<th>TD\textsubscript{50} / ED\textsubscript{50} (TI)</th>
<th>ip ED\textsubscript{50} NMDA</th>
<th>ip ED\textsubscript{50} MES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remacemide</td>
<td>48.0</td>
<td>370</td>
<td>7.7</td>
<td>57.4</td>
<td>21.5</td>
<td>21.5</td>
</tr>
<tr>
<td>APL 14144AJ (+)</td>
<td>94.2</td>
<td>650</td>
<td>6.9</td>
<td>&gt; 75.0</td>
<td>38.7</td>
<td>17.8</td>
</tr>
<tr>
<td>APL 14145AJ (-)</td>
<td>29.9</td>
<td>620</td>
<td>20.7</td>
<td>77.2</td>
<td>27.8</td>
<td>27.8</td>
</tr>
<tr>
<td>APL 12495AA (±)</td>
<td>40.0</td>
<td>98</td>
<td>2.4</td>
<td>32.5</td>
<td>17.1</td>
<td>17.1</td>
</tr>
<tr>
<td>MK 801 (±)</td>
<td>1.4</td>
<td>0.9</td>
<td>0.6</td>
<td>1.1</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.1: Efficacy and safety profiles for remacemide, APL14144AJ(+), APL14145AJ(-), APL12495AA and MK 801 (dizocilpine) in C51 mice (Harlan Laboratories). Oral ED\textsubscript{50} MES test at 30 minutes post dose. Oral TD\textsubscript{50} inverted screen test at 30 minutes post dose. TI = therapeutic index. ED\textsubscript{50} (ip) for NMDA-induced convulsions. From Porter, 1984.

3.3.2. Protection against chemically induced seizures

Like phenytoin, remacemide has little or no anti-seizure activity against convulsions induced by picrotoxin, pentylentetrazol (metrazol), strychnine or bicuculline. [Stagnitto, 1990] In vitro studies have shown that neither remacemide nor its desglycine metabolite possesses any significant affinity for adenosine A-1, central GABA\textsubscript{A}, glutamate or quinuclidinylbenzilate-muscarinic receptors in rat brain, nor for adenosine uptake sites, and benzodiazepine or strychnine-insensitive glycine receptor sites in mice. [Stagnitto, 1990; Garske, 1991] Remacemide was found to inhibit convulsions induced by N-methyl-D-aspartic acid (NMDA), a property shared with dizocilpine (MK801). APL12495AA was almost twice as potent as the parent
compound. Intraperitoneal remacemide, but not APL12495AA, is active against kainic acid induced seizures.

3.3.3. Protection against kindling seizures

Unlike MK 801, phenobarbitone or valproate, neither remacemide nor APL 12495AA prevented the development of kindled seizures or acted to inhibit established kindled seizures elicited in rats by subthreshold corneal stimulation. [Kupferberg, 1989] (Table 3.2) In behavioural tests remacemide, its enantiomers and APL 12495AA exhibited a tendency to increase spontaneous motor activity at large doses. (Table 3.3) This may reflect pro-convulsant activity evidenced by a shortening of the time to first clonus and twitch following iv administration of phenylenetetrazol (PTZ - metrazol). [Swinyard, 1962]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Doses in mg/kg</th>
<th>po ED₅₀ MES</th>
<th>Safety TD₅₀</th>
<th>TD₅₀ / ED₅₀ (TI)</th>
<th>ip ED₅₀ NMDA</th>
<th>ip ED₅₀ MES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remacemide</td>
<td>33.0*</td>
<td>581</td>
<td>17.6</td>
<td></td>
<td></td>
<td>23.0</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>11.0*</td>
<td>608</td>
<td>57.4</td>
<td></td>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>13.0*</td>
<td>137</td>
<td>10.2</td>
<td></td>
<td></td>
<td>11.7</td>
</tr>
<tr>
<td>Valproate</td>
<td>631.0*</td>
<td>&gt; 2000</td>
<td>&gt; 3.0</td>
<td></td>
<td></td>
<td>172.0</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>20.0*</td>
<td>105</td>
<td>5.1</td>
<td></td>
<td></td>
<td>22.0</td>
</tr>
</tbody>
</table>

Table 3.2: Efficacy and safety profiles for remacemide and reference compounds in Charles River, CFI mice. From Stagnitto, 1990. Oral ED₅₀ MES test at 30 minutes post dose. Oral TD₅₀ inverted screen test at 30 minutes post dose. TI = therapeutic index. ED₅₀ (ip) for NMDA-induced convulsions. *All ED₅₀'s differ significantly (p<0.01) except phenytoin and carbamazepine.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Doses in mg/kg</th>
<th>po ED₅₀ MES</th>
<th>TD₅₀</th>
<th>TD₅₀ / ED₅₀ (TI)</th>
<th>Kindling</th>
<th>SMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remacemide</td>
<td>21.4</td>
<td>847</td>
<td>39.6</td>
<td></td>
<td>Inactive</td>
<td>200</td>
</tr>
<tr>
<td>APL 14144AJ (+)</td>
<td>*33.0</td>
<td>~1000</td>
<td>~30.3</td>
<td></td>
<td></td>
<td>&gt; 400</td>
</tr>
<tr>
<td>APL 14145AJ (-)</td>
<td>20.0</td>
<td>529</td>
<td>26.5</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>APL 12495AA (±)</td>
<td>10.0</td>
<td>152</td>
<td>15.2</td>
<td></td>
<td>Inactive</td>
<td>100</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>3.4</td>
<td>71</td>
<td>*20.9</td>
<td></td>
<td>Active (a+b)</td>
<td>&gt; 1000</td>
</tr>
<tr>
<td>MK 801 (±)</td>
<td>0.1</td>
<td>0.3</td>
<td>3.0</td>
<td></td>
<td>Active (a+b)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3.3: Efficacy and safety profiles for remacemide, APL 14144AJ(+), APL 14145AJ(-), APL 12495AA(±), MK 801 (dizocilpine) and reference compounds in Sprague Dawley rats. From Palmer, 1990. Oral ED₅₀ MES test at 60 minutes post dose. Oral TD₅₀ gang plank escape test at 60 minutes post dose. TI = therapeutic index. Effects on (a) development of kindled seizures or (b) inhibition of established kindled seizures. SMA = Spontaneous motor activity measured in the 'Optovarimex', the values represent the lowest doses in which motor activity is influenced. *Significantly different (p<0.02) from both remacemide (APL12924AA) and APL14145AJ (-). †TI ratios are significantly different (p<0.01) from remacemide. (Data from Fisons studies).
In vitro electrophysiological studies with remacemide have demonstrated that both remacemide and APL12495AA limited sustained repetitive firing in cultured mouse neuroblasts. [Macdonald, 1989] The development of tolerance to remacemide was evaluated in rodents by administration of 3 x ED$_{50}$ doses of the drug for five days. The ED$_{50}$ for protection against MES was then compared to an untreated control group of animals. The ED$_{50}$ in the treated animals was higher than controls suggesting the possibility of tolerance. In separate studies, hexobarbitone sleep time was determined in control animals and in animals treated with ED$_{50}$ or 3 x ED$_{50}$ doses of remacemide for one week. On day 1, sleep time in the remacemide-treated animals was prolonged at both doses relative to controls, suggesting initial inhibition of hexobarbitone metabolism. On day 7, however, no difference in sleep time was observed between the remacemide-treated animals and controls, suggesting induction of hexobarbitone metabolism by virtue of the difference between day 1 and day 7 sleep time.

3.3.4. Protection against audiogenic seizures

In young DBA/2 mice (genetically susceptible to sound induced seizures), oral remacemide was protective against audiogenic seizures with an ED$_{50}$ of 86 mg/kg. Following intraperitoneal administration, the desglycine metabolite was more potent (ED$_{50}$ 11.9 mg/kg) than the parent compound (ED$_{50}$ 19.6 mg/kg). In similar experiments phenobarbitone was significantly more potent (ED$_{50}$ 5.1 mg/kg) than either compound. [Stagnitto, 1990]

3.3.5. Neuroprotection

In keeping with the excitotoxic hypothesis of glutamate in ischaemic neuronal injury, it is expected that NMDA receptor antagonists, such as remacemide and its desglycine metabolite, should be neuroprotective. [Choi, 1990]

The observation that mice pretreated with remacemide survived longer than controls when exposed to a hypoxic environment suggested that the compound had potential neuroprotective properties. [Palmer, 1991] With the exception of the gerbil model of global forebrain ischaemia, all subsequent studies in models of global cerebral ischaemia (Table 3.4) demonstrated that remacemide was neuroprotective. Plasma levels of ARL12495AA were barely detectable following administration to gerbils suggesting metabolic differences between gerbils and other rodent species. [Palmer, 1995]
<table>
<thead>
<tr>
<th>Model</th>
<th>Species</th>
<th>Effect(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>Mice</td>
<td>Prolonged survival</td>
<td>Palmer, 1991; 1995</td>
</tr>
<tr>
<td>Four vessel occlusion for 15 minutes</td>
<td>Rat</td>
<td>Modest protection. CA1 histology at 14 days.</td>
<td></td>
</tr>
<tr>
<td>Four vessel occlusion for 30 minutes</td>
<td>Rat</td>
<td>Protection of CA1. Modest protection of CA1 electrophysiology at 7 days.</td>
<td>Harris, 1992</td>
</tr>
<tr>
<td>Four vessel occlusion for 30 minutes</td>
<td>Rat</td>
<td>Prevented memory loss. T maze performance at 28 days</td>
<td></td>
</tr>
<tr>
<td>Two vessel occlusion for 10 minutes</td>
<td>Rat</td>
<td>Modest protection. CA1 histology at 7 days.</td>
<td></td>
</tr>
<tr>
<td>Drug induced Parkinsonism</td>
<td>Rat</td>
<td>Increased locomotion</td>
<td>Greenamyre, 1994</td>
</tr>
<tr>
<td>Permanent middle cerebral artery occlusion</td>
<td>Cat</td>
<td>Significant reduction in infarct volume.</td>
<td>Bannan, 1994</td>
</tr>
<tr>
<td>Experimental subarachnoid haemorrhage</td>
<td>Rabbit</td>
<td>Reduction in cerebral vasospasm</td>
<td>Zuccarello, 1994</td>
</tr>
<tr>
<td>Ascending aortic clamp for 8 minutes</td>
<td>Dog</td>
<td>Marked protection of CA1. Improved neurological scores at 4 days.</td>
<td>Palmer, 1995</td>
</tr>
<tr>
<td>Bilateral carotid occlusion for 3-5 minutes</td>
<td>Gerbil</td>
<td>No protection of CA1. No effect on open field motor behaviour at 4 days.</td>
<td>Palmer, 1995</td>
</tr>
<tr>
<td>Parasagittal fluid-percussion brain injury</td>
<td>Rat</td>
<td>Significantly reduced posttraumatic cortical lesion volume.</td>
<td>Smith, 1997</td>
</tr>
</tbody>
</table>

**Table 3.4: Preclinical neuroprotection studies.**

Plasma concentrations required for neuroprotection vary according to the animal model used, ranging from 243 ng/ml in a rat four-vessel occlusion model, to over 6000 ng/ml in a feline model of focal cerebral ischaemia. In human volunteers, a single intravenous dose of remacemide 400 mg administered over 15 minutes yielded plasma remacemide concentrations of 2428 ng/ml (Table 3.5). [Dyker, 1999]

<table>
<thead>
<tr>
<th>Model</th>
<th>NP Dose</th>
<th>Plasma total remacemide $C_{max}$ (ng/ml)</th>
<th>Plasma total ARL12495AA $C_{max}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat 4 vessel occlusion</td>
<td>20 mg/kg IP</td>
<td>243 *</td>
<td>254 *</td>
</tr>
<tr>
<td>Dog global ischaemia</td>
<td>7.5 mg/kg IV @ reflow</td>
<td>3405 *</td>
<td>158 *</td>
</tr>
<tr>
<td></td>
<td>7.5 mg/kg IV @ 6 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cat focal ischaemia</td>
<td>25 mg/kg IVI (90 mins)</td>
<td>6120</td>
<td>633</td>
</tr>
<tr>
<td>Human (comparison)</td>
<td>400 mg (total) IVI (15 mins)</td>
<td>2428</td>
<td>370</td>
</tr>
</tbody>
</table>

**Table 3.5: Plasma concentrations of remacemide and ARL12495AA required for neuroprotection in animal models (* Extrapolated values) [Dyker, 1999].**
3.3.6. Preclinical toxicology

The median lethal single dose of remacemide (for mice, rats and rabbits - Table 3.6) is approximately 780 mg/kg (oral) or 50mg/kg (intravenous). The median lethal single dose for rats is approximately 900 mg/kg (oral). These doses did not differ significantly between males and females. At high doses (ED<sub>97</sub>) remacemide, its enantiomers and its desglycine metabolite all reduce the pentylenetetrazol seizure threshold in mice indicating proconvulsant activity. [Palmer, 1991] Clinical manifestations of acute toxicity including tremor, ataxia, depressed respiration, loss of righting reflex tended to decrease with repeated administration suggesting the development of tolerance.

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>450-700 mg/kg PO</td>
<td>Tremor, ataxia, decreased activity, seizures, salivation, loss of righting reflex, gasping, biting, red nasal and oral discharge, dehydration, hunched posture. Erythematous gastric mucosal lesions.</td>
</tr>
<tr>
<td>Mouse</td>
<td>42-72 mg/kg IV</td>
<td>Tremors, decreased activity, prostration, ataxia, gasping, loss of righting reflex, frank seizures.</td>
</tr>
<tr>
<td>Rat</td>
<td>750-2000 mg/kg PO</td>
<td>Ataxia, salivation, decreased activity, episode hyperactivity, prostration, tremor, twitching, gasping, dyspnoea, dehydration, circling, lack of grooming. Diffuse erythema of the gastrointestinal tract.</td>
</tr>
<tr>
<td>Rat</td>
<td>138-158 mg/kg IP</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>150-1200 mg/kg PO</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.6: Results of (positive) acute toxicity studies on remacemide hydrochloride.

Thirty-day toxicology studies in rats showed that remacemide was well tolerated at doses of up to 100 mg/kg/day. Mean liver weights increased in a dose-related manner. Thirty-day toxicology studies in dogs at doses up to 60 mg/kg revealed no gross or microscopic evidence of treatment-related abnormalities. There was evidence of central nervous stimulation, and seizures occurred in some animals in the 40-60 mg/kg dose range during the first week of testing.

Ninety-day toxicology studies in rats showed remacemide to be well tolerated at doses up to 80 mg/kg/day. Liver weights were increased at doses of 80 mg/kg/day and above. Ninety-day toxicology studies in dogs revealed no gross histopathological or laboratory findings. Elevations in terminal liver weight were seen in the dose group (60 mg/kg/day). Clinical signs (including seizures) were seen at doses of 30-60 mg/kg/day in a dose-related manner, but the severity and frequency were higher during the first week of dosing.

Remacemide had no effect on male fertility in mice at doses up to 100 mg/kg/day for 1 month. No embryonic or teratogenic effects were seen in rats at doses up to 100 mg/kg/day or in rabbits at doses of up to 75 mg/kg/day.

Neuropathological studies in the brains of animals sacrificed after dosing with the NMDA-receptor antagonists dizocilpine (MK801), phencyclidine (PCP), ketamine and tiletamine have demonstrated vacuolization of some neurones in the posterior cingulate and retrosplenial...
3.3.7. Pharmacokinetics

The pharmacokinetics of remacemide have been investigated in the dog, rat and monkey.

Following a single oral dose of [\(^{14}\)C]-remacemide (15 mg/kg) to rats and (10 mg/kg) to dogs, greater than 70% of the radiolabel was absorbed relative to intravenous administration of the same dose. In the cynomolgus monkey >80% of an oral dose of [\(^{14}\)C]-remacemide (10 mg/kg) was absorbed. The apparent elimination half life of total radioactivity was 6.4 hours. In combination with the data obtained from studies with cold drug, these observations suggest extensive first pass metabolism of remacemide in the rat.

After oral administration of a single dose (80 mg/kg) to female rats, the compound was rapidly absorbed (t\(_{\text{max}}\)=0.5 hours) and eliminated with an apparent half-life of 5.89 hours. The bioavailability was approximately 12%. Renal clearance of the parent drug was less than 1% of total drug clearance, suggesting extensive hepatic metabolism. After 24 hours <2% of the dose remained in the tissues.

After oral administration of the ED50 of remacemide to rats, the plasma and cerebrospinal fluid (CSF) concentrations of the drug were correlated with those associated with protection against MES-induced seizures in a separate group of animals. The results suggest that remacemide and/or its metabolites were present at 20-150 ng/ml in the CSF during protection. [Wilson, 1988]

After oral administration of remacemide in capsule form (10 mg/kg) to dogs, the drug was rapidly absorbed (t\(_{\text{max}}\)=1.5 hours) and eliminated with an apparent half-life of 1.21 hours. The bioavailability was approximately 42%. The elimination of unchanged remacemide in the urine was minimal.

After intravenous administration of a single dose of remacemide (15 mg/kg) to rats the drug was extensively distributed (VD=3.3 l/kg) and rapidly eliminated (t\(_{1/2}\)=0.36 hours) with a clearance of 6.4 l/kg/hour. Similar results were found when intravenous remacemide (10 mg/kg) was given to dogs (VD=3.8 l/kg, t\(_{1/2}\)=1.12 hours, clearance of 2.3 l/kg/hour).

The metabolites of remacemide formed in the rat, dog and man are broadly similar, although there are quantitative differences between species.
3.4. Clinical pharmacology

After single oral doses of 10-400 mg remacemide in healthy volunteers, the drug was rapidly absorbed (tmax=1-2 hours) and eliminated with a mean half-life of 4 hours, regardless of dose. Peak plasma concentrations after single doses of 150 mg were similar to those observed in rats one hour after ED50 doses of the drug. Concentrations of the desglycinated metabolite (APL12495XX) could not be detected in plasma at doses up to 300 mg. At higher doses the concentrations of this metabolite were low and variable. Single doses of remacemide up to 300 mg were well tolerated. Above this dose, lightheadedness and gastrointestinal upset were observed with increasing frequency.

After multiple oral dosing of remacemide in healthy volunteers (25 mg, 6 hourly – 150 mg, 6 hourly), the pharmacokinetic characteristics of the drug were consistent with those seen after single doses and the half life was similar (approximately 4 hours). Steady state plasma concentrations of the parent drug were achieved after 24 hours and remained constant over the remainder of the dosing period. Plasma concentrations of the desglycinated metabolite were quantitated at all dose levels, although they were close to the assay detection limits at the lowest dose. Steady state peak concentrations of this metabolite were achieved over 2-3 days and fluctuations during the 6 hour dose interval were very small. The apparent elimination half-life of this metabolite was 12-24 hours and appeared to be independent of dose. The drug is generally well tolerated in the dose range studied. Lightheadedness and gastrointestinal upset were seen with increased frequency at the higher doses but lightheadedness appeared to resolve on continued administration.

The metabolic fate of remacemide after single doses has been partially determined in man. Approximately 25% of the administered dose has been accounted for in urine. This was present as the parent compound (APL12924XX), the desglycinated metabolite (APL12495XX), the benzyl-p-hydroxy metabolites (APL14464XX and APL14431XX respectively) and phenyl-p-hydroxy metabolites (APL14430XX and APL14465XX respectively) of these two compounds, and the desglycinated N-hydroxide (APL15053XX). These compounds were present primarily as their glucoride conjugates.

Preliminary evaluation of the pharmacokinetics of remacemide in epileptic patients on monotherapy with carbamazepine or phenytoin has shown that the steady state plasma concentrations of the parent compound and the desglycinated metabolite are lower than those seen in healthy volunteers at similar doses (25 mg to 150 mg, 6 hourly). This has been attributed to the induction of oxidative hepatic drug metabolism pathways by these compounds. The drug was well tolerated by patients when administered for up to one month at these doses. Minimal systemic or central nervous system adverse experiences were reported but gastrointestinal symptoms were similar to those reported by healthy volunteers. These observations are consistent with pharmacokinetic observations in patients versus healthy volunteers.
Evaluation of the effects of remacemide on interictal EEG phenomena and on seizure frequency is currently being evaluated in medically refractory patients. (Table 3.7)

<table>
<thead>
<tr>
<th>Patients with ≥50% reduction in seizures (n=23)</th>
<th>Remacemide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥75% reduction in seizures (n=23)</td>
<td>30%</td>
<td>9%</td>
</tr>
<tr>
<td>Patients with 100% reduction in seizures (n=23)</td>
<td>26%</td>
<td>0%</td>
</tr>
<tr>
<td>Median seizures per month (n=23)</td>
<td>13%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* p<0.05.

Further studies in epileptic patients continue. [Leach, 1997; Davies, 1997]

A preliminary safety and tolerability study in stroke patients was commenced just prior to the completion of the study described in this report. Initial indications were that the drug was reasonably well tolerated in this group of patients. [Muir, 1995c] More recently, a safety and tolerability study was conducted in patients with acute ischaemic stroke. [Dyker, 1999] Groups of 8 patients (6 active, 2 placebo) were randomly assigned to receive twice daily (BD) treatment with 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg remacemide as 2 intravenous infusions followed by 6 days' oral treatment. Remacemide was well tolerated in doses up to 400 mg BD. Doses of 200 mg BD or greater attained the putative neuroprotective plasma concentrations of remacemide predicted from animal models (250-600 ng/ml).

### 3.4.1. Coronary artery bypass surgery

Prior to undertaking the present study, a small double-blind, placebo-controlled, group comparative study of the safety and tolerability of escalating doses of remacemide was conducted in 36 patients undergoing coronary artery bypass surgery at the Middlesex Hospital between July 1991 and August 1992. [Astra Charnwood, 1995; 1997]

In each of the six treatment groups four patients received remacemide and two received placebo. Dose groups were treated sequentially, with each group receiving a higher dose than the last. Doses of 100 mg/day, 200 mg/day, 300 mg/day, 400 mg/day, 500 mg/day and 600 mg/day were administered by mouth in four divided doses for up to 5 consecutive days prior to surgery. Patients were generally admitted to hospital on the day before surgery (i.e. treatment day 5) and received a final dose of remacemide on the day of surgery (i.e. treatment day 6) one hour before the induction of anaesthesia.

An initial 'trough' blood sample was taken immediately before the third (18:00 hrs) dose on the fifth day of treatment. A second steady-state predose blood sample was taken at 08:00 hrs the following morning – the day of surgery. Blood sampling was resumed 1 hour after the induction of anaesthesia (up to 2 hours after the last dose of remacemide) and continued at 30-
minute intervals during surgery, at 3 hours and 6 hours after surgery, and on the next two mornings after surgery. Plasma concentrations of remacemide and ARL12495XX were measured at Astra Charnwood, Loughborough using either solid phase extraction following by high-performance liquid chromatography (HPLC) and ultraviolet detection, or a derivatisation process using o-phthaldialdehyde followed by HPLC and quantification of fluorescent derivatives. The pharmacokinetic parameters selected for evaluation were:

- $C_{\text{min}}(\text{Day}5)$: true 'trough' sample
- $C_{\text{min}}(\text{Day}6)$: predose sample taken 1 hour before induction of anaesthesia
- $C(2)$: concentration at a nominal 2 hours post-dose
- $\text{AUC}_{t_1-t_2}$: area under the data during surgery ($t_1=$ start time, $t_2=$ end time)
- $\text{AUC}_{\text{data}}$: area under the data from first to last sample during surgery
  - calculated using linear trapezoid method

Dose linearity was evaluated by regressing remacemide dose (the independent variable) onto each of these pharmacokinetic parameters.

The extent and times of blood sampling were dependent upon the length of surgery hence were not consistent across patients. As a consequence comparisons between subjects of exposure based on AUC over a common time frame were difficult. Extrapolation of AUC using the terminal half-life was also not possible due to the lack of data available for terminal phase elimination rate determination. Total exposure was therefore estimated by measuring area under all the concentration versus time data collected ($\text{AUC}_{\text{data}}$). The design of the sampling schedule, particularly at the start of surgery, made it appropriate to use the parameters $C(2)$ and $\text{AUC}_{t_1-t_2}$ - measures of maximum drug concentrations and drug exposure respectively during surgery. Although for remacemide these parameters were successfully computed, incomplete concentration data for ARL 12495XX made it difficult to make comparisons and draw conclusions about its disposition and its relationship to dose. For ARL 12495XX some data were available at all doses except the lowest dose level (25 mg QDS) where concentrations were too low to be reported or were unreliable.

A summary of the pharmacokinetic results for remacemide and ARL 12495XX are shown in Tables 3.8 and 3.9. Of particular note is the large variability in data within dose groups to the extent that data from all 6 dose groups overlap extensively.
<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>C_{min(Day6)} (ng.ml^-1)</th>
<th>C_{min(Day6)} (ng.ml^-1)</th>
<th>C(2) (ng.ml^-1)</th>
<th>AUC_{min} (ng.h.ml^-1)</th>
<th>AUC_{min} (ng.h.ml^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>92.3 ±41.7</td>
<td>47.2 ±47.5</td>
<td>29.9 ±9.1</td>
<td>53.1 ±9.8</td>
<td>380.6 ±363.4</td>
</tr>
<tr>
<td>200</td>
<td>106.0 ±40.2</td>
<td>22.9 ±4.9</td>
<td>90.8 ±32.5</td>
<td>173.2 ±61.5</td>
<td>872.6 ±765.5</td>
</tr>
<tr>
<td>300</td>
<td>196.0 ±118.1</td>
<td>159.7 ±127.9</td>
<td>103.8 ±85.3</td>
<td>252.8 ±213.3</td>
<td>718.5 ±539.9</td>
</tr>
<tr>
<td>400</td>
<td>215.4 ±142.7</td>
<td>91.4 ±68.4</td>
<td>63.5 ±32.4</td>
<td>163.4 ±104.0</td>
<td>955.2 ±655.6</td>
</tr>
<tr>
<td>500</td>
<td>337.5 ±131.0</td>
<td>278.8 ±127.0</td>
<td>142.6 ±93.8</td>
<td>490.6 ±342.9</td>
<td>1891.9 ±1247.3</td>
</tr>
<tr>
<td>600</td>
<td>420.8 ±142.9</td>
<td>409.0 ±152.3</td>
<td>57.0 ±21.7</td>
<td>141.4 ±56.4</td>
<td>517.7 ±259.2</td>
</tr>
</tbody>
</table>

Table 3.8: Mean ±SD steady-state remacemide pharmacokinetic data before, during, and after cardiac surgery (t₁ = start of surgery and t₂ = end of surgery) following multiple dosing orally with remacemide hydrochloride (100-600 mg/day) [Astra Charnwood, 1995; 1997].

<table>
<thead>
<tr>
<th>Dose (mg.day^-1)</th>
<th>C_{min(Day6)} (ng.ml^-1)</th>
<th>C_{min(Day6)} (ng.ml^-1)</th>
<th>C(2) (ng.ml^-1)</th>
<th>AUC_{min} (ng.h.ml^-1)</th>
<th>AUC_{min} (ng.h.ml^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>10.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>200</td>
<td>41.7 ±12.6</td>
<td>30.4 ±10.4</td>
<td>27.2 ±6.7</td>
<td>58.3 ±3.8</td>
<td>580.3 ±456.4</td>
</tr>
<tr>
<td>300</td>
<td>53.7 ±4.2</td>
<td>50.0 ±9.5</td>
<td>33.6</td>
<td>79.3</td>
<td>855.0</td>
</tr>
<tr>
<td>400</td>
<td>63.3 ±17.5</td>
<td>62.4 ±22.1</td>
<td>57.4 ±13.1</td>
<td>157.6 ±77.4</td>
<td>1528.7 ±688.7</td>
</tr>
<tr>
<td>500</td>
<td>80.4 ±35.1</td>
<td>98.0 ±45.0</td>
<td>213.0 ±153.4</td>
<td>246.9 ±136.5</td>
<td>1304.0 ±651.7</td>
</tr>
<tr>
<td>600</td>
<td>85.5 ±60.2</td>
<td>104.0 ±42.4</td>
<td>45.7 ±23.6</td>
<td>-</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Table 3.9: Mean ±SD steady-state ARL12495XX pharmacokinetic data before, during, and after cardiac surgery (t₁ = start of surgery and t₂ = end of surgery) following multiple dosing orally with remacemide hydrochloride (100-600 mg/day) [Astra Charnwood, 1995; 1997].

'Trough' concentrations of remacemide decreased from Day 5 to Day 6 for all dose levels, as expected by the lengthening of the time of the sample post-dose from 4 hours to 9 hours respectively. Mean C(2) exceeded the pre-induction sample concentration (C_{min(Day6)}) in only one dose group (90.8 ng.ml^-1 (C(2)) versus 22.9 ng.ml^-1 (C_{min(Day6)}) respectively for the 50 mg group) and one dose group for ARL 12495XX (213 ng.ml^-1 (C(2)) versus 98 ng.ml^-1 (C_{min(Day6)}) respectively for the 125 mg group). For all the other dose groups mean C(2) did not show the expected rise to maximum concentration following the oral dose of remacemide. However results from individual patients showed that C(2) was the highest in-surgery concentration in 13 out of 24 patients studied for remacemide. Thus, in approximately half the patients, C(2) was the highest in-surgery concentration, and therefore a reasonable marker for in-surgery maximum concentration.

Comparison of AUC_{t₁-t₂} and AUC measured in the post-operative period (difference of AUC_{t₁-t₂} and AUC_{data}) shows that, on average, at the end of surgery, there was a large proportion of remacemide still to be eliminated. It was notable that in the 600 mg/day dose group, exposure was considerably lower than expected from AUC data at the other dose levels.
Mean profiles for remacemide in CABS patients are given in Figure 3.2. All profiles show multiple peaks. This is particularly evident for the 300 mg/day and 500 mg/day dose groups. The major secondary peak occurs within the operative period at about 4 to 6 hours post-dose and is largest for the 300 mg/day and 500 mg/day dose groups but occurs only to a minor extent in the 100 mg/day, 200 mg/day and 400 mg/day dose groups. In two dose groups (100 mg/day and 600 mg/day) significant peaks occur after the end of surgery from 9 to 12 hours post-dose and, in the case of the 100 mg/day dose group, contribute to a continuing effect of unusually elevated drug concentrations after 1 day post-dose.

![Figure 3.2: Mean plasma concentrations of remacemide hydrochloride following oral administration of multiple doses of remacemide to CABS patients [AstraCharnwood, 1995; 1997].](image)

Generally, ‘trough’ concentrations of ARL 12495XX decreased from Day 5 to Day 6 up to the 400 mg/day dose level, as expected by the lengthening of the sample time post-dose from 4 hours to 9 hours respectively. However in the highest dose groups (500 mg/day and 600 mg/day) slight increases in concentrations were found on Day 6 compared with Day 5. Mean C(2) exceeded the pre-induction sample concentration (C_{min(Day5)}) in only one dose group (213.0 ng.ml\(^3\) versus 98.0 ng.ml\(^4\) respectively for the 500 mg/day group). For all the other dose groups mean C(2) was lower than the predose concentration. However results from individual patients showed that C(2) was the highest in-surgery concentration in 6 out of 13 patients studied for ARL 12495XX. Thus, in approximately half the patients, C(2) was the highest in-surgery concentration, and therefore a reasonable marker for in-surgery maximum concentration.

Comparison of AUC_{\text{int-o}} and AUC measured in the post-operative period (difference of AUC_{\text{int-o}} and AUC_{\text{data}}) shows that, on average, at the end of surgery, there was a large proportion of the desglycinyl metabolite still to be eliminated. Although little data could be obtained for the
top dose level (600 mg/day), those which were available, in keeping with parent drug, sug-
gested a much lower exposure than expected based on data from other dose levels.

Mean profiles for ARL 12495XX in CABS patients are given in Figure 3.3. All profiles show
multiple peaks. This was most evident for the dose groups 200 mg/day, 400 mg/day, and 500
mg/day with the secondary peak occurring at about 5 to 6 hours post-dose (at about the end of
the operative period). Two dose levels also showed the presence of a secondary peak outside
the operative period (300 mg/day and 400 mg/day groups both at 12 hours post-dose). Indi-
vidual profiles from two patients were noteworthy as concentration of ARL 12495XX increased
between 1 and 2 days post-dose. These results, concentrations that are around three times
higher than the limit of detection, were unexplainable in the light of known pharmacokinetics
of ARL 12495XX.

![Figure 3.3: Mean plasma concentrations of ARL12495XX following oral administration of multiple
doses of remacemide to CABS patients [AstraCharnwood, 1995; 1997].](image)

Due to the large number of co-medications being taken by the patients in the study, a high in-
cidence of analyte interference problems was encountered with the analytical methods em-
ployed. Consequently, although for remacemide a full data set of pharmacokinetic param-
eters was available, only a limited data set was available for ARL12495XX.

Of particular note was the high variability in the pharmacokinetic parameters computed
between patients at all dose levels. Moreover, the variability was so extreme that parameters
overlapped considerably across dose levels. This was particularly evident from the plotted
data designed to provide a visual appreciation of the dose-exposure relationships across
the dose range. The variability meant that definitive conclusions on dose linearity could not
be drawn. However, overall 'trough' concentrations determined prior to the third dose on the
day of admission ($C_{\text{min(Day5)}}$) and prior to surgery ($C_{\text{min(Day6)}}$) did appear to demonstrate a rea-
sonably linear relationship with dose for both remacemide and ARL12495XX (Figures 3.4 and

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In contrast, concentrations \( C(2) \) and AUC parameters \( \text{AUC}_{\text{t-2}} \) and \( \text{AUC}_{\text{data}} \) determined for remacemide and the ARL12495XX during surgery, when regressed against dose, did not produce such apparent linearity. For these parameters, a number of dose levels had average residuals, which deviated significantly from the fitted parameter. The top (600 mg/day) dose level was of particular note and produced considerably lower exposure to parent drug and metabolite than that anticipated from other dose groups.

![Figure 3.4: Remacemide dose linearity of \( C_{\text{min/day}} \), \( C(2) \), and \( \text{AUC}_{\text{t-2}} \) and \( \text{AUC}_{\text{data}} \) following multiple dosing of remacemide hydrochloride to CABS patients (AstraCharnwood, 1995; 1997).](image-url)
As a result of the pre- and in-surgery procedures, blood sampling times were difficult to control. A window of up to 2 hours existed between administration of the last dose and taking of the first blood sample. Consequently, the absorption and distribution processes, which for remacemide normally occur rapidly, were not distinguishable in the profiles generated. It was not possible to determine the rapidity or extent of absorption from the last dose, however, the fact that the first in-surgery concentrations (nominal 2 hours post-dose samples) were in-
variably lower than those taken predose, suggests poor absorption over the first few hours post-dose.

One objective of the study was to obtain an estimate of terminal half-life for remacemide and desglycinyl metabolite. Unfortunately, the fluctuating concentrations found during surgery and the secondary peaks which were seen in many patients’ profiles, and which generally occurred between 4 and 12 hours post-dose, precluded the estimation of terminal rate constant, and hence the half-life, with any confidence.

Taking all of these observations into account, it was clear that during the period of surgery, the pharmacokinetic profiles of remacemide and ARL12495XX were different to those encountered in previous studies. Although the precise causal factor or factors producing this effect on the pharmacokinetics was not known, there could have been a number of explanations – low and/or delayed absorption, redistribution of remacemide from tissue sites back into the central compartment, a change in the volume of distribution and/or reduced drug clearance during surgery. For those parameters determined during surgery, blood loss (hence drug loss) due to the surgical manipulations could also have affected the pharmacokinetic profile and probably accounts for some of the variability seen within dose levels and for the poor dose linearity for the in- and post-surgery pharmacokinetics.

The patients in the study were exposed to many different potentially causal factors compared with subjects in previous pharmacokinetic studies with remacemide hydrochloride. They were administered a large number of drugs during the pre-, in- and post-surgery phases. In addition they were subjected to a number of surgical procedures one of which, cardiopulmonary bypass (CPB), has previously been shown to be responsible for altering the pharmacokinetics of several drugs. Drugs such as fentanyl, propranolol and papaverine, which have high hepatic extraction ratios, are characterised by a reduced clearance during CPB compared with control subjects (i.e. patients undergoing similar surgical procedures but not requiring CPB). The reduced elimination rate is thought to be due to the lower hepatic perfusion occurring during CPB.

In this study, due to the large number of possible influencing factors, and the absence of control groups of patients, defining the factor or factors responsible for the unusual pharmacokinetic profile found in this patient population is impossible.

Overall, remacemide was well tolerated for up to 5 days before surgery, in doses up to 600 mg daily. No clinically significant abnormalities in laboratory values or vital signs could be ascribed to treatment with remacemide. The most common adverse event reported was dyspepsia, which was consistent with previous human tolerability studies.
3.5. Summary

Remacemide has been shown to have anticonvulsant activity in a number of pre-clinical paradigms as well as in humans with refractory epilepsy. Clinical studies indicate that the drug is well tolerated and that psychotomimetic and gastrointestinal side effects are mild.

In vitro and animal evidence suggests that Remacemide has neuroprotective properties in drug induced Parkinson's disease and focal, but not global, cerebral ischaemia.

Based on these findings, it was concluded that a formal Phase II efficacy study be conducted.
The Sunday Telegraph
11th September 1994

Heart surgery changes your personality

LARGE numbers of heart patients are suffering brain damage after operations, with some undergoing a personality change.

The Government is to fund a research project after reports that one in four heart patients suffers significant loss of mental ability.

The new study, by scientists at Glasgow University, will concentrate on the effects of the upheaval in the body’s blood supply during surgery. It is then that tiny clots and fragments of tissue can enter the bloodstream and pass into the brain.

In the early days of cardiac surgery, half of all patients became delirious from brain damage. Modern techniques are more sophisticated, greatly reducing the risks. But doctors remain concerned.

A recent study of more than 300 patients by doctors in Newcastle upon Tyne found that 79 per cent had reduced intellectual performance, with decreased attention span, short-term memory and learning ability. Almost a quarter had moderate or severe difficulties.

Most recovered virtually completely after six months, but about one in 30 had persistent mental problems. A member of the Glasgow team, Dr John Asbury, a lecturer in anaesthesia at the university’s Western Infirmary, said: “Surgical procedures today are very sophisticated, and it is going to be very difficult indeed to minimise any further the amount of debris produced when tissue is cut.

“Unfortunately the brain is very unforgiving, and the effects can be subtle.”

Two groups of 100 patients are to be studied, one made up of cardiac patients, the other a control group of patients having major surgery which does not require heart-lung machines.

The team also plans to experiment with a new sensor that uses a beam of infrared radiation shone on the skull to measure the amount of oxygen used by the brain. Doctors suspect that debris in the bloodstream causes damage by blocking off blood supply to parts of the brain.

Dr Asbury said that the machine may prove useful as an early warning system, alerting surgeons to problems so that countermeasures such as “clot-busting” drugs can be given.
Chapter 4

Clinical Investigation - Methods

“Sir, I have found you an argument, but I am not obliged to find you an understanding”

Samuel Johnson
4.1. Study overview

This chapter describes, in detail, the objectives, methodologies and results of a single-centre clinical study undertaken by me in collaboration with the Departments of Anaesthesia, Cardiothoracic Surgery, Neurology and Psychiatry at the Middlesex Hospital, London between November 1992 and September 1994.

4.1.1. Descriptive title

A Double-Blind, Placebo Controlled, Group-Comparative Study of the Effects of Remacemide Hydrochloride (600 mg daily) on Neuropsychological Performance following Coronary Artery Bypass Surgery.

4.1.2. Hypothesis

Remacemide hydrochloride, a glutamate receptor antagonist prodrug, reduces neuropsychological deficits following coronary artery bypass surgery.

4.1.3. Study objectives

This study had four objectives:

1. To investigate the putative neuroprotective effect of remacemide in patients undergoing CABS by comparing the incidence and severity of postoperative neuropsychological deficits with a matched control group.

2. To compare the safety and tolerability of remacemide with that of placebo in patients undergoing CABS by monitoring laboratory variables and recording unusual events observed by either the patient or the clinician.

3. To correlate observed neuropsychological deficits with perioperative cerebral blood flow velocity (CBV), microembolic events (MEE) and with cerebrovenous lactate measurements.

4. To monitor plasma concentrations of remacemide and ARL12495XX (its principal des-glycine metabolite) to ensure patient compliance and confirm adequate (i.e. putatively neuroprotective) concentrations before and after surgery.
4.1.4. Intervention

The study was conducted in accordance with the provisions of the Declaration of Helsinki (amended 1989) and with the approval of the University College London (UCL) Hospitals Ethical Review Committee. Table 4.1 details the principle time points in the study.

Patients were randomly assigned to receive either remacemide or placebo for four days before and five days after surgery.

4.1.5. Assessment

All patients underwent neuropsychological assessment one week before and six days and eight weeks after surgery.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>One Month before surgery</td>
<td>Recruitment &amp; Consent, LABs, Plasma remacemide concentration</td>
</tr>
<tr>
<td>One Week before surgery</td>
<td>Eligibility confirmed, Randomisation, NP tests, Study medication issued</td>
</tr>
<tr>
<td>Four Days before surgery</td>
<td>Study medication started</td>
</tr>
<tr>
<td>One Day before surgery</td>
<td>Admission to hospital, LABs, Plasma remacemide concentration</td>
</tr>
<tr>
<td>Day of Surgery</td>
<td>MEE monitoring, LABs</td>
</tr>
<tr>
<td>One Day after surgery</td>
<td>LABs</td>
</tr>
<tr>
<td>Five Days after surgery</td>
<td>Plasma remacemide concentration, Study medication discontinued</td>
</tr>
<tr>
<td>Six Days after surgery</td>
<td>NP tests, LABs</td>
</tr>
<tr>
<td>Seven Days after surgery</td>
<td>Patient discharged home</td>
</tr>
<tr>
<td>Eight Weeks after surgery</td>
<td>Clinical assessment, NP tests, LABs</td>
</tr>
<tr>
<td>Twelve Weeks after surgery</td>
<td>Clinical assessment (by 'phone)</td>
</tr>
</tbody>
</table>

Table 4.1: Study design.

4.2. Patients and methods

The following section describes, in considerable detail, the study protocol and methods of data analysis.

4.2.1. Recruitment

The clinical records of all new referrals to the weekly Cardiothoracic Surgery Outpatient Clinic at UCL Hospitals were screened by the author to select potentially suitable study subjects.

All patients aged between 18 and 75 years, referred for elective, primary coronary revascularisation were considered and personally interviewed by the author. Females with childbearing potential were not considered. Following a detailed discussion with the author of both the proposed surgical procedure and the clinical study, patients expressing interest in the
study were asked to provide witnessed, written, informed consent. (Appendix 1) A brief medical history questionnaire was used to confirm eligibility. In addition, a record of current medications was made. Each patient enrolled into the study was given a unique patient identification number starting from ‘001’.

4.2.2. Exclusion criteria

Patients were excluded from further participation in the study if any of the following exclusion criteria was met:

1. The presence and/or a history of clinically significant neurological (including previous transient ischaemic attacks, stroke, seizures and ‘blackouts’), psychiatric, gastrointestinal (specifically peptic ulceration and haemorrhage), hepatic, renal or haematological disorder.

2. Evidence of a history of drug (prescribed or non-prescribed) or alcohol abuse (14 units a week or more for women; 21 units for men) within the previous two years.

3. The regular use of non-steroidal inflammatory agents (except aspirin), anti-epileptics, anti-depressants (used as an indicator of psychiatric disease), nimodipine or H1 type anti-histamines.

4. Emergency cases and redo procedures.

Each new patient entering the study was allocated a unique entry number (starting from 001). The patients’ height, weight, resting arterial blood pressure, heart rate and 12-lead electrocardiograph were recorded. ‘Dip-Stick’ analysis of a fresh, mid-stream specimen of urine was performed and blood was drawn for baseline remacemide levels and routine biochemical and haematological investigations.

4.2.3. Randomisation

In accordance with usual departmental practice, all patients scheduled for elective cardiac surgery attended the hospital on an outpatient, daycase basis during the week before surgery. This allowed medical and nursing staff to perform routine pre-admission clinical and administrative tasks and gave the local blood transfusion service advanced warning of forthcoming demand. During this visit, patients had the opportunity to meet with the staff responsible for their perioperative care. This visit to hospital provided the investigators with the opportunity to confirm study eligibility and consent, perform pre-operative neuropsychological evaluation and dispense supplies of pre-operative study medication.
Study subjects who had not started any disallowed medications since recruitment and who had no clinically significant abnormality in routine blood biochemistry and haematology were allocated a unique randomisation number (starting at '501').

Randomisation was performed by the study sponsor using a computerised random number generator. Study medication kits (containing either remacemide or an identical placebo) each labelled with the randomisation code, were transported by courier from the study sponsor to the Middlesex Hospital Pharmacy. For regulatory and safety reasons the randomisation code was communicated to the chief pharmacist.

4.2.4. Preoperative study medication

All patients were interviewed and examined by the author on the cardiothoracic surgical ward about one week before surgery for clinical assessment, routine 'clerking', venepuncture, and other clinical investigations.

Following baseline neuropsychological testing, preoperative test medication kits corresponding to the randomisation number were formally prescribed by the author and dispensed by the hospital pharmacy. Test medication kits contained either remacemide or an identical placebo. Patients were issued with a medications diary card (Appendix) and written self-administration instructions.

Patients were instructed to commence study medication four days before the scheduled day of surgery. Patients were instructed to take one tablet, four times daily at the following times; 08:00, 11:00, 18:00 and 23:00 hours. In medication kits containing remacemide the doses on the first day were gradually increased from 25 mg to 150 mg in an attempt to reduce the minor side-effects (nausea and lightheadedness) experienced by subjects in previous studies. (Table 4.2) To assist compliance the first four doses were individually packaged, as all tablets were identical.

<table>
<thead>
<tr>
<th>TIME</th>
<th>08:00</th>
<th>13:00</th>
<th>18:00</th>
<th>23:00</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAY 1</td>
<td>25 mg</td>
<td>50 mg</td>
<td>100 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>DAY 2</td>
<td>150 mg</td>
<td>150 mg</td>
<td>150 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>DAY 3</td>
<td>150 mg</td>
<td>150 mg</td>
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<td>DAY 4</td>
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<tr>
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<td>*150 mg</td>
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</tr>
<tr>
<td>DAY 6</td>
<td>*150 mg</td>
<td>*150 mg</td>
<td>*150 mg</td>
<td>*150 mg</td>
</tr>
</tbody>
</table>

Table 4.2: Preoperative dosing schedule for patients receiving remacemide hydrochloride. Additional doses (*) could be given for an additional 36 hours if surgery was delayed.
Although it was anticipated that most patients would undergo surgery after the first dose on the fifth preoperative treatment day, sufficient doses were provided to permit surgery to be carried out up to 36 hours later than planned.

The author instructed patients to record self-administration of both the test medication and other regular medications on their diary card. If a dose of study medication was inadvertently missed or delayed, patients were instructed to omit that dose unless the next dose was not scheduled for four or more hours.

In addition, patients were instructed to record on their diary card any adverse event or unusual symptom experienced from commencement of the test medication. Patients were issued with several contact telephone numbers so that in case of a major problem they could speak to one of the investigators.

4.2.5. Admission to hospital

Whenever possible patients were admitted to hospital during the afternoon of the day prior to surgery. The medications diary card was checked to ensure that both test medication and other regular medications had been taken correctly. The remaining doses of test medication were counted to confirm patient compliance. Any reported adverse effects were recorded. Patients who had omitted more than three consecutive doses or more than four non-consecutive doses of test medication were excluded from further study participation.

Resting arterial blood pressure, heart rate and 12-lead electrocardiograph were recorded. Urinalysis and routine blood biochemistry and haematology were performed and blood was drawn for remacemide levels immediately before the 18:00 dose. Patients were instructed to take the 18:00 and 23:00 doses of study medication as usual.

In the majority of cases the author undertook and documented the routine preoperative anaesthetic evaluation on behalf of the Anaesthetic Department, prescribed appropriate premedication, and communicated the results to the consultant anaesthetist assigned to the case.

4.2.6. Day of surgery

Patients continued taking test medication such that the last dose was administered one hour before the induction of anaesthesia and not less than four hours after the penultimate dose. The medications diary card was collected by the author and any unused pre-operative test medication returned to the hospital pharmacy for drug accountability purposes.
4.2.7. Conduct of anaesthesia

Patients were premedicated with oral diazepam and intramuscular papaveretum (Omnopon) and hyoscine hydrobromide (Scopolamine) one hour before the induction of anaesthesia. Supplemental oxygen was delivered via a Hudson mask at 4 l/min from the time of premedication until induction of anaesthesia.

The author was present in the operating room for the duration of all cases in the study. In the majority of cases the author assisted the anaesthetists assigned to the case. On many occasions, and with the consent of the attending consultant anaesthetist, the author was the lead anaesthetist for the case.

On arrival in the anaesthetic room, patients were first identified by a member of the operating department staff. Continuous monitoring of the electrocardiograph and arterial oxygen saturation, by pulse oximetry was then commenced. Following sedation with intravenous midazolam (Hypnovel®) cannulae were sited in a forearm vein (14G), the left radial artery (20G) and the right internal jugular vein (triple lumen, 16G and 2 x 18G). Continuous arterial pressure monitoring and an infusion of Hartmann’s solution were then commenced. Anaesthesia was induced with thiopentone sodium (pentothal) 2-5 mg/kg, fentanyl citrate (Sublimaze®) 1-10 μg/kg and/or alfentanil (Rapifen®) 10-15 μg/kg and pancuronium (Pavulon®) 0.1 mg/kg. The trachea was intubated with a cuffed endotracheal tube and the lungs mechanically ventilated to achieve an end tidal carbon dioxide tension of 5.3 kPa (40 mmHg). Antimicrobial prophylaxis was administered according to local protocol. This consisted of flucloxacillin and gentamicin, or erythromycin in patients allergic to penicillins.

A retrograde cannula (16G) was place in the left internal jugular vein of those patients randomised to have plasma lactate levels measured during the procedure. In these patients, samples were drawn immediately after induction of anaesthesia, 15 minutes after the onset of CPB, during rearming and immediately after the termination of CPB. Following catheterisation of the urinary bladder, the patient was transferred to the operating theatre.

Prior to the onset of CPB anaesthesia was maintained with nitrous oxide in oxygen (FiO₂ 0.3-0.5), lorazepam (Ativan®) 2-4 mg, and incremental doses of pancuronium and an opiate. Nitrous oxide was not used following the termination of CPB. Volatile anaesthetic agents (e.g. isoflurane) were not used at any time during the procedure. Infusions of crystalloid (typically Hartmann’s solution), colloid solutions (hydrolysed gelatine and hydroxyethyl starch), and blood products (red cells, frozen plasma and platelets) were used at the discretion of the attending anaesthetist.

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4.2.8. Intraoperative monitoring

Standard physiological monitoring - electrocardiograph, arterial pressure, central venous pressure, nasopharyngeal temperature, inspired oxygen tension ($F_1O_2$), end tidal carbon dioxide tension ($F_eCO_2$), airway pressure, arterial oxygen saturation ($SpO_2$), and urine output - was used throughout the procedure. (Harvard)

In addition to maintaining the routine hospital anaesthetic record, a more detailed record was kept by the author on a form designed specifically for this study by the author (Appendix).

4.2.9. Quantification of cerebral microemboli

Left middle cerebral artery (MCA) blood flow velocity and microembolic events were monitored using transcranial Doppler sonography. (TC2000, Eden Medical Electronics, Überlingen, Germany) In all cases TCD monitoring was conducted by the author. The left MCA was insonated via the left temporal window using a lightweight 2 MHz 'Improved Monitoring' probe (IMP) mounted in an elasticated fixation harness. Monitoring of the right MCA via the right temporal window was not used because of the potential for inadvertent movement of the probe during use of the right internal jugular venous cannula. Because of the electrical (radio frequency) interference caused by unipolar electrocautery, MCA insonation was performed whilst the operative site was being prepared, prior to the start of surgery and discontinued during the early part of surgery. With the co-operation of the surgeon, electrocautery was used as little as possible. This allowed continuous transcranial sonographic monitoring from before aortic cannulation until aortic decannulation.

The continuous monitoring (TC-TRAK®) software option, which offers automated embolus detection, was used. The probe power output and signal gain were reduced to the minimum level required to produce a clear spectral display. The embolus detection threshold was set at an arbitrary level of 25. Video (VGA) signals from the TC2000 were converted to 'under-scanned' PAL format using an interface unit (Mediator, VideoLogic, UK) and were recorded in real time, with corresponding stereo audio signals, on standard VHS videotape (AG6200, Panasonic, Matsushita Electric Co. Ltd., Japan).
Figure 4.1: Transcranial Doppler (TC2000, Eden Medical Electronic, Überlingen) and associated equipment used to quantify cerebral microembolic events during the intraoperative period. A small trolley was used to make the equipment portable. To aid visibility a standard Super VGA computer monitor was slaved off the internal TC2000 monitor. The Mediator converts RGB video output from the TC2000 to a composite video signal, in either PAL or NTSC standard, suitable for recording onto standard VHS videotape. The 'underscan' mode was used to ensure that data at the edges of the SVGA display was not lost. The smaller of the two keyboards shown allowed remote control of Doppler signal intensity, gain and insonation depth from the bedside during use.

Microembolic events, which were associated with a characteristic 'chirping' sound and spectral pattern, were counted 'off-line' by the author. An embolic signal was defined as a signal $\geq 3$ dB above background towards the probe. On occasions when short bursts of overlapping or continuous microembolic signals (typically 200-2000 mS in duration) were observed, their number was estimated by dividing the duration of the burst, in milliseconds, by 25 (approximately twice the fast Fourier transform time of 12 mS). The microembolic event counts were divided into; (1) the period between aortic cannulation and the onset of CPB, (2) the period during CPB - in 15 minute epochs, and (3) the period between the termination of CPB and aortic decannulation.

Figure 4.2: Typical TC2000 screen display during middle cerebral artery monitoring. In this example, the left middle cerebral artery has been insonated at a depth of 56 mm. The line outlining the spectral signal above the zero baseline represents the maximum velocity envelope. The spectral signal below the zero baseline probably represents flow away from the probe in an adjacent vessel. The peak flow velocity is in the order of 50 cm/s, the mean flow velocity (displayed) is 31 cm/s and the pulsatility index (PI on display) is 0.81.
4.2.10. Conduct of cardiopulmonary bypass

Cardiopulmonary bypass was established between right atrial and proximal aortic cannulae using the ‘Middlesex Hospital’ extracorporeal circuit (Bard, Crawley, UK) and a “Multi-flow” roller pump (Stockert, USA) assembly. A flat bed membrane oxygenator (model 5400, Bard, Crawley, UK) with integral heat exchanger and soft-shell venous reservoir was used in conjunction with a Harvey cardiotomy reservoir / filter and two or three low pressure cardiotomy suckers. An arterial line filter was not used. The extracorporeal circuit was primed with Hartmann’s solution (1500-2000 ml) and heparin sodium (5000iu). Full anticoagulation, with heparin (300 iu/kg), was achieved prior to aortic cannulation. Further doses of heparin were given to maintain a celite activated whole blood clotting time (ACT) of greater than 400 seconds. Moderate hypothermia (32 °C) was used during CPB. Pump flow was adjusted to achieve 2.4 l/min/m² at 37 °C and 1.8 l/min/m² at 32 °C. Mean arterial pressure (MAP) was maintained at 50-60 mmHg using either vasoconstrictors (typically phenylephrine, ephedrine or metaraminol) or vasodilators (typically phentolamine, sodium nitroprusside or glyceryl trinitrate) as required.

Alpha-stat acid-base management (i.e. no temperature correction) was employed throughout. Arterial blood samples were drawn at suitable intervals for blood gas analysis and the measurement of sodium, potassium and glucose concentrations. At the termination of CPB, the anticoagulant effect of heparin was reversed with protamine sulphate such that the ACT approached the pre-CPB value. Other procedures (e.g. epicardial pacing, IABP) and other cardioactive agents (e.g. atropine, potassium chloride, dopamine, adrenaline, noradrenaline, isoprenaline, amiodarone) were used as deemed necessary.

4.2.11. Conduct of coronary artery bypass surgery

Where indicated the left internal mammary artery and/or adequate lengths of saphenous vein were harvested prior to the institution of CPB. The ‘cross-clamp fibrillation’ technique for myocardial protection was used in all cases. Distal coronary anastomoses were fashioned with the proximal aorta cross-clamped and the heart in electrically induced ventricular fibrillation. Proximal (aorto-saphenous) anastomoses were made with the aorta unclamped and the heart beating. Pulsatile CPB flow was used during periods when the aortic cross clamp was applied.

4.2.12. Postoperative management

Following the conclusion of surgery, patients were transferred to an intensive or high dependency care ward for extended recovery. In the majority of cases the author was responsible for escorting the patient to the intensive or high dependency care ward, and for ensuring that all
relevant details were communicated to nursing and medical staff. Patients typically remained sedated and ventilated until physiological variables had stabilised at which time they were weaned from mechanical ventilatory support and extubated. Patients were usually transferred to the cardiac surgical ward within 48 hours of surgery.

All patients were visited daily by the author or, on occasion, J. Stygall. For the purposes of this study, resting arterial pressure and pulse were recorded daily for the first six postoperative days. Resting 12 lead electrocardiographs were recorded on the first and sixth postoperative days. Urinalysis and blood biochemistry and haematology testing were performed immediately after surgery and on the first and sixth postoperative days. Blood samples were drawn by the author. Patients underwent interim neuropsychological testing on the sixth postoperative day. Testing in the first few days after surgery reveals a higher prevalence of neuropsychological deficit. However, the use of medications with psychotropic properties (e.g. analgesics) and the persistence of any metabolic derangement may make results difficult to interpret. Whenever possible, patients were discharged home on the seventh postoperative day.

4.2.13. Postoperative study medication

Using a separate postoperative medication kit - corresponding to the randomisation number - remacemide 150 mg (or placebo) four times daily was recommenced at 08:00 on the day after surgery. In all cases the author wrote the prescription for postoperative medication, personally collected the kits from the pharmacy, and ensured that nursing staff were familiar with the instructions for the postoperative administration of study medication. Patients who had not been extubated by this time or who were unable to receive oral medications started test medication at the next convenient dosing time. Patients unable to start postoperative test medication within five days of surgery did not receive any further test medication. The postoperative test medication containers and any unused tablets were collected and returned to the hospital pharmacy for drug accountability purposes.

Blood was drawn by the author for plasma remacemide concentration immediately before the 08:00 dose on the morning after surgery and immediately before the 18:00 dose on the fifth day after surgery.

4.2.14. Concomitant medication

All clinically indicated medications were permitted in the postoperative period with the exception of non-steroidal anti-inflammatory (NSAI) agents, anti-epileptic agents, nimodipine, anti-depressants and H1 type anti-histamines. In cases where an NSAI agent was clinically indicated (for example, in cases of post-operative pleuropercarditis) diclofenac (Vol-
or ibuprofen (Brufen) were administered under strict supervision with particular refer-
ence to upper gastrointestinal symptoms and indices of renal function.

With reference to the hospital in-patient prescription chart, the author was responsible for
the daily documentation of all postoperative medication.

4.2.15. Discharge from hospital

Patients were usually discharged home or to their referring hospital or institution on the sev-
enth postoperative day. Patients remaining in hospital for longer than seven days for other
than purely social or administrative reasons were deemed to have suffered a major adverse
event. (See below)

All patients were interviewed by the author prior to discharge in order to reinforce informa-
tion previously given regarding follow-up procedures and to encourage outpatient clinic at-
tendance.

4.2.16. Follow-up

All patients were routinely reviewed by the author in the Cardiothoracic Surgery Outpatient
Clinic eight weeks after surgery. This time was selected as being sufficiently distant from
surgery to produce stable results unconfounded by acute aspects of surgery and anaesthesia. In
the majority of cases, with the approval of the consultant surgeons involved, follow-up by the
author constituted the formal postoperative clinical assessment. Details of the consultation
(i.e. history, physical examination, investigations etc.) were duly recorded in the patients’
hospital record and any necessary correspondence generated.

In addition to chest radiography, electrocardiography and clinical examination, patients
underwent final neuropsychological evaluation and urinalysis and blood biochemistry and
haematology were performed. At approximately twelve weeks after surgery, patients were
contacted by telephone to confirm satisfactory recovery.

4.2.17. Laboratory tests

In addition to other routine clinical investigations, routine testing of urine and blood were per-
formed, as indicated above, at the following times; (1) Recruitment, (2) Admission, (3) Imme-
diately after surgery, (4) The morning after surgery, (5) The sixth day after surgery, and (6)
Eight weeks after surgery. Details of the tests are shown in Table 4.3.
Table 4.3: Details of routine biochemical, haematological and urine investigations performed during the study.

Additional investigations were carried out on those patients whose results were markedly deranged. In the vast majority of cases, blood samples were drawn by the author.

4.2.18. Neuropsychological evaluation

As described above patients underwent neuropsychological testing using a battery of neuropsychological tests developed by the Department of Psychiatry and Behavioural Medicine at UCLMS. (Appendix 6) All tests were conducted by either J.Stygall or N.TIMBERLAKE. The tests used were; the Rey Auditory Verbal Learning Test (AVLT), the Non-Verbal Recognition Memory (NVRM) test, the Trailmaking A (TMA) and B (TMB) tests, the Block Design Test (BDT) of the Wescheler Adult Intelligence Scale - Revised (WAIS-R), the Hand Tapping Test (HTT), the Letter Cancellation Test (LCT), the Symbol Digit Replacement (SDR) test, the Choice Reaction Time (CRT) test, and the Displaced Reaction Time (DRT) test. An assessment of mood and anxiety - thought to influence cognitive function - was made using the Beck Depression Inventory (BDI; Appendix 3) and the Spielberger State Anxiety Index (SSAI - Appendix 4). The tests were administered on three occasions;

1. One week before surgery before commencing study medication.
2. Six days after surgery after completion of study medication.
3. Eight weeks after surgery.

The Spielberger Trait Anxiety Index (STAI; Appendix 5) was administered pre-operatively. An assessment of intellectual capacity (intelligence quotient) was made using the Vocabulary Subtest (WVS) and Picture Completion Subtest (WPCS) of the Wescheler Adult Intelligence Scale - Revised (WAIS-R), and the National Adult Reading Test (NART). (Table 4.4)
Neuropsychological testing was conducted during office hours in one of two quite rooms set aside specifically for this purpose in the Department of Behavioural Sciences. A small number of patients underwent preoperative assessment in a quiet room in the Outpatient Department of University Hospital, Cardiff. On these occasions the author and J. Stygall travelled to Wales in order to interview and recruit patients to the study. Patients enrolled in this manner underwent all preoperative investigations on the same day.

Whenever possible the same examiner conducted assessments for any particular patient at all three time points. No attempt was made to conduct each of the three assessments at the same time of the day. The physicians involved in this investigation were unaware of the results of these assessments until after completion of the entire study. In the event that test results suggested a clinically significant psychological or psychiatric disorder, the finding would be discussed with the head of department and appropriate action initiated.

### 4.2.19. Subjective outcome assessment

In addition to the objective cognitive function outcome measures detailed above, patients were asked to report their subjective assessment of outcome in nine cognitive 'domains' by answering a short questionnaire (Appendix 2) 6 days and 8 weeks after surgery. Patients were asked to report whether there was an improvement, no change, or a worsening in ability compared to their preoperative baseline. The domains used were: (1) alertness and clarity of thought, (2) forgetfulness, (3) having minor accidents, (4) reaction time, (5) problem solving, (6) decision making, (7) attention, (8) making mistakes and (9) concentration.

<table>
<thead>
<tr>
<th>Test</th>
<th>Type</th>
<th>-1 Wk</th>
<th>6 Dys</th>
<th>8 Wks</th>
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<tr>
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</table>

Table 4.4: Summary neuropsychological tests, and measures of anxiety, depression and intelligence used and timing of administration. (Test types: Q= Questionnaire based test, M= Manually administered test, C= Computer assisted or based test administration)
4.2.20. Adverse events

The author was available (by either telephone or radiopager) 24 hours a day, 7 days a week to deal with queries from patients, relatives, general practitioners and nursing staff. During times of absence and annual leave, this function was performed by W. Pugsley.

An adverse event was defined as any symptom, sign, illness or experience developing or increasing in severity during the study period. This included any major alteration in laboratory values, apparently unrelated illness, accident or unanticipated procedure. Adverse events were recorded from the time of recruitment by the author.

Major adverse events were considered to include; death of the patient, any life threatening condition or situation, unexpected or prolonged hospitalisation, severe or permanent disability, the occurrence of malignant neoplasm at any time during or after the study, events related to congenital abnormality, symptoms of drug overdose, abnormalities in laboratory variables leading to withdrawal of the patient from the study or any other event of major clinical significance.

Minor adverse events were considered to include all those conditions which were not common or expected sequelae of cardiac surgery, and associated routine investigations and/or treatment. Some minor adverse events (e.g. post-operative atrial fibrillation) were considered to have become major events when a defined end point had been achieved. (i.e. direct current cardioversion under general anaesthesia in cases of atrial fibrillation resistant to standard pharmacological antiarrhythmic treatments)

Where indicated adverse events, both minor and major, were followed up until their conclusion or the end of the study period. In cases where additional follow-up was conducted at other institutions, copies of correspondence and details of clinical investigations pertaining to clinical progress were obtained.

The general practitioner of every patient and, where appropriate, the referring hospital physician were informed of the participation of their patient in the study and were requested to inform the investigators of any late adverse event or events.

4.2.21. Remacemide Assay

Blood samples for estimation of plasma levels of remacemide and its desglycine metabolite (ARL12495) were drawn on four occasions. On entry to the study, just before the third dose on the day before surgery, on the morning after surgery, and just before the third dose on the fifth postoperative day. Plasma was immediately separated from whole blood by centrifugation by the author and stored at -20 °C for batch processing. Samples were analysed using HPLC with selective fluorescence using o-phthalaldialdehyde detection. (Department of
Bioanalysis and Physical Chemistry, Astra Charnwood, Loughborough, UK) The lower limit of quantification for remacedmide and ARL12495 was 10 ng/ml. Samples drawn from patients dosed with placebo were not analysed.

4.2.22. Patient withdrawal

All patients recruited to the study were made aware of their right to withdraw from the study at any time without prejudice. Upon completion of pre-operative study medication, however, patients were not withdrawn from follow-up. Patients could be withdrawn from the study by the investigators because of the occurrence of an adverse event, a protocol violation, any significant intercurrent illness, worsening cardiac status, pregnancy, clinically significant abnormalities in laboratory variables.

4.2.23. Data collection, storage and analysis

All data collected in this study was stored in duplicate by both Astra Charnwood and the Middlesex Hospital research group. At the latter, data were stored on Macintosh computers in a series of Excel (Microsoft) spreadsheets. Data were entered by the author and research assistants (S. Cutler and T. Shah). Statistical analyses were performed independently at both sites. All statistical hypothesis tests were 2-tailed (unless otherwise stated) and carried out at the 5% level of significance. In cases were multiple comparisons were made, a more stringent level of statistical significance (1%) was used. Post hoc statistical analyses were performed by J. Stygall (using SPSS), the author (using Excel and StatView versions 4 & 5) and statisticians within the Department of Anesthesiology at Duke University, North Carolina (using SAS).

Demographic and other normally distributed parametric data were analysed using Student’s t test. Post-operative social and subjective assessments were compared using chi-squared or Fisher’s Exact probability, as appropriate.

Changes in biochemical and haematological variables from baseline at each time-point were analysed by Mann-Whitney U tests. Spearman’s rank correlation was used to compare maximal, early preoperative changes in biochemical test results with cerebral microembolic event count, number of bypass grafts performed, and CPB duration.

Correlation between the number of cerebral microemboli events detected and patient age, CPB duration, and cognitive deficits were made using Spearman’s Rank Correlation.

Prospective analysis of neuropsychological data was conducted using two methods. Firstly, changes in neuropsychological test performance (change scores) after surgery were compared to baseline for the two groups using the Mann-Whitney U test. Secondly, a categorical defini-
tion of neuropsychological deficit (a change in test score of one or more standard deviations from baseline in two or more tests) was used to compare the groups.

In light of the results (primary endpoint) of this study and issues raised in a number of articles published both during the course of the study and after its completion, further methods of data analysis were deemed appropriate. In summary, the data were analysed in four different ways with respect to both decline and improvement in performance. For convenience the methods (both prospective and retrospective) used are presented together.

In the first and second analyses, conventional categorical definitions (applied in previously reported studies) were used. In the third, changes in neuropsychological test performance (change scores) after surgery were compared to baseline for the two groups using the Mann-Whitney U test. In the fourth, a continuous method was used similar to that described by Grieco. [Grieco, 1996] (see below)

From the results of the pre-operative neurological evaluations a mean and standard deviation was calculated for each test. Multiple scores on a single test were not considered as independent. In the case of the Rey AVLT the results of seven components of the test were summed to give a single result, as were the left and right hand scores from the tapping tests.

Because of the potential for all neuropsychological tests to show learning it was hypothesised that if any neuroprotective effect was to be discerned in the remacemide treated group they should show a greater improvement (i.e. greater learning). For this reason neuropsychological test performance was analysed in terms of both deterioration and improvement.

The methods used are summarised in Table 4.5 and discussed in detail below.

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<thead>
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</tr>
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<td>Deficit</td>
<td>Deterioration in 2 or more tests</td>
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<tr>
<td></td>
<td>Improvement</td>
<td>≥ 1SD improvement in test score</td>
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Table 4.5: Definitions of statistical methods used to analyse neuropsychological test data. Terms in italics represent post hoc analyses.
4.2.23.1. Neuropsychological test analysis method #1

A patient was defined as having sustained a significant post-operative neuropsychological deterioration in a particular test if their score in that test was one or more standard deviations below the study population mean. A patient was considered to have sustained a neuropsychological deficit if they had a deterioration in two or more neuropsychological tests. To date this has been the method of data analysis used by the Middlesex Hospital Behavioural Sciences Unit and was the original primary data analysis method for this study.

In addition, and for the purposes of this report, a patient was defined as having improved their performance in a particular test if their score was one or more standard deviations above the study population mean. Patients were considered to have had a significant improvement in neuropsychological test performance if they had an improvement in two or more neuropsychological tests.

4.2.23.2. Neuropsychological test analysis method #2

A method of analysis, similar to that described above, has been reported by others including the neurological outcomes group at Bowman Gray Medical Center, NC which uses a fixed percentage decline in test performance to define neuropsychological deficit.

A patient was defined as having sustained a significant post-operative neuropsychological deterioration in a particular test if their score in that test was 20% or more below their preoperative test score. A patient was considered to have sustained a neuropsychological deficit if they had a deterioration in two or more neuropsychological tests. Again, for the purposes of this report, a patient was defined as having improved their performance in a particular test if their score was 20% or more above their preoperative test score. Patients were considered to have had a significant improvement in neuropsychological test performance if they had an improvement in two or more neuropsychological tests.

4.2.23.3. Neuropsychological test analysis method #3

In this method individual changes scores (i.e. postoperative test score - preoperative test score) were compared for the two treatment groups by the Mann-Whitney U test. The component parts of the Rey AVLT and tapping tests were analysed separately.

4.2.23.4. Neuropsychological test analysis method #4

This method was used because of suggestions that the falling incidence of neuropsychological dysfunction after cardiac surgery has made deficit analysis using categorical definitions increasingly insensitive. Using this method each test subject's test score on each occasion was
converted into a standard score using the standard deviation of the preoperative group performance. (i.e. $Z = \frac{x_1 - x_2}{SD}$, where $x_1$ is the preoperative score, $x_2$ is the postoperative score, and $SD$ is the standard deviation of the preoperative group scores. When poorer test performance resulted in a higher test score, $x_1$ and $x_2$ were swapped so that poorer postoperative test performances always yielded a negative $Z$ score) From these standard scores a difference score was calculated for each subject by subtracting the postoperative standard score from the preoperative standard score to reflect the relative change in performance from before to after surgery. If improved performance in any test was reflected by a lower score (e.g. in timed tasks) the directional data were reversed so that all improvements gave rise to positive differences.

The incidence of neuropsychological deteriorations and deficits in the treatment and placebo groups were compared using the Student $t$ test, Mann-Whitney U test, Fisher's exact probability or Chi squared test as appropriate. In all analyses, two-tailed tests were used and statistical significance was assumed at the 0.05 level.

4.2.24. Sample size

Currently available literature suggests that neuropsychological deficit following coronary artery bypass surgery ranges between 30% and 70%. Assuming that 30% of patients in the placebo group sustain a clinically significant neuropsychological deficit following surgery a sample size of 180 (90 in each group) would be adequate to detect a 20% or more improvement in remacemide-treated patients (i.e. less than or only 10% experiencing a clinically significant deficit) If, however, 70% of patients in the placebo group experience a clinically significant neuropsychological deficit following surgery, this sample size would be adequate to detect a 20% or more improvement in remacemide-treated patients (i.e. less than or only 50% experiencing a clinically significant deficit) Calculations were based on two-tailed tests with a 5% level of significance and a power (1-8) of 80%.
Chapter 5

Clinical Investigation - Results
5.1. Enrollment

During the period of study (November 1992 to July 1994) some 400 cases suitable for study were referred to the cardiothoracic surgical team. The author approached virtually all patients suitable for study enrollment. Those not recruited to the study were mostly emergency cases or re-operations, the remainder failed to meet inclusion criteria. Some 20 patients declined the invitation to participate in the study. A total of 200 patients were eventually recruited to the study. Of these, 29 (14.5%) were excluded at baseline. (Table 5.1) The majority of these exclusions were made on the basis of abnormal laboratory values (10) or withdrawal of consent (5). After discussion with the sponsor, a small number of patients with significant but isolated elevations in serum gamma glutamyl transferase were not excluded from further study participation.

<table>
<thead>
<tr>
<th>Reason for Withdrawal</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal laboratory values</td>
<td>13*</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>5</td>
</tr>
<tr>
<td>Disallowed medication</td>
<td>3*</td>
</tr>
<tr>
<td>Surgery delayed</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal medical history</td>
<td>3</td>
</tr>
<tr>
<td>Surgery no longer indicated</td>
<td>1</td>
</tr>
<tr>
<td>Surgery expedited due to unstable angina</td>
<td>1</td>
</tr>
<tr>
<td>Poor eyesight - unable to perform neuropsychological tests</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 5.1: Summary of reasons for exclusion from study following recruitment. (*)One patient was excluded on the basis of both abnormal laboratory results and use of a disallowed medication.

<table>
<thead>
<tr>
<th>No. Patients</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male : Female)</td>
<td>78 : 9</td>
<td>72 : 12</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>59 ±1 [35 - 74]</td>
<td>59 ±1 [36 - 74]</td>
<td>0.65</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 ±1 [150 - 188]</td>
<td>171 ±1 [155 - 189]</td>
<td>0.66</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.2 ±1.5 [54.1 - 127.2]</td>
<td>79.8 ±1.4 [51.9 - 109.8]</td>
<td>0.91</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>40 (46%)</td>
<td>43 (51%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetics</td>
<td>9 (10.3%)</td>
<td>6 (7.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Vessels to be grafted</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 5.2: Summary of patient characteristics. Data are expressed as mean ±SEM and [range] unless otherwise specified. There were no significant differences between treatment and placebo groups.

The remaining 171 patients were randomised to receive either Remacemide Hydrochloride (87) or placebo (84). The groups were well matched in terms of age, height, and weight. (Ta-
Cardiac medical histories were similar for both groups. The mean number of vessels to be grafted was 2.7 for both groups.

5.2. Withdrawals after randomisation

Twelve patients (7 in the placebo group) were withdrawn from the study before the 8 week postoperative assessment. (Table 5.3)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Remacemide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events</td>
<td>2</td>
<td>3*</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Consent Withdrawn</td>
<td>0</td>
<td>2*</td>
</tr>
<tr>
<td>Surgery Delayed</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 5.3: Summary of reasons for withdrawal following randomisation. (*) One patient refused to consent to undergo follow-up assessment at eight weeks because of a major adverse event (sternal wound infection).

The timing of withdrawal was as follows. One patient in each group completed both pre- and post-operative dosing, 5 patients (4 in the placebo group) completed the pre-surgery dosing and 5 patients (2 in the placebo group) withdrew during the pre-surgery dosing period. Five patients (3 in the placebo group) withdrew due to adverse events. Three patients (2 in the placebo group) had surgery delayed for administrative reasons.

5.3. Adverse Events

Eight patients were withdrawn from the study because of adverse events. (Table 5.4) Of these half (4) had adverse events leading to death. (see below)

<table>
<thead>
<tr>
<th>Group</th>
<th>Adverse Event(s)</th>
<th>Days on Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remacemide</td>
<td>Gastric ulcer, gastrointestinal haemorrhage, death</td>
<td>11</td>
</tr>
<tr>
<td>Remacemide</td>
<td>Coughing, dysphonia</td>
<td>4</td>
</tr>
<tr>
<td>Remacemide</td>
<td>Nausea, ataxia, paraesthesia, insomnia</td>
<td>2</td>
</tr>
<tr>
<td>Remacemide</td>
<td>Coma, cerebral infarction, death</td>
<td>5</td>
</tr>
<tr>
<td>Placebo</td>
<td>Bacterial infection, chest pain, phlebitis, dyspnoea, palpitation</td>
<td>10</td>
</tr>
<tr>
<td>Placebo</td>
<td>Bradycardia, hypotension, cardiac failure, renal failure, death</td>
<td>5</td>
</tr>
<tr>
<td>Placebo</td>
<td>Chest pain</td>
<td>1</td>
</tr>
<tr>
<td>Placebo</td>
<td>Hypotension, chest pain, myocardial infarction, ventricular fibrillation, cardiac arrest, death</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 5.4: Patients withdrawn because of adverse events.

In the remacemide group, adverse events were reported for 5 patients during the pre-treatment period, 58 patients during the pre-surgery treatment period, 12 patients during surgery, 34 patients during the post-surgery treatment period, and 25 patients in the post-treatment period.
The corresponding numbers for the placebo group were 4 patients during the pre-treatment period, 25 patients during the pre-surgery treatment period, 17 patients during surgery, 31 patients during the post-surgery treatment period, and 13 patients in the post-treatment period.

The most frequently reported adverse events are summarised in Table 5.5. Dizziness was reported by 41 patients in the remacemide group and 5 patients in the placebo group during both the treatment and post-treatment periods (p<0.0001). All 41 patients in the remacemide group reported dizziness in the pre-surgery treatment period compared with 4 in the placebo group.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Remacemide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness *</td>
<td>41</td>
<td>5</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Dysnoea</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Ataxia</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Other atrial arrhythmia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Other surgery during study period</td>
<td>4 2</td>
<td></td>
</tr>
<tr>
<td>Stupor</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 5.5: Numbers of patients with most frequently reported adverse events during treatment and post-treatment periods. * p<0.0001 (Fisher’s exact).

Adverse events that were considered to be major adverse events were recorded for 28 patients in the remacemide group and 24 patients in the placebo group. One patient in the remacemide treated group developed severe nausea that was considered to be related to remacemide. Four patients in the placebo group had events that were considered to be related to study medication.

Major adverse events, their clinical severity and possible relationship to study medication or participation are shown for the two treatment groups in Tables 5.6 and 5.7.
<table>
<thead>
<tr>
<th>Major Adverse Event(s) - Remacemide Group</th>
<th>Severity</th>
<th>Related ?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia and hypotension during placement of lines after induction of anaesthesia</td>
<td>++++</td>
<td>UR</td>
</tr>
<tr>
<td>Postoperative thrombophlebitis, peripheral oedema, chest pain, pulmonary embolism</td>
<td>++++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative gastric ulcer, gastrointestinal haemorrhage, death</td>
<td>++++</td>
<td>UL</td>
</tr>
<tr>
<td>Intraoperative hypotension</td>
<td>++++</td>
<td>UR</td>
</tr>
<tr>
<td>Postoperative chest pain, pulmonary embolism</td>
<td>+++</td>
<td>UL</td>
</tr>
<tr>
<td>Pleural effusion, dyspnoea</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative bronchitis, fever, cough</td>
<td>++</td>
<td>UR</td>
</tr>
<tr>
<td>Postoperative dysphasia, muscle weakness</td>
<td>+</td>
<td>UL</td>
</tr>
<tr>
<td>Reoperation for surgical bleeding</td>
<td>+++</td>
<td>UR</td>
</tr>
<tr>
<td>Fever</td>
<td>++</td>
<td>UR</td>
</tr>
<tr>
<td>Fever, bronchitis</td>
<td>+</td>
<td>UR</td>
</tr>
<tr>
<td>Intraoperative hypotension</td>
<td>+++</td>
<td>UR</td>
</tr>
<tr>
<td>Wound haematoma, bacterial infection</td>
<td>++</td>
<td>UR</td>
</tr>
<tr>
<td>Reoperation for surgical bleeding</td>
<td>++++</td>
<td>UR</td>
</tr>
<tr>
<td>Chest pain, broken sternal wires, reoperation for rewiring of sternum</td>
<td>++</td>
<td>UR</td>
</tr>
<tr>
<td>Postoperative atrial arrhythmia</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative wound infection</td>
<td>++</td>
<td>UR</td>
</tr>
<tr>
<td>Atrial fibrillation, somnolence, dyspnoea</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative pneumonia</td>
<td>++</td>
<td>UR</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation, anaemia</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative nausea</td>
<td>++</td>
<td>POSS</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>+++</td>
<td>UR</td>
</tr>
<tr>
<td>Atrioventricular block, atrial arrhythmia</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Intraoperative myocardial infarction, hypotension, ventricular fibrillation</td>
<td>+++</td>
<td>UL</td>
</tr>
<tr>
<td>Pneumonia, coma, cerebrovascular accident (thromboembolic), Death</td>
<td>++++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative angina pectoris, myocardial infarction</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative limb pain/neuralgia</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative bronchospasm, dyspnoea, hypertension, hyperhidrosis</td>
<td>++</td>
<td>UL</td>
</tr>
<tr>
<td>Postoperative dyspnoea, dizziness, angina pectoris</td>
<td>++</td>
<td>UR</td>
</tr>
</tbody>
</table>

Table 5.6: Summary of major adverse events in 28 patients receiving remacemide reported during the study. (abbreviations: +=mild, ++=moderate, +++=severe, ++++=very severe, UR=unrelated, UL=unlikely, POSS=possible)
5.4. Deaths

There were four deaths; two in each study group.

Patient #1 (remacemide): A 58 year old male with non insulin dependent diabetes mellitus who had incomplete coronary revascularisation because of severe distal coronary artery disease. Weaning from CPB was complicated by left ventricular dysfunction and ventricular dysrhythmias thought to be due to intraoperative myocardial infarction. Following a prolonged period of inotropic and ventilatory support on the Intensive Care Unit, the patient became comatose. A cerebral CT scan confirmed a cerebral infarction (thought to be thromboembolic).

The patient died a few days later from multi-system organ failure.
Patient #2 (remacemide): A 67 year old male who had a completely uneventful operative and early postoperative course who died at home two weeks after as a result of massive gastrointestinal haemorrhage. At autopsy the cause was found to be an large gastric ulcer that had been asymptomatic and previously undiagnosed.

Patient #3 (placebo): A 66 year old male suffered an acute anterior myocardial infarction complicated by intractible ventricular fibrillation just three hours before surgery. Despite exhaustive attempts, the patient could not be resuscitated.

Patient #4 (placebo): A 65 year old male with insulin dependent diabetes mellitus who had postoperative left ventricular failure complicated by bradyarrhythmias, cardiogenic pulmonary oedema, hepatic dysfunction and acute renal failure. The patient died from sepsis and multi-system organ failure four weeks after surgery.

No death was thought to be attributable either to treatment with remacemide or to study participation.

5.5. Intelligence / intellectual capacity

The intellectual capacity (IQ) of the patients at entry to the study is summarised in Table 5.8. The mean values of all the IQ tests were higher in the placebo group. Assessment of IQ by the National Adult Reading Test (NART) was started after half of the patients had entered the study.

<table>
<thead>
<tr>
<th></th>
<th>Remacemide HCl</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (n)</td>
<td>Range</td>
</tr>
<tr>
<td>WAIS VS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw Score</td>
<td>47.7 (87)</td>
<td>9 - 66</td>
</tr>
<tr>
<td>Standardised Score</td>
<td>10.1 (87)</td>
<td>3 - 16</td>
</tr>
<tr>
<td>WAIS PCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw Score</td>
<td>16.3 (87)</td>
<td>5 - 20</td>
</tr>
<tr>
<td>Standardised Score</td>
<td>10.7 (87)</td>
<td>4 - 17</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>105.1 (87)</td>
<td>64 - 148</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>121.0 (87)</td>
<td>76 - 150</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>113.5 (87)</td>
<td>78 - 144</td>
</tr>
<tr>
<td>NART</td>
<td>29.7 (53)</td>
<td>4 - 46</td>
</tr>
<tr>
<td>NART Verbal IQ</td>
<td>110.3 (53)</td>
<td>87 - 125</td>
</tr>
<tr>
<td>NART Performance IQ</td>
<td>110.5 (53)</td>
<td>94 - 121</td>
</tr>
<tr>
<td>NART Full Scale IQ</td>
<td>110.9 (53)</td>
<td>90 - 124</td>
</tr>
</tbody>
</table>

Table 5.8: Intellectual capacity at entry to the study. Data expressed as mean (n), [range]. (WAIS, Weschler Adult Intelligence Scale; VS, Vocabulary Subtest; PCS, Picture Completion Subtest; NART, National Adult Reading Test).

All the IQ tests mean values were higher in the placebo group. The mean for the Weschler Adult Intelligence Full Scale IQ was 113.5 for the remacemide group (range 78-144) and 117.5 for the placebo group (range 67-150). Assessment of IQ by the National Adult Reading Test
was started after half the patients had entered the study. The mean NART IQ values were 110.9 for the remacemide group (range 90-124) and 112.0 for the placebo group (range 95-125).

5.6. Mood and anxiety

Mood and anxiety states at entry to the study are summarised in Table 5.9. These were similar in both groups.

![Table 5.9: Mood and anxiety states at entry to the study. Data expressed as mean, (n).](image)

Beck Depression Inventory (BDI) scores and Spielberger State Anxiety Inventory scores were analysed for all patients included in the efficacy analyses. The mean scores for both tests were similar for the treatment groups at all three assessments. The scores at 6 days after surgery were similar to those at baseline (entry to the study) whilst those at 8 weeks after surgery were reduced in both groups. (Table 5.10)

![Table 5.10: Summary of indices of depression and anxiety at baseline and 6 days and 8 weeks after surgery in patients included in the efficacy analyses. (BDI=Beck Depression Inventory, SSAI=Spielberger State Anxiety Index)](image)

Combining the data from both groups, mean±SD BDI scores were 7.4±4.7 before surgery, and 8.2±5.4 and 5.1±4.7 at 1 week and 8 weeks, respectively, after surgery. The number of depressed patients (i.e. BDI score ≥10) was 41 (26.1%) before surgery, and 60 (38.7%) and 28 (18.1%) at 1 week and 8 weeks, respectively, after surgery.

One week after surgery 34/116 (29.3%) patients, who were not depressed before surgery, were depressed, whereas 26/41 (63.4%) preoperatively depressed patients remained depressed (p=0.0001, χ²). Eight weeks after surgery only 7/116 (6.0%) patients, who were not depressed before surgery, were depressed, whereas 21/41 (51.2%) preoperatively depressed patients re-
mained depressed (p<0.0001, χ²). The incidence of new postoperative depression in this investigation was low. Of those patients who were depressed before surgery more than half remained depressed after surgery. [Arrowsmith, 1999]

There was a weak but statistically significant association between increasing patient age and increase in BDI score from baseline at both 1 week (rho=0.168, p=0.036) and 8 weeks (rho=0.300, p=0.0002) after surgery (Spearman).

5.7. Intraoperative variables

The total length of surgery, CPB time, estimated blood loss, aortic cross-clamp (ischaemic) time and total volume of fluids lost/infused were similar in both groups. (Table 5.11) Data were incomplete in a total of 8 cases (3 in the remacemide group and 5 in the placebo group).

<table>
<thead>
<tr>
<th></th>
<th>Remacemide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery Time (Minutes)</td>
<td>193 ±5 (84)</td>
<td>83-323</td>
</tr>
<tr>
<td>Bypass Time (Minutes)</td>
<td>81 ±3 (84)</td>
<td>25-164</td>
</tr>
<tr>
<td>Total Aortic Cross-Clamp Time (Minutes)</td>
<td>37 ±1 (81)</td>
<td>8-73</td>
</tr>
<tr>
<td>Estimated Blood Loss (Litres)</td>
<td>0.6 (83)</td>
<td>0.3-1.2</td>
</tr>
<tr>
<td>Fluids Administered (Litres)</td>
<td>5.6 (84)</td>
<td>2.5-8.8</td>
</tr>
</tbody>
</table>

Table 5.11: Summary of operative characteristics. Data are expressed as mean (±SEM) and [range] unless otherwise specified. There were no significant differences between treatment and placebo groups.

Mean arterial (perfusion) pressures during 15-minute epochs before, during and after CPB were similar in both groups. (Table 5.12) In the first 15 minutes after induction of anaesthesia, mean ±SD arterial pressure in the placebo group were statistically significantly higher than those in the remacemide group (85 ±16 versus 77 ±18 mmHg; p<0.01). The difference, however, is unlikely to have been clinically significant at this time point.
Table 5.12: Mean arterial pressure measurements (mmHg) in 15 minute epochs before (Pre), during (CPB) and after (Post) cardiopulmonary bypass. Data are expressed as mean ±SD and (range). *n=1, **n=2, ***n=3

<table>
<thead>
<tr>
<th></th>
<th>Pre 1</th>
<th>Pre 2</th>
<th>Pre 3</th>
<th>Pre 4</th>
<th>Pre 5</th>
<th>Pre 6</th>
<th>Pre 7</th>
<th>Pre 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>35.9 ±0.6</td>
<td>35.6 ±0.6</td>
<td>35.2 ±0.5</td>
<td>35.0 ±0.5</td>
<td>34.9 ±0.5</td>
<td>34.3 ±0.8</td>
<td>33.2 *</td>
<td>33.2 *</td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>35.5 ±0.4</td>
<td>35.1 ±0.5</td>
<td>34.9 ±0.5</td>
<td>34.0 *</td>
<td>33.8 *</td>
<td>33.7 *</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5.13: Mean nasopharyngeal temperature measurements in 15 minute epochs before (Pre), during (CPB) and after (Post) cardiopulmonary bypass, and mean maximum temperature prior to termination of cardiopulmonary bypass (CPB Max). Data are expressed as mean ±SD and range. There were no significant differences between remacemide (R) and placebo (P) groups. *n=1, **n=2

<table>
<thead>
<tr>
<th></th>
<th>Post 1</th>
<th>Post 2</th>
<th>Post 3</th>
<th>Post 4</th>
<th>Post 5</th>
<th>Post 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>36.6 ±0.7</td>
<td>35.8 ±0.5</td>
<td>35.6 ±0.9</td>
<td>35.7 *</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>35.7 ±0.7</td>
<td>35.8 ±0.5</td>
<td>35.7 ±0.7</td>
<td>34.8 **</td>
<td>33.8 *</td>
</tr>
</tbody>
</table>

In all patients studied, nasopharyngeal temperature tended, as expected, to drift downward in the period between the induction of anaesthesia and the onset on CPB. The variability in duration of CPB probably explains the much of the observed variability in nasopharyngeal temperature during CPB, but maximum temperature at separation from CPB was similar in both groups of patients (Table 5.13). Statistical analysis revealed no significant differences.
As rewarming rates were stipulated in the investigation protocol, it is likely that all patients were subjected to similar levels of cerebral 'thermal stress' during rewarming. As expected temperatures tended to drift downward following separation from CPB.

Pump flow rates during CPB were similar in both groups (Table 5.14). Body surface area (BSA) was estimated using the Haycock geometric method, where $\text{BSA} = 0.024265 \times H^{0.3944} \times W^{0.5378}$ (H=height in cm, W=weight in kg). [Haycock, 1978] The intraoperative data available and the wide variation in duration of CPB makes it difficult to demonstrate that pump flows were adjusted – in compliance with the investigation protocol (see 4.2.10) – according to nasopharyngeal temperature.

<table>
<thead>
<tr>
<th>L/min</th>
<th>CPB 1</th>
<th>CPB 2</th>
<th>CPB 3</th>
<th>CPB 4</th>
<th>CPB 5</th>
<th>CPB 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>4.4±0.5</td>
<td>4.4±0.4</td>
<td>4.4±0.6</td>
<td>4.5±0.6</td>
<td>4.0±0.3</td>
<td>5.3*</td>
</tr>
<tr>
<td></td>
<td>(3.5–5.4)</td>
<td>(3.0–5.6)</td>
<td>(2.6–5.9)</td>
<td>(3.3–5.5)</td>
<td>(3.7–4.3)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>4.4±0.5</td>
<td>4.4±0.5</td>
<td>4.3±0.6</td>
<td>4.5±0.5</td>
<td>4.1*</td>
<td>4.3*</td>
</tr>
<tr>
<td></td>
<td>(3.0–5.4)</td>
<td>(3.0–5.2)</td>
<td>(3.0–5.4)</td>
<td>(3.6–5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t=0.038</td>
<td>t=-1.099</td>
<td>t=0.276</td>
<td>t=-0.065</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>p=0.97</td>
<td>p=0.28</td>
<td>p=0.78</td>
<td>p=0.95</td>
<td></td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>L/min/m²</th>
<th>CPB 1</th>
<th>CPB 2</th>
<th>CPB 3</th>
<th>CPB 4</th>
<th>CPB 5</th>
<th>CPB 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>2.3±0.2</td>
<td>2.3±0.2</td>
<td>2.2±0.3</td>
<td>2.3±0.3</td>
<td>2.3±0.3***</td>
<td>3.0*</td>
</tr>
<tr>
<td></td>
<td>(1.6–3.0)</td>
<td>(1.6–3.0)</td>
<td>(1.3–2.9)</td>
<td>(1.8–2.7)</td>
<td>(2.1–2.4)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>2.0±0.2</td>
<td>2.3±0.2</td>
<td>2.2±0.3</td>
<td>2.3±0.2</td>
<td>2.2*</td>
<td>2.3*</td>
</tr>
<tr>
<td></td>
<td>(1.5–2.4)</td>
<td>(1.6–2.9)</td>
<td>(1.5–2.9)</td>
<td>(1.8–2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t=-0.234</td>
<td>t=-0.803</td>
<td>t=-0.034</td>
<td>t=0.417</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>p=0.82</td>
<td>p=0.43</td>
<td>p=0.97</td>
<td>p=0.68</td>
<td></td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.14: Mean bypass pump flow rates (in L/min and L/min/m²) in 15 minute epochs during cardiopulmonary bypass. Data are expressed as mean (±SD) and range. There were no significant differences between remacemide (R) and placebo (P) groups. *n=1, ***=3

Satisfactory measurements of cerebral (left middle cerebral artery) blood flow velocity (CBFV) before, during and after CPB were made in 133/148 patients (65 placebo, 68 remacemide) in whom TCD monitoring was attempted. In both groups, CBFV tended to fall after the onset of CPB and then gradually rise over the remainder of CPB. Although measured CBFV was subject to considerable variability – particularly in the placebo group – there were no statistically significant differences between the groups (Figure 5.1). The lack of a detailed, contemporaneous record of arterial pressure, pump flow rate, core temperature and arterial CO₂ makes more precise comparisons impossible.

A consistent record of the results of intraoperative blood gas analyses could not be located. It is, therefore, impossible to demonstrate the degree of compliance with α-stat blood gas management.
In summary there were no significant inter-group differences in terms of: duration of surgery, duration of CPB, and intraoperative arterial pressure, temperature, cerebral blood flow velocity and bypass pump flow.

5.8. Study medication compliance

Compliance with test treatment was good. Two patients were excluded from efficacy analyses because surgery was delayed (4 days and 5 days) beyond the completion of pre-surgery dosing. Patients who missed any test treatment after surgery were included in efficacy analyses. This included one patient in the remacemide group who refused to take any test treatment after surgery but agreed to undergo neuropsychological assessments. Also excluded from the efficacy analyses was one patient in the placebo group, who was discovered to have been taking amitriptyline at entry to the study and during both the pre- and post-operative periods. Patients given non-steroidal anti-inflammatory agents for the relief of persistent post-operative pleuro-pericardial pain were not excluded from the efficacy analyses. Three patients were excluded from efficacy analyses because of delayed post-operative neuropsychological assessments. The calculation of baseline standard deviations for neuropsychological tests included data from patients withdrawn from the study with the exception of two patients who had inadequate comprehension of the neuropsychological tests.

5.9. Plasma remacemide and ARL12495XX concentrations

Plasma concentrations of remacemide and ARL12495XX were successfully determined in at least one sample from 65/87 patients in the remacemide group. It was disappointing that analytical results were not available for all samples from these patients for a variety of reasons including loss of sample through tube breakage and, in the event of an unsuccessful first analy-
sis, through inability to reanalyse samples due to inadequate sample size. No analytical data were available for any of the sets of blood samples taken from the remaining 22 patients. In 18 of these the samples were of inadequate size, or lost due to tube breakage. One set of samples was lost during transit. Premature withdrawal from the study accounted for a further 3 sets of samples. There were two instances where measureable concentrations were recorded in 'pre-dose' samples. In the absence of a reason for these false positive results, the values from these patients were excluded from pharmacokinetic analysis. The data from one patient, who refused to take study medication in the postoperative period, were also excluded from the analysis. Of the 84 patients in the remacemide group providing plasma samples for analysis, the number of patients providing remacemide concentration data for inclusion in mean computations were; 53 for Sample#2 (pre-surgery trough sample), 61 for Sample#3 (24 hours post-surgery), and 47 for Sample#4 (post-surgery trough sample). The concentration of ARL12495XX was simultaneously determined in all of these samples. In addition an additional 3 post-surgery trough samples were analysed for ARL12495XX only. (Table 5.15)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Time from previous dose (hours)</th>
<th>Plasma Remacemide (ng/ml)</th>
<th>Plasma ARL12495XX (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Admission</td>
<td>4.2 ±0.3 (3.8-5.3)</td>
<td>232.2 ±94.3 (41.7-453.0)</td>
<td>102.6 ±35.3 (26.6-179.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=53</td>
<td>n=53</td>
</tr>
<tr>
<td>2. 24 hours</td>
<td>23.3 ±2.4 (18.2-32.8)</td>
<td>28.6 ±61.1 (&lt;10-299.0)</td>
<td>35.8 ±28.8 (&lt;10-190.0)</td>
</tr>
<tr>
<td>post surgery</td>
<td></td>
<td>n=61</td>
<td>n=64</td>
</tr>
<tr>
<td>3. Day 5 post surgery</td>
<td>404 ±0.4 (3.8-5.7)</td>
<td>171.8 ±114.3 (&lt;10-448.0)</td>
<td>76.9 ±44.7 (&lt;10-220.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=47</td>
<td>n=47</td>
</tr>
</tbody>
</table>

Table 5.15: Summary of plasma concentrations of remacemide and the desglycine metabolite ARL12495XX. Data expressed as mean±SD (range).

Mean±SD plasma levels of remacemide and ARL12495XX just before the third dose on the day of admission (Sample#2) were 232±94 ng/ml and 102±35 ng/ml respectively. Remacemide levels were clustered in the 195-210 ng/ml range and levels of ARL12495XX in the 30-45 ng/ml range. One patient, whose levels of remacemide (41.7 ng/ml) and ARL12495XX (26.6 ng/ml) were particularly low at this time in comparison with other patients, was thought to have missed the previous dose.

On the morning after surgery, before restarting oral medication, (Sample#3) the levels of remacemide and ARL12495XX were 28.6±61.1 ng/ml and 35.8±28.8 ng/ml respectively. The time from the previous dose to sample time varied from 18.2 to 32.8 hours. Remacemide levels were clustered in the 0-15 ng/ml range with 34 (83%) patients in this group having concentrations lower than the lower limit of quantification. Levels of ARL12495XX were clustered in the 16-24 ng/ml range reflecting a terminal half-life longer than that of the parent drug. In 5/50 (10%) patients the level of ARL12495XX was below the LOQ.
Just before the third dose on the fifth postoperative day (Sample#4) the levels of remacemide and ARL12495XX were 172±114 ng/ml and 76.9±44.7 ng/ml respectively. Although the time window over which samples were drawn was narrow (3.8 to 5.7 hours post-dose) the variability in concentrations was high. Remacemide levels were clustered in the 150-180 ng/ml range and ARL12495XX in the 80-88 ng/ml range. In seven patients the levels of both remacemide and ARL12496XX were low or below the LOQ suggesting poor compliance.

The similar means but higher variability in post-surgery levels of both remacemide and ARL12495XX may represent an effect of surgery, CPB and/or anaesthesia on uptake, distribution, metabolism and/or elimination.

Despite incomplete analyses for all patients these data suggest that the majority of patients in the remacemide group were exposed to ARL12495XX during and following surgery. In comparison to the dose ranging, safety and tolerability study (see section 3.5), mean pre-surgery trough remacemide concentrations in this study were lower (232.2±94.3 versus 420.8±142.9 ng/ml). In contrast, mean pre-surgery trough ARL12495XX concentrations in this study were higher (102.6±35.3 versus 85.5±60.2 ng/ml). Twenty-four hours after surgery, average plasma concentrations of both remacemide and ARL12495XX were higher than those reported in the previous study. Given the range of plasma concentrations found to neuroprotective in animal models it is unclear whether; (a) truly neuroprotective concentrations of either remacemide or ARL 12495XX were ever attained, and (b) neuroprotective concentrations were maintained throughout the period of presumed vulnerability (i.e. during and immediately after surgery).
5.10. Cerebral microembolic events

Intraoperative assessment of left middle cerebral artery blood flow velocity and microembolic events (MEE) was attempted in 148 (86%) patients. As described in section 4.2.9, MEE were quantified ‘off-line’. A small number of patients could not be studied as their surgery pre-dated the arrival of the TCD equipment. Equipment faults and absence of the research fellow precluded TCD monitoring in the others. Acceptable intraoperative monitoring of the left MCA was achieved in 140 (95%) of these 148 patients. The characteristics of these patients are summarised in Table 5.16.

<table>
<thead>
<tr>
<th></th>
<th>Remacemide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males : Females</td>
<td>65 : 6</td>
<td>60 : 9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ±8</td>
<td>60 ±8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 ±11</td>
<td>172 ±8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 ±14</td>
<td>80 ±12</td>
</tr>
<tr>
<td>IQ (n=138)</td>
<td>114 ±17</td>
<td>119 ±18</td>
</tr>
<tr>
<td>CPB Duration (min)</td>
<td>81 ±25</td>
<td>80 ±28</td>
</tr>
<tr>
<td>Bypass grafts (median)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>MEE (median)</td>
<td>171 54-1824</td>
<td>198 18-1098</td>
</tr>
<tr>
<td>MEE/CPB (median)</td>
<td>3 ±5</td>
<td>4 ±4</td>
</tr>
</tbody>
</table>

Table 5.16: Summary of patient characteristics and intraoperative variables for the 140 patients in whom TCD sonography was possible. (Data expressed as mean ±SD and range unless otherwise stated).

In all, nearly 250 hours of VHS video tape were analysed off-line by the author. Cerebral microembolic events were detected in all patients in every monitoring period during CPB. In 109 (78%) patients microembolic events occurred before the onset of CPB. There were invariably associated with aortic cannulation - that is, during digital palpation of the ascending aorta, placement of the purse-string suture, aortotomy and/or cannulation itself. (Figure 5.2)

Figure 5.2: The typical appearance of microembolic events (MEE) detected in the left middle cerebral artery with transcranial Doppler (TCD) sonography. MEE were detected during cardiopulmonary bypass (CPB) in every patient studied (left panel). Following the termination of CPB, MEE were frequently detected during manipulation of the ascending aorta. (right panel)
Overall, the median (range) number of microembolic events detected was 171 (18-1824) at a mean (range) rate of 2.33 (0.43-30.00) per minute of CPB. The majority of MEE were detected during the first 30-45 minutes of CPB. The numbers of MEE detected declined over the remainder of CPB and rose again in the 15-minute period immediately prior to the termination of CPB. (Figure 5.3) In all cases MEE were detected that appeared to be unrelated to any identifiable event and during periods of 'surgical inactivity'. In most cases MEE were associated with release of the aortic cross-clamp. In two cases large numbers of MEE were associated with venous air entrainment. MEE were detected in 82 (59%) patients following termination of CPB. In one case MEE were associated with inflation of an IABP after termination of CPB. Details of this case have been reported elsewhere. [Arrowsmith, 1997b]

Figure 5.3: Box and whisker plots of the incidence of cerebral microembolic events in remacemide group [Top] and placebo group [Bottom] before (Pre), during (15 - 165 minutes) and after (Post) cardiopulmonary bypass. Microembolic events occurring during the last 15 minutes of cardiopulmonary bypass are shown separately (Last).

Overall, there was a small but significant correlation between MEE and the number of bypass grafts performed. There did not, however, appear to be any correlation between the total MEE count and either the duration of CPB or patient age. (Table 5.17)
Curiously, in the placebo group, there did appear to be a small but significant correlation between MEE and both the number of bypass grafts performed and the duration of CPB. Quite why this apparent relationship is not evident in the remacemide group is unclear.

5.11. Neuropsychological assessments

In all 82/87 (94%) patients in the remacemide group and 74/84 (88%) patients in the placebo group underwent technically satisfactory (as judged by the psychologist) first postoperative neuropsychological evaluation between 6 and 8 days after surgery. 80/87 (92%) patients in the remacemide group and 74/84 (88%) patients in the placebo group underwent satisfactory second postoperative neuropsychological evaluation between 6 and 12 weeks after surgery. (Table 5.18)

Of the 62/171 (36%) patients who did not have evaluations as planned at 8 weeks after surgery, 29/171 (17%) patients were assessed before the 8th week and 33/171 (19%) patients after the 8th week. The number of patients who were not assessed at 8 weeks was similar in both the placebo and remacemide groups. (Table 5.18) In many instances these protocol violations were the result of patients requests (e.g. holidays etc.) and administrative reasons (e.g. public holidays, cancelled outpatient clinics etc.). Poor general health and/or an unwillingness to comply with follow-up many have accounted for the remainder. It is difficult to predict whether those patients who were not assessed at 8 weeks would have had significantly different test performances had they been assessed at 8 weeks as planned.

One patient in the placebo group did not undergo the first postoperative neuropsychological assessment until 20 days after surgery. One patient in each group did not undergo the second postoperative neuropsychological assessment until 16.5 weeks (remacemide) and 20 weeks (placebo) after surgery. The results of these tests were excluded from the analysis, as were those for two patients who had inadequate comprehension of the tests.
Pre-operative neuropsychological test data from 168/171 (98%) patients (87 remacemide, 81 placebo) were used to calculate baseline population means and standard deviations for each of the tests used.

As previously described the scores from the seven separate components of the Rey AVLT and the left and right hand tapping tests were summed to give aggregate AVLT and tapping test scores yielding a total of ten test scores. No statistically significant differences in preoperative scores were found between the two patient groups on any of the neuropsychological tests. (Table 5.19)
Table 5.19: Means ±SD, ranges and t-tests of the raw preoperative neuro-psychological test scores used in the efficacy analyses for patients in the remacemide group (n=87), the placebo group (n=81) and both groups (n=168) combined. (* n=167, ** n=86, † n=166, ‡ n=80) See text for definition of neuropsychological test abbreviations.

<table>
<thead>
<tr>
<th>Test</th>
<th>Combined n=168</th>
<th>Remacemide n=87</th>
<th>Placebo n=81</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS</td>
<td>9.4 ±2.7</td>
<td>9.3 ±2.4</td>
<td>9.5 ±2.9</td>
<td>-0.50</td>
<td>0.62</td>
</tr>
<tr>
<td>BDT</td>
<td>4 - 17</td>
<td>5 - 17</td>
<td>4 - 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>0.63 ±0.18</td>
<td>0.64 ±0.21</td>
<td>0.61 ±0.14</td>
<td>0.92</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>0.38 - 1.51</td>
<td>0.43 - 1.51</td>
<td>0.38 - 1.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRT</td>
<td>0.86 ±0.35</td>
<td>0.86 ±0.35</td>
<td>0.86 ±0.35</td>
<td>0.02</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>0.34 - 2.14</td>
<td>0.38 - 1.81</td>
<td>0.34 - 2.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCT</td>
<td>95 ±22</td>
<td>93 ±19</td>
<td>96 ±26</td>
<td>-0.87</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>57 - 220</td>
<td>62 - 168</td>
<td>57 - 220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVRM</td>
<td>332 ±33</td>
<td>333 ±39</td>
<td>332 ±26</td>
<td>0.08</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>284 - 556</td>
<td>286 - 556</td>
<td>284 - 396</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVLT</td>
<td>56 ±12</td>
<td>55 ±13</td>
<td>56 ±11</td>
<td>-0.68</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>28 - 96</td>
<td>28 - 96</td>
<td>29 - 85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDR</td>
<td>177 ±49&quot;</td>
<td>177 ±43&quot;</td>
<td>177 ±54</td>
<td>-0.02</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>116 - 437</td>
<td>118 - 437</td>
<td>116 - 405</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTT</td>
<td>61 ±11&quot;</td>
<td>60 ±12&quot;</td>
<td>62 ±10&quot;</td>
<td>-1.19</td>
<td>0.24</td>
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<tr>
<td></td>
<td>30 - 87</td>
<td>30 - 87</td>
<td>39 - 85</td>
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<tr>
<td>TMA</td>
<td>40 ±14</td>
<td>41 ±13</td>
<td>40 ±14</td>
<td>0.34</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>19 - 85</td>
<td>19 - 85</td>
<td>19 - 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMB</td>
<td>89 ±36</td>
<td>90 ±35</td>
<td>88 ±37</td>
<td>0.45</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>31 - 223</td>
<td>34 - 199</td>
<td>31 - 223</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The normality of the distributions of the results of each of the neuropsychological tests was examined by means of the Kolmogorov-Smirnov goodness of fit test. Six of the tests were found to have results that were not normally distributed. Square root transformations rendered the displaced reaction time, trailmaking A, trailmaking B and block design tests to a normal distribution. Natural logarithm rendered the symbol digit test to a normal distribution. It was not possible to render the choice reaction time test. For this reason interpretations using this test were treated with caution. (see below)
5.11.1. Rey auditory verbal learning test (AVLT)

Raw group mean AVLT scores (total words recalled in trials 1-7) for the study groups are shown in Figure 5.4.

![Figure 5.4: Box and whisker plots of the results of the Rey AVLT (total words recalled on 7 trials) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.]

Changes in Rey AVLT scores from preoperative performance at 6 days and 8 weeks after surgery are shown in Figure 5.5. Change in test performance at 6 days after surgery was a weak but statistically significant predictor of change in test performance at 8 weeks after surgery ($r^2=0.159$, $p<0.0001$).

![Figure 5.5: [Left] Box and whisker plots of changes in Rey AVLT scores (total words recalled on 7 trials) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. [Right] Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.]

A change in postoperative test score of ±1 SD (12.197 points) represents a mean±SD change in performance of ±23.54±6.10% (range 12.71 - 43.56%) for the remacemide group and ±22.30±4.85% (range 14.35 - 36.96%) for the placebo group. Both categorical methods sug-
gested a trend towards improvement in test performance in the remacemide group 8 weeks after surgery.

<table>
<thead>
<tr>
<th>METHOD#1</th>
<th>Change in Score</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rem</td>
<td>Plac</td>
<td>Total</td>
</tr>
<tr>
<td>≥ +1SD</td>
<td>9 (11%)</td>
<td>9 (12%)</td>
<td>18 (12%)</td>
</tr>
<tr>
<td>&gt;0 and &lt; +1SD</td>
<td>27</td>
<td>23</td>
<td>50</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>4</td>
<td>3 (1)</td>
<td>8</td>
</tr>
<tr>
<td>&lt;0 and &gt; -1SD</td>
<td>29</td>
<td>28</td>
<td>57</td>
</tr>
<tr>
<td>≤ -1SD</td>
<td>13 (16%)</td>
<td>10 (14%)</td>
<td>23 (15%)</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>74</td>
<td>156</td>
</tr>
</tbody>
</table>

Table 5.20: Results of analysis of Rey AVLT using Method#1. A rise in test score of 1SD or more from baseline represents a significant improvement and a fall in test score of 1SD or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>METHOD#2</th>
<th>Change in Score</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rem</td>
<td>Plac</td>
<td>Total</td>
</tr>
<tr>
<td>≥ +20%</td>
<td>14 (17%)</td>
<td>11 (15%)</td>
<td>25 (16%)</td>
</tr>
<tr>
<td>&gt;0 and &lt; +20%</td>
<td>22</td>
<td>21</td>
<td>43</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>4</td>
<td>3 (1)</td>
<td>8</td>
</tr>
<tr>
<td>&lt;0 and &gt; -20%</td>
<td>25</td>
<td>27</td>
<td>52</td>
</tr>
<tr>
<td>≤ -20%</td>
<td>17 (21%)</td>
<td>11 (15%)</td>
<td>28 (18%)</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>74</td>
<td>156</td>
</tr>
</tbody>
</table>

Table 5.21: Results of analysis of Rey AVLT using Method#2. A rise in test score of 20% or more from baseline represents a significant improvement and a fall in test score of 20% or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any improvement -vs- no change / deterioration</td>
<td>0.993</td>
<td>0.320</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #1</td>
<td>0.793</td>
<td>0.067</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #2</td>
<td>0.735</td>
<td>0.113</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #1</td>
<td>0.706</td>
<td>0.683*</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #2</td>
<td>0.360</td>
<td>0.331*</td>
</tr>
</tbody>
</table>

Table 5.22: Statistical probabilities of a difference in Rey AVLT outcomes. (All results are χ² probabilities. Those labelled with an asterix are 2-Tail Fisher’s Exact probabilities.)

Analysis of standardised (z) scores at 8 weeks after surgery is shown in Table 5.23.

<table>
<thead>
<tr>
<th>Combined</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>t-value</th>
<th>P (2 tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.140 ±0.77 [-2.28 – 2.20]</td>
<td>0.1606 ±0.849 (81)</td>
<td>0.1252 ±0.673 (76)</td>
<td>0.29</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Table 5.23: Rey AVLT - analysis of z scores at 8 weeks after surgery. Data expressed as mean ±SD [range] and (n).
5.11.2. Non verbal recognition memory (NVRM) test

Raw group mean NVRM test times (seconds) for the study groups are shown in Figure 5.6.

![Box and whisker plots of the results of the NVRM test times (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.](image)

**Figure 5.6:** Box and whisker plots of the results of the NVRM test times (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.

Changes in NVRM test times from preoperative performance at 6 days and 8 weeks after surgery are shown in Figure 5.7. Change in test performance at 6 days after surgery was a statistically significant predictor of change in test performance at 8 weeks after surgery ($r^2=0.596$, $p<0.0001$).

![Box and whisker plots of changes in NVRM test time (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.](image)

**Figure 5.7:** [Left] Box and whisker plots of changes in NVRM test time (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. [Right] Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.

A change in postoperative test time of ±1 SD (33.496 seconds) represents a mean±SD change in performance of ±10.185±1.00% (range 6.02 - 11.71%) for the remacemide group and ±10.15±0.79% (range 8.46 - 11.79%) for the placebo group. At 6 days after surgery the number of patients showing any improvement in test performance was greater in the remacemide group. Using Method #1, fewer patients in the remacemide group had a significant detriora-
tion in performance at 6 days (p=0.019). No such differences were apparent 8 weeks after surgery.

<table>
<thead>
<tr>
<th>METHOD#1</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Score</td>
<td>Rem</td>
<td>Plac</td>
</tr>
<tr>
<td>&gt;= +1SD</td>
<td>9 (11%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>&gt;0 and &lt; +1SD</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -1SD</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>&lt;= -1SD</td>
<td>2 (2%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>82</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 5.24: Results of analysis of NVRM test using Method#1. A rise in test score of 1SD or more from baseline represents a significant improvement and a fall in test score of 1SD or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>METHOD#2</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Score</td>
<td>Rem</td>
<td>Plac</td>
</tr>
<tr>
<td>&gt;= +20%</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>&gt;0 and &lt; +20%</td>
<td>44</td>
<td>30</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -20%</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>&lt;= -20%</td>
<td>1 (1%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>82</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 5.25: Results of analysis of NVRM test using Method#2. A rise in test score of 20% or more from baseline represents a significant improvement and a fall in test score of 20% or more from baseline represents a significant deterioration.

Comparisons | 6 Days | 8 Weeks |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any improvement -vs- no change / deterioration</td>
<td>0.073</td>
<td>0.675</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #1</td>
<td>0.106</td>
<td>0.579</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #2</td>
<td>1.000*</td>
<td>1.000*</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #1</td>
<td>0.019</td>
<td>0.314*</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #2</td>
<td>0.604*</td>
<td>1.000*</td>
</tr>
</tbody>
</table>

Table 5.26: Statistical probabilities of a difference in NVRM outcomes. (All results are $\chi^2$ probabilities. Those labelled with an asterix are 2-Tail Fisher's Exact probabilities.)

Analysis of standardised (z) scores at 8 weeks after surgery is shown in Table 5.27.

<table>
<thead>
<tr>
<th>Combined</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>t-value</th>
<th>P (2 tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.150 ±0.95</td>
<td>0.2981 ±1.088 (81)</td>
<td>0.0016 ±0.743 (76)</td>
<td>1.98</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Table 5.27 NVRM test – analysis of z scores at 8 weeks after surgery. Data expressed as mean ±SD [range] and (n).
5.11.3. Trailmaking A (TMA) test

Raw group mean TMA test times (seconds) for the study groups are shown in Figure 5.8.

![Figure 5.8: Box and whisker plots of the results of the TMA test times (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.](image)

Changes in TMA test times from preoperative performance at 6 days and 8 weeks after surgery are shown in Figure 5.9. Change in test performance at 6 days after surgery was a statistically significant predictor of change in test performance at 8 weeks after surgery ($r^2=0.503$, $p<0.0001$).

![Figure 5.9: [Left] Box and whisker plots of changes in TMA test time (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. [Right] Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.](image)

A change in postoperative test time of ±1 SD (13.595 seconds) represents a mean±SD change in performance of ±36.57±10.62% (range 16.00 - 71.55%) for the remacemide group and ±38.78±12.62% (range 17.00 - 71.55%) for the placebo group. A small number of patients; 8(10%) in the remacemide group and 12(16%) in the placebo group would have to have taken over 50% longer than baseline to complete the test in order to have their performance graded as a significant deterioration by Method#1.
### Table 5.28: Results of analysis of TMA test using Method#1. A rise in test score of 1SD or more from baseline represents a significant improvement and a fall in test score of 1SD or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Change in Score</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= +1SD</td>
<td>12 (15%)</td>
<td>7 (9%)</td>
<td>19 (12%)</td>
<td>16 (20%)</td>
<td>13 (18%)</td>
<td>29 (19%)</td>
</tr>
<tr>
<td>&gt;0 and &lt; +1SD</td>
<td>37</td>
<td>29</td>
<td>66</td>
<td>42</td>
<td>36</td>
<td>78</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>2</td>
<td>3 (1)</td>
<td>5 (1)</td>
<td>3 (2)</td>
<td>5</td>
<td>8 (2)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -1SD</td>
<td>27</td>
<td>32</td>
<td>59</td>
<td>19</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>&lt;= -1SD</td>
<td>4 (5%)</td>
<td>2 (3%)</td>
<td>6 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>82</td>
<td>74</td>
<td>156</td>
<td>82</td>
<td>74</td>
<td>156</td>
</tr>
</tbody>
</table>

**Note:** All results are two-tailed Fisher’s Exact probabilities.

### Table 5.29: Results of analysis of TMA test using Method#2. A rise in test score of 20% or more from baseline represents a significant improvement and a fall in test score of 20% or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Change in Score</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= +20%</td>
<td>28 (34%)</td>
<td>17 (23%)</td>
<td>45 (29%)</td>
<td>35 (43%)</td>
<td>23 (31%)</td>
<td>58 (37%)</td>
</tr>
<tr>
<td>&gt;0 and &lt; +20%</td>
<td>21</td>
<td>19</td>
<td>40</td>
<td>23</td>
<td>26</td>
<td>49</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>2</td>
<td>3 (1)</td>
<td>5 (1)</td>
<td>3 (2)</td>
<td>5</td>
<td>8 (2)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -20%</td>
<td>17</td>
<td>21</td>
<td>38</td>
<td>14</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>&lt;= -20%</td>
<td>14 (17%)</td>
<td>13 (18%)</td>
<td>27 (17%)</td>
<td>5 (6%)</td>
<td>6 (8%)</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>82</td>
<td>74</td>
<td>156</td>
<td>82</td>
<td>74</td>
<td>156</td>
</tr>
</tbody>
</table>

**Note:** All results are two-tailed Fisher’s Exact probabilities.

### Table 5.30: Statistical probabilities of a difference in TMA outcomes. (All results are χ² probabilities. Those labelled with an asterix are 2-Tail Fisher’s Exact probabilities.)

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any improvement -vs- no change / deterioration</td>
<td>0.192</td>
<td>0.398</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #1</td>
<td>0.339</td>
<td>0.700</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #2</td>
<td>0.137</td>
<td>0.105</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #1</td>
<td>0.685*</td>
<td>???</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #2</td>
<td>0.904</td>
<td>0.655</td>
</tr>
</tbody>
</table>

### Analysis of standardised (z) scores at 8 weeks after surgery

Analysis of standardised (z) scores at 8 weeks after surgery is shown in Table 5.31.

### Table 5.31: TMA test – analysis of z scores at 8 weeks after surgery. Data expressed as mean ±SD [range] and (n).

<table>
<thead>
<tr>
<th>Combined</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>t-value</th>
<th>P (2 tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.410 ±0.68 [-0.95 – 3.43]</td>
<td>0.4809 ±0.719 (81)</td>
<td>0.3417 ±0.636 (76)</td>
<td>1.28</td>
<td>0.20</td>
</tr>
</tbody>
</table>
5.11.4. Trailmaking B (TMB) test

Raw group mean TMB test times (seconds) for the study groups are shown in Figure 5.10.

Changes in TMB test times from preoperative performance at 6 days and 8 weeks after surgery are shown in Figure 5.11. Change in test performance at 6 days after surgery was a weak but statistically significant predictor of change in test performance at 8 weeks after surgery ($r^2=0.187$, $p<0.0001$).

A change in postoperative test time of ±1 SD (35.835 seconds) represents a mean±SD change in performance of ±44.25±15.36% (range 18.00 - 105.40%) for the remacemide group and ±47.57±18.13% (range 16.07 - 115.60%) for the placebo group. The wide variation in test performance produced a large standard deviation. A significant number of ‘fast’ patients were subject to a floor effect. In all, 26(32%) patients in the remacemide group and 29(39%) patients in the placebo group, would have to have taken over 50% longer than baseline to complete the...
test in order to have their performance graded as a significant deterioration by Method1. At 8 weeks after surgery a greater number of patients in the remacemide group were found to have any improvement in test performance (p=0.033).

<table>
<thead>
<tr>
<th>METHOD1</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in Score</strong></td>
<td><strong>Rem</strong></td>
<td><strong>Plac</strong></td>
</tr>
<tr>
<td>&gt;= +1SD</td>
<td>5 (6%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>&gt;0 and &lt; +1SD</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>2</td>
<td>1 (3)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -1SD</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>&lt;= -1SD</td>
<td>8 (10%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>82</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 5.32: Results of analysis of TMB test using Method1. A rise in test score of 1SD or more from baseline represents a significant improvement and a fall in test score of 1SD or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>METHOD2</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in Score</strong></td>
<td><strong>Rem</strong></td>
<td><strong>Plac</strong></td>
</tr>
<tr>
<td>&gt;= +20%</td>
<td>13 (16%)</td>
<td>13 (18%)</td>
</tr>
<tr>
<td>&gt;0 and &lt; +20%</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>2</td>
<td>1 (3)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -20%</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>&lt;= -20%</td>
<td>17 (21%)</td>
<td>15 (20%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>82</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 5.33: Results of analysis of TMB test using Method2. A rise in test score of 20% or more from baseline represents a significant improvement and a fall in test score of 20% or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any improvement -vs- no change / deterioration</td>
<td>0.885</td>
<td>0.033</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #1</td>
<td>0.217*</td>
<td>0.165</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #2</td>
<td>0.687</td>
<td>0.211</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #1</td>
<td>0.983</td>
<td>0.349*</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #2</td>
<td>0.952</td>
<td>0.332</td>
</tr>
</tbody>
</table>

Table 5.34: Statistical probabilities of a difference in TMB outcomes. (All results are χ² probabilities. Those labelled with an asterix are 2-Tail Fisher’s Exact probabilities.)

Analysis of standardised (z) scores at 8 weeks after surgery is shown in Table 5.35.

<table>
<thead>
<tr>
<th>Combined</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>t-value</th>
<th>P (2 tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.280 ±0.62</td>
<td>0.3911 ±0.612 (81)</td>
<td>0.1662 ±0.605 (76)</td>
<td>2.31</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Table 5.35: TMB test – analysis of z scores at 8 weeks after surgery. Data expressed as mean ±SD [range] and (n).
5.11.5. WAIS-R block design subtest (BDT)

Raw group mean BDT scores (points) for the study groups are shown in Figure 5.12.

![Box and whisker plots of the results of the BDT scores (points) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.]

Changes in BDT scores from preoperative performance at 6 days and 8 weeks after surgery are shown in Figure 5.13. Change in test performance at 6 days after surgery was a weak but statistically significant predictor of change in test performance at 8 weeks after surgery ($r^2=0.271$, $p<0.0001$).

![Box and whisker plots of changes in BDT score (points) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. [Right] Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.]

A change in postoperative test score of ±1 SD (2.654 points) represents a mean±SD change in performance of ±30.74±8.58% (range 15.61 - 53.08%) for the remacemide group and ±30.38±9.99% (range 15.61 - 66.35%) for the placebo group. At 6 days after surgery a greater number of patients in the remacemide group had any improvement in test performance ($p=0.061$) and, using Method #2, fewer remacemide patients had significant detriorations...
Neither difference was considered statistically significant and neither was apparent 8 weeks after surgery.

Table 5.36: Results of analysis of WAIS-R BDT using Method#1. A rise in test score of 1SD or more from baseline represents a significant improvement and a fall in test score of 1SD or more from baseline represents a significant deterioration.

Table 5.37: Results of analysis of WAIS-R BDT using Method#2. A rise in test score of 20% or more from baseline represents a significant improvement and a fall in test score of 20% or more from baseline represents a significant deterioration.

Table 5.38: Statistical probabilities of a difference in WAIS-R BDT outcomes. (All results are χ² probabilities. Those labelled with an asterix are 2-Tail Fisher’s Exact probabilities.)

Analysis of standardised (z) scores at 8 weeks after surgery is shown in Table 5.39.
5.11.6. Hand tapping test (HTT)

Raw group mean HTT test scores (points) for the study groups are shown in Figure 5.14.

![Box and whisker plots of HTT scores](image)

**Figure 5.14:** Box and whisker plots of the results of the HTT scores (taps) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.

Changes in HTT scores from preoperative performance at 6 days and 8 weeks after surgery are shown in Figure 5.15. Change in test performance at 6 days after surgery was a weak but statistically significant predictor of change in test performance at 8 weeks after surgery ($r^2=0.379, p<0.0001$).

![Box and whisker plots of changes in HTT scores](image)

**Figure 5.15:** [Left] Box and whisker plots of changes in HTT score (taps) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. [Right] Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.

A change in postoperative test performance of $\pm1$ SD (11.058 taps) represents a mean $\pm$SD change in performance of $\pm19.23\pm4.24\%$ (range 12.71-36.86%) for the remacemide group and $\pm18.23\pm3.13\%$ (range 13.01-28.35%) for the placebo group. One patient in each group was unable to comply with pre- or postoperative testing. Using Method #1, fewer patients in the remacemide group had significant deteriorations in test performance 6 days after surgery.
Significantly most patients in the remacemide group had any improvement 8 weeks after surgery \( (p=0.015) \).

<table>
<thead>
<tr>
<th>METHOD#1</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Score</td>
<td>Rem</td>
<td>Plac</td>
</tr>
<tr>
<td>&gt;= +1SD</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>&gt;0 and &lt; +1SD</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>3 (3)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -1SD</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>&lt;= -1SD</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>TOTAL</td>
<td>81</td>
<td>73</td>
</tr>
</tbody>
</table>

Table 5.40: Results of analysis of HTT using Method#1. A rise in test score of 1SD or more from baseline represents a significant improvement and a fall in test score of 1SD or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>METHOD#2</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Score</td>
<td>Rem</td>
<td>Plac</td>
</tr>
<tr>
<td>&gt;= +20%</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>&gt;0 and &lt; +20%</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>3 (3)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -20%</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>&lt;= -20%</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>81</td>
<td>73</td>
</tr>
</tbody>
</table>

Table 5.41: Results of analysis of HTT using Method#2. A rise in test score of 20% or more from baseline represents a significant improvement and a fall in test score of 20% or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any improvement -vs- no change / deterioration</td>
<td>0.305</td>
<td>0.015</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #1</td>
<td>0.447*</td>
<td>0.359</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #2</td>
<td>0.722*</td>
<td>0.561</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #1</td>
<td>0.097</td>
<td>0.610*</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #2</td>
<td>0.282</td>
<td>0.232*</td>
</tr>
</tbody>
</table>

Table 5.42: Statistical probabilities of a difference in HTT outcomes. (All results are \( \chi^2 \) probabilities. Those labelled with an asterix are 2-Tail Fisher's Exact probabilities.)

Analysis of standardised \( z \) scores at 8 weeks after surgery is shown in Table 5.43.

<table>
<thead>
<tr>
<th>Combined</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>t-value</th>
<th>P (2 tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.320 ±0.68</td>
<td>0.4359 ±0.611 (81)</td>
<td>0.1939 ±0.724 (76)</td>
<td>1.98</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Table 5.43 HTT - analysis of \( z \) scores at 8 weeks after surgery. Data expressed as mean ±SD [range] and (n).
5.11.7. Letter cancelation test (LCT)

Raw group mean LCT times (seconds) for the study groups are shown in Figure 5.16.

![Box plot of LCT times](image)

Figure 5.16: Box and whisker plots of the results of the LCT times (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.

Changes in LCT times from preoperative performance at 6 days and 8 weeks after surgery are shown in Figure 5.17. Change in test performance at 6 days after surgery was a weak but statistically significant predictor of change in test performance at 8 weeks after surgery ($r^2=0.387$, $p<0.0001$).

![Box plot of LCT changes](image)

Figure 5.17: [Left] Box and whisker plots of changes in LCT time (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. [Right] Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.

A change in postoperative test time of ±1 SD (22.369 seconds) represents a mean±SD change in performance of ±24.75±4.56% (range 13.33 - 36.123%) for the remacemide group and ±24.57±5.69% (range 10.18 - 39.29%) for the placebo group.
### Table 5.44: Results of analysis of LCT using Method#1. A rise in test score of 1SD or more from baseline represents a significant improvement and a fall in test score of 1SD or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Change in Score</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= +1SD</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>&gt;0 and &lt; +1SD</td>
<td>16</td>
<td>18</td>
<td>34</td>
<td>25</td>
<td>22</td>
<td>47</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>3</td>
<td>1</td>
<td>4(1)</td>
<td>1</td>
<td>2</td>
<td>3(2)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -1SD</td>
<td>45</td>
<td>37</td>
<td>82</td>
<td>46</td>
<td>39</td>
<td>85</td>
</tr>
<tr>
<td>&lt;= -1SD</td>
<td>17</td>
<td>14</td>
<td>31</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>82</td>
<td>74</td>
<td>156</td>
<td>82</td>
<td>74</td>
<td>156</td>
</tr>
</tbody>
</table>

### Table 5.45: Results of analysis of LCT using Method#2. A rise in test score of 20% or more from baseline represents a significant improvement and a fall in test score of 20% or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Change in Score</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= +20%</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>&gt;0 and &lt; +20%</td>
<td>17</td>
<td>18</td>
<td>35</td>
<td>25</td>
<td>23</td>
<td>48</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>3</td>
<td>1</td>
<td>4(1)</td>
<td>1</td>
<td>2</td>
<td>3(2)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -20%</td>
<td>37</td>
<td>31</td>
<td>68</td>
<td>44</td>
<td>34</td>
<td>78</td>
</tr>
<tr>
<td>&lt;= -20%</td>
<td>25</td>
<td>20</td>
<td>45</td>
<td>7</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>82</td>
<td>74</td>
<td>156</td>
<td>82</td>
<td>74</td>
<td>156</td>
</tr>
</tbody>
</table>

### Table 5.46: Statistical probabilities of a difference in LCT outcomes. (All results are \( \chi^2 \) probabilities. Those labelled with an asterix are 2-Tail Fisher's Exact probabilities.)

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any improvement -vs- no change / deterioration</td>
<td>0.246</td>
<td>0.847</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #1</td>
<td>0.343*</td>
<td>0.482*</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #2</td>
<td>0.102*</td>
<td>0.711*</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #1</td>
<td>0.809</td>
<td>0.655</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #2</td>
<td>0.672</td>
<td>0.238</td>
</tr>
</tbody>
</table>

### Analysis of standardised (z) scores at 8 weeks after surgery is shown in Table 5.47.

<table>
<thead>
<tr>
<th>Combined</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>t-value</th>
<th>P (2 tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.180 ±0.86</td>
<td>-0.1909 ±0.681</td>
<td>-0.1673 ±1.015</td>
<td>-0.17</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Table 5.47 LCT – analysis of z scores at 8 weeks after surgery. Data expressed as mean ±SD [range] and (n).
5.11.8. Symbol digit replacement (SDR) test

Raw group mean SDR test times (seconds) for the study groups are shown in Figure 5.18.

![Box and whisker plots of the results of the SDR test times (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.](image)

**Figure 5.18:** Box and whisker plots of the results of the SDR test times (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.

Changes in SDR test times from preoperative performance at 6 days and 8 weeks after surgery are shown in Figure 5.19. Change in test performance at 6 days after surgery was a statistically significant predictor of change in test performance at 8 weeks after surgery ($r^2=0.398$, $p<0.0001$).

![Box and whisker plots of changes in SDR test time (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.](image)

**Figure 5.19:** [Left] Box and whisker plots of changes in SDR test time (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. [Right] Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.

A change in postoperative test time of $\pm 1$ SD (48.727 seconds) represents a mean±SD change in performance of $\pm 13.16\pm 2.51\%$ (range 5.12 - 18.98%) for the remacemide group and $\pm 13.53\pm 2.99\%$ (range 5.53 - 19.31%) for the placebo group. One patient in the remacemide group was unable to comply with pre- or postoperative testing. At 8 weeks after surgery a greater number of remacemide patients had *any* improvement in test performance ($p=0.086$).
<table>
<thead>
<tr>
<th>METHOD#1</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Score</td>
<td>Rem</td>
<td>Plac</td>
</tr>
<tr>
<td>&gt;= +1SD</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>&gt;0 and &lt; +1SD</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>1 (2)</td>
<td>0 (2)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -1SD</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>&lt;= -1SD</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>TOTAL</td>
<td>81</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 5.48: Results of analysis of SDR test using Method#1. A rise in test score of 1SD or more from baseline represents a significant improvement and a fall in test score of 1SD or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>METHOD#2</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Score</td>
<td>Rem</td>
<td>Plac</td>
</tr>
<tr>
<td>&gt;= +20%</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>&gt;0 and &lt; +20%</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>1 (2)</td>
<td>0 (2)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -20%</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>&lt;= -20%</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>TOTAL</td>
<td>81</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 5.49: Results of analysis of SDR test using Method#2. A rise in test score of 20% or more from baseline represents a significant improvement and a fall in test score of 20% or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any improvement -vs- no change / deterioration</td>
<td>0.913</td>
<td>0.086</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #1</td>
<td>0.670*</td>
<td>0.683</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #2</td>
<td>0.446*</td>
<td>0.184</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #1</td>
<td>0.644</td>
<td>1.000*</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #2</td>
<td>0.483</td>
<td>1.000*</td>
</tr>
</tbody>
</table>

Table 5.50: Statistical probabilities of a difference in SDR outcomes. (All results are $\chi^2$ probabilities. Those labelled with an asterix are 2-Tail Fisher’s Exact probabilities.)

Analysis of standardised (z) scores at 8 weeks after surgery is shown in Table 5.51.

<table>
<thead>
<tr>
<th>Combined</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>t-value</th>
<th>P (2 tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.280 ±0.63</td>
<td>0.3183 ±0.602 (81)</td>
<td>0.2329 ±0.660 (76)</td>
<td>0.85</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 5.51: SDR - analysis of z scores at 8 weeks after surgery. Data expressed as mean ±SD [range] and (n).
5.11.9. Choice reaction time (CRT) test

Raw group mean CRT test times (seconds) for the study groups are shown in Figure 5.20.

![Box and whisker plots of the results of the CRT times (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.](image1)

Changes in CRT times from preoperative performance at 6 days and 8 weeks after surgery are shown in Figure 5.21. Change in test performance at 6 days after surgery was a weak but statistically significant predictor of change in test performance at 8 weeks after surgery ($r^2=0.132$, $p<0.0001$).

![Box and whisker plots of changes in CRT time (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.](image2)

A change in postoperative test time of ±1 SD (0.183 seconds) represents a mean±SD change in performance of ±30.79±7.34% (range 12.12 - 42.59%) for the remacemide group and ±31.35±6.11% (range 15.78 - 48.16%) for the placebo group.
### Table 5.52: Results of analysis of CRT test using Method#1. A rise in test score of 1SD or more from baseline represents a significant improvement and a fall in test score of 1SD or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Change in Score</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= +1SD</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>&gt;0 and &lt; +1SD</td>
<td>20</td>
<td>16</td>
<td>36</td>
<td>29</td>
<td>32</td>
<td>61</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>4 (1)</td>
<td>6</td>
<td>10 (1)</td>
<td>3 (3)</td>
<td>3</td>
<td>6 (3)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -1SD</td>
<td>45</td>
<td>40</td>
<td>85</td>
<td>37</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>&lt;= -1SD</td>
<td>7</td>
<td>7</td>
<td>14</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>TOTAL</td>
<td>82</td>
<td>74</td>
<td>156</td>
<td>82</td>
<td>74</td>
<td>156</td>
</tr>
</tbody>
</table>

### Table 5.53: Results of analysis of CRT test using Method#2. A rise in test score of 20% or more from baseline represents a significant improvement and a fall in test score of 20% or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Change in Score</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
<th>Rem</th>
<th>Plac</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= +20%</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>&gt;0 and &lt; +20%</td>
<td>20</td>
<td>15</td>
<td>35</td>
<td>29</td>
<td>32</td>
<td>61</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>4 (1)</td>
<td>6</td>
<td>10 (1)</td>
<td>3 (3)</td>
<td>3</td>
<td>6 (3)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -20%</td>
<td>38</td>
<td>34</td>
<td>72</td>
<td>35</td>
<td>30</td>
<td>65</td>
</tr>
<tr>
<td>&lt;= -20%</td>
<td>14</td>
<td>13</td>
<td>27</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>TOTAL</td>
<td>82</td>
<td>74</td>
<td>156</td>
<td>82</td>
<td>74</td>
<td>156</td>
</tr>
</tbody>
</table>

### Table 5.54: Statistical probabilities of a difference in CRT outcomes. (All results are $\chi^2$ probabilities. Those labelled with an asterix are 2-Tail Fisher’s Exact probabilities.)

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any improvement -vs- no change / deterioration</td>
<td>0.735</td>
<td>0.703</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #1</td>
<td>1.000*</td>
<td>0.408</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #2</td>
<td>0.639</td>
<td>0.408</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #1</td>
<td>0.859</td>
<td>0.713*</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #2</td>
<td>0.963</td>
<td>1.000*</td>
</tr>
</tbody>
</table>

### Table 5.55: CRT - analysis of z scores at 8 weeks after surgery. Data expressed as mean ±SD [range] and (n).

<table>
<thead>
<tr>
<th>Combined</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>t-value</th>
<th>P (2 tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>±0.050 ±0.83 [3.63 - 3.79]</td>
<td>±0.129 ±0.891 (80)</td>
<td>±0.0249 ±0.748 (76)</td>
<td>1.17</td>
</tr>
</tbody>
</table>

Analysis of standardised ($z$) scores at 8 weeks after surgery is shown in Table 5.55.
5.11.10. Displaced reaction time (DRT) test

Raw group mean DRT test times (seconds) for the study groups are shown in Figure 5.22.

![Box and whisker plots of the results of the DRT test times (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. P=placebo, R=remacemide.](image)

Changes in DRT times from preoperative performance at 6 days and 8 weeks after surgery are shown in Figure 5.23. Change in test performance at 6 days after surgery was a weak but statistically significant predictor of change in test performance at 8 weeks after surgery ($r^2=0.319, p<0.0001$).

![Box and whisker plots of changes in DRT time (seconds) before (Pre), and 6 days (6d) and 8 weeks (8w) after surgery. Correlation between change in test score at 6 days and at 8 weeks for all patients studied. P=placebo, R=remacemide.](image)

A change in postoperative test time of $\pm 1$ SD (0.346 seconds) represents a mean$\pm$SD change in performance of $\pm 46.88\pm17.18\%$ (range 19.12 - 91.05%) for the remacemide group and $\pm 46.27\pm16.11\%$ (range 16.17 - 101.77%) for the placebo group. Two patients in the remcamide group were unable to comply with pre-or postoperative testing. Significantly fewer patients in the remacemide group had any improvement in test performance at both 6 days ($p=0.003$) and 8 weeks ($p=0.041$) after surgery. More patients in the remacemide had significant dete-
iorations in test performance at 6 days (Method #2, p=0.077) and 8 weeks (Method #1, p=0.083) after surgery.

<table>
<thead>
<tr>
<th>METHOD#1</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rem</td>
<td>Plac</td>
</tr>
<tr>
<td>Change in Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= +1SD</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>&gt;0 and &lt; +1SD</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>3 (2)</td>
<td>0 (2)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -1SD</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>&lt;= -1SD</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>TOTAL</td>
<td>80</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 5.56: Results of analysis of DRT test using Method#1. A rise in test score of 1SD or more from baseline represents a significant improvement and a fall in test score of 1SD or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>METHOD#2</th>
<th>Day 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rem</td>
<td>Plac</td>
</tr>
<tr>
<td>Change in Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= +20%</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>&gt;0 and &lt; +20%</td>
<td>11</td>
<td>30</td>
</tr>
<tr>
<td>None (No Data)</td>
<td>1 (2)</td>
<td>0 (2)</td>
</tr>
<tr>
<td>&lt;0 and &gt; -20%</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>&lt;= -20%</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>TOTAL</td>
<td>80</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 5.57: Results of analysis of DRT test using Method#2. A rise in test score of 20% or more from baseline represents a significant improvement and a fall in test score of 20% or more from baseline represents a significant deterioration.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any improvement -vs- no change / deterioration</td>
<td>0.003</td>
<td>0.041</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #1</td>
<td>0.193</td>
<td>0.656</td>
</tr>
<tr>
<td>Significant improvement -vs- improvement / no change / deterioration #2</td>
<td>0.699</td>
<td>0.702</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #1</td>
<td>0.665</td>
<td>0.083</td>
</tr>
<tr>
<td>Deterioration / no change / improvement -vs- significant deterioration #2</td>
<td>0.077</td>
<td>0.343</td>
</tr>
</tbody>
</table>

Table 5.58: Statistical probabilities of a difference in DRT outcomes. (All results are $\chi^2$ probabilities. Those labelled with an asterix are 2-Tail Fisher's Exact probabilities.)

Analysis of standardised (z) scores at 8 weeks after surgery is shown in Table 5.59.

<table>
<thead>
<tr>
<th>Combined</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>t-value</th>
<th>P (2 tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.070 ±0.91</td>
<td>0.0473 ±0.973 (79)</td>
<td>0.0913 ±0.845 (76)</td>
<td>-0.30</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Table 5.59 DRT - analysis of z scores at 8 weeks after surgery. Data expressed as mean ±SD [range] and (n).
5.11.11. Overall neuropsychological testing results

Using the conventional prospectively defined definition of neuropsychological deficit (Method #1), 34 (41%) patients in the remacemide group and 28 (37%) in the placebo group had a neuropsychological deficit 6 days after surgery. At 8 weeks after surgery, 7 (9%) patients in the remacemide group and 9 (12%) in the placebo group had a neuropsychological deficit. (Table 5.60) Neither result attained statistical significance (p>0.6; Fisher’s exact).

The proportion of patients with no deteriorations in test performance, however, was higher in the placebo group. (37 versus 45; p=0.08)

<table>
<thead>
<tr>
<th>METHOD#1</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Remacemide</td>
<td>Placebo</td>
</tr>
<tr>
<td>0 or 1 tests</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td>2 or more tests</td>
<td>34 (41%)</td>
<td>28 (37%)</td>
</tr>
</tbody>
</table>

Table 5.60: Incidence of significant postoperative cognitive deficits using method #1.

Further, exhaustive post hoc analysis using another popular definition of neuropsychological deficit (i.e. Method #2) and an arbitrary definition of improvement in neuropsychological test performance revealed no statistically significant inter-group differences. (Tables 5.61, 5.62, 5.63)

<table>
<thead>
<tr>
<th>METHOD#2</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Remacemide</td>
<td>Placebo</td>
</tr>
<tr>
<td>0 or 1 tests</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>2 or more tests</td>
<td>18 (22%)</td>
<td>9 (12%)</td>
</tr>
</tbody>
</table>

Table 5.61: Incidence of significant postoperative cognitive improvements using method #1.

<table>
<thead>
<tr>
<th>METHOD#2</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Remacemide</td>
<td>Placebo</td>
</tr>
<tr>
<td>0 or 1 tests</td>
<td>43</td>
<td>35</td>
</tr>
<tr>
<td>2 or more tests</td>
<td>39 (48%)</td>
<td>39 (53%)</td>
</tr>
</tbody>
</table>

Table 5.62: Incidence of significant postoperative cognitive deficits using method #2.

<table>
<thead>
<tr>
<th>METHOD#2</th>
<th>6 Days</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Remacemide</td>
<td>Placebo</td>
</tr>
<tr>
<td>0 or 1 tests</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>2 or more tests</td>
<td>65 (79%)</td>
<td>61 (82%)</td>
</tr>
</tbody>
</table>

Table 5.63: Incidence of significant postoperative cognitive improvements using method #2.
Correlations between significant deteriorations / improvements and CPB duration, cerebral microembolic events, and number of bypass grafts performed are shown in Table 5.64.

<table>
<thead>
<tr>
<th></th>
<th>METHOD #1</th>
<th></th>
<th>METHOD #2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>versus</td>
<td>Day 6</td>
<td>Week 8</td>
<td>Day 6</td>
</tr>
<tr>
<td>Deficits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPB</td>
<td>r=0.12</td>
<td>p=0.15</td>
<td>r=0.11</td>
<td>p=0.19</td>
</tr>
<tr>
<td>MEE</td>
<td>r=0.13</td>
<td>p=0.14</td>
<td>r=0.25</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Grafts</td>
<td>r=0.20</td>
<td>p=0.02</td>
<td>r=0.24</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Improvements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPB</td>
<td>r=-0.01</td>
<td>p=0.94</td>
<td>r=0.01</td>
<td>p=0.89</td>
</tr>
<tr>
<td>MEE</td>
<td>r=-0.09</td>
<td>p=0.30</td>
<td>r=0.01</td>
<td>p=0.89</td>
</tr>
<tr>
<td>Grafts</td>
<td>r=0.12</td>
<td>p=0.16</td>
<td>r=0.07</td>
<td>p=0.43</td>
</tr>
</tbody>
</table>

Table 5.64: Spearman correlation coefficients (r=rho) and p-values for relationships between the number of significant deteriorations / improvements in postoperative neuropsychological test performance and duration of cardiopulmonary bypass (CPB), total microembolic event count (MEE), and number of bypass grafts performed.

Small, but statistically significant, relationships between MEE and cognitive deficits at 8 weeks after surgery, and number of bypass graft performed and cognitive deficits at both 6 days and 8 weeks after surgery were found using Method #1. Similarly, a small but significant relationship between number of bypass grafts performed and cognitive deficits at 6 days after surgery was found using Method #2. The relationship between deficits and MEE at both 6 days and 8 weeks after surgery approached statistical significance. Negative correlations between intraoperative factors and improvements in cognitive function testing were statistically insignificant.

As planned, the changes in individual neuropsychological performance at 8 weeks after surgery from baseline were compared in both study groups using the Mann-Whitney U test. The results are summarised in Table 5.65.

Although overall test performances tended to be superior in the remacemide group, these were, for the most part, insignificant. Statistically significant differences between treatment groups were seen for the Trailmaking B test (p=0.02) and the Left Hand Tapping test (p=0.007). The Trailmaking B test was completed more quickly and the number of taps made with the left hand were greater in the remacemide group.
## Table 5.66: Comparison of median changes in neuropsychological test performance (scores or times) from baseline at 8 weeks after surgery.

<table>
<thead>
<tr>
<th>Test</th>
<th>Change in test score</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey AVL Test Score 1</td>
<td></td>
<td>1 (80)</td>
<td>1 (74)</td>
<td>2711.5</td>
<td>0.36</td>
</tr>
<tr>
<td>Rey AVL Test Score 2</td>
<td></td>
<td>0 (80)</td>
<td>1 (74)</td>
<td>2824.0</td>
<td>0.62</td>
</tr>
<tr>
<td>Rey AVL Test Score 3</td>
<td></td>
<td>0 (80)</td>
<td>0 (74)</td>
<td>2727.0</td>
<td>0.39</td>
</tr>
<tr>
<td>Rey AVL Test Score 4</td>
<td></td>
<td>0 (80)</td>
<td>0 (74)</td>
<td>2734.5</td>
<td>0.41</td>
</tr>
<tr>
<td>Rey AVL Test Score 5</td>
<td></td>
<td>0 (80)</td>
<td>0 (74)</td>
<td>2715.5</td>
<td>0.37</td>
</tr>
<tr>
<td>Rey AVL Test Score 6</td>
<td></td>
<td>1 (80)</td>
<td>0.5 (74)</td>
<td>2758.5</td>
<td>0.46</td>
</tr>
<tr>
<td>Rey AVL Test Score 7</td>
<td></td>
<td>0 (80)</td>
<td>0 (74)</td>
<td>2902.0</td>
<td>0.83</td>
</tr>
<tr>
<td>NVRM Score</td>
<td></td>
<td>0 (80)</td>
<td>1 (74)</td>
<td>2745.5</td>
<td>0.43</td>
</tr>
<tr>
<td>NVRM Time</td>
<td></td>
<td>-6 (80)</td>
<td>-2 (74)</td>
<td>2519.0</td>
<td>0.11</td>
</tr>
<tr>
<td>Trailmaking A Time</td>
<td></td>
<td>-5.5 (80)</td>
<td>-3.5 (74)</td>
<td>2703.5</td>
<td>0.35</td>
</tr>
<tr>
<td>Trailmaking B Time</td>
<td></td>
<td>-13.5 (80)</td>
<td>-7.0 (74)</td>
<td>2336.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Block Design Raw Score</td>
<td></td>
<td>2 (80)</td>
<td>3 (74)</td>
<td>2805.0</td>
<td>0.57</td>
</tr>
<tr>
<td>Block Design Standardised Score</td>
<td></td>
<td>1 (80)</td>
<td>1 (74)</td>
<td>2921.0</td>
<td>0.88</td>
</tr>
<tr>
<td>Right Hand Tapping</td>
<td></td>
<td>2 (79)</td>
<td>1 (73)</td>
<td>2378.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Left Hand Tapping</td>
<td></td>
<td>2 (79)</td>
<td>1 (73)</td>
<td>2149.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Letter Cancellation Time</td>
<td></td>
<td>5 (80)</td>
<td>5 (74)</td>
<td>2936.5</td>
<td>0.93</td>
</tr>
<tr>
<td>Letter Cancellation Targets Missed</td>
<td></td>
<td>0.5 (80)</td>
<td>0 (74)</td>
<td>2945.0</td>
<td>0.95</td>
</tr>
<tr>
<td>Symbol Digit Replacement Score</td>
<td></td>
<td>0 (79)</td>
<td>0 (74)</td>
<td>2914.5</td>
<td>0.97</td>
</tr>
<tr>
<td>Symbol Digit Replacement Time</td>
<td></td>
<td>-15 (79)</td>
<td>-7 (74)</td>
<td>2478.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Choice Reaction Time Accuracy</td>
<td></td>
<td>0 (79)</td>
<td>0 (74)</td>
<td>2601.5</td>
<td>0.16</td>
</tr>
<tr>
<td>Choice Reaction Time</td>
<td></td>
<td>0.01 (79)</td>
<td>0 (74)</td>
<td>2840.5</td>
<td>0.76</td>
</tr>
<tr>
<td>Displaced Reaction Time Errors</td>
<td></td>
<td>0 (78)</td>
<td>0 (74)</td>
<td>2658.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Displaced Reaction Time</td>
<td></td>
<td>0.01 (78)</td>
<td>-0.05 (74)</td>
<td>2679.0</td>
<td>0.45</td>
</tr>
</tbody>
</table>

The results of comparisons of the difference in Z score performance of the two groups (Method #4) showed that all but two of the tests showed a greater improvement in the remacemide group at 8 weeks after surgery. (Table 5.66) The remacemide group showed significantly greater improvement in performance on the composite measure of neuropsychological outcome (total Z score; p=0.014). When the choice reaction time test results were removed from the analysis (because of their non-normal distribution) the difference between the two groups remained statistically significant (p<0.018). Further analysis indicated that in three of the tests the remacemide group showed significantly superior performance compared to the placebo group. In these cases this indicates a greater learning effect in the remacemide group.
<table>
<thead>
<tr>
<th>Test</th>
<th>Remacemide (n)</th>
<th>Placebo (n)</th>
<th>t</th>
<th>p (2 tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS BDT</td>
<td>0.2104 (81)</td>
<td>0.2093 (76)</td>
<td>0.01</td>
<td>0.500</td>
</tr>
<tr>
<td>CRT</td>
<td>0.1296 (80)</td>
<td>-0.0249 (76)</td>
<td>1.17</td>
<td>0.122</td>
</tr>
<tr>
<td>DRT</td>
<td>0.0473 (79)</td>
<td>0.0913 (76)</td>
<td>-0.30</td>
<td>0.380</td>
</tr>
<tr>
<td>LCT</td>
<td>-0.1909 (81)</td>
<td>-0.1673 (76)</td>
<td>-0.17</td>
<td>0.432</td>
</tr>
<tr>
<td>NVRM</td>
<td>0.2981 (81)</td>
<td>0.0016 (76)</td>
<td>1.98</td>
<td>0.024</td>
</tr>
<tr>
<td>Rey AVLT</td>
<td>0.1606 (81)</td>
<td>0.1252 (76)</td>
<td>0.29</td>
<td>0.380</td>
</tr>
<tr>
<td>SDR</td>
<td>0.3183 (80)</td>
<td>0.2329 (76)</td>
<td>0.85</td>
<td>0.200</td>
</tr>
<tr>
<td>TAT</td>
<td>0.4359 (80)</td>
<td>0.1939 (75)</td>
<td>2.25</td>
<td>0.013</td>
</tr>
<tr>
<td>TMA</td>
<td>0.4809 (81)</td>
<td>0.3417 (76)</td>
<td>1.28</td>
<td>0.101</td>
</tr>
<tr>
<td>TMB</td>
<td>0.3911 (81)</td>
<td>0.1662 (76)</td>
<td>2.31</td>
<td>0.011</td>
</tr>
<tr>
<td>Total</td>
<td>2.3235 (78)</td>
<td>1.2190 (75)</td>
<td>2.22</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Table 5.66: Mean differences Z scores (n) for each neuropsychological test at 8 weeks after surgery. One tailed tests were performed as the hypothesis suggested a directional difference with greater improvements in the remacemide treated group.

For each patient the Z scores for each individual neuropsychological test were summed to give a composite neuropsychological test Z score. (Figure 5.24)

![Figure 5.24: Frequency distributions for composite Z scores for neuropsychological test performance 8 weeks after surgery for patients in the remacemide group (left) and placebo group (right).](image)

### 5.12. Subjective assessments

The results of the social and subjective assessment questionnaire are summarised in Table 5.67. The results were compared for the two treatment groups using $\chi^2$ tests. When the expected value was less than five in any category the comparisons made were either improvement and no change versus deterioration, or improvement versus no change and deterioration.
There were no significant differences between the treatment groups at either 6 days or 8 weeks after surgery. Although some patients reported impairment of mental processes at 6 days, the majority reported either an improvement or no change by 8 weeks.

### 5.13. Laboratory investigations

Laboratory data was available for virtually all patients at each of the six planned sampling times. Mean changes from pre-operative (baseline) values were calculated for each individual test and analysed using ANOVA. Although virtually every parameter measured showed wide variation in the postoperative period (Figures 5.25 to 5.32), the only statistically significant differences between the two treatment groups were found for serum potassium and platelet count. On the day before surgery, patients in the remacemide group had a mean±SD change in serum potassium of -0.13±0.42 mmol/l compared to +0.05±0.45 mmol/l in the placebo group (p=0.009). Eight weeks after surgery, patients in the remacemide group had a mean±SD change in serum potassium of -0.13±0.42 mmol/l compared to +0.05±0.45 mmol/l in the placebo group (p=0.009).
change in platelet count of $+35.8 \pm 45.4 \times 10^9/l$ compared with $+14.2 \pm 51.5 \times 10^9/l$ in the placebo group ($p=0.006$). Neither of these differences were thought to be of any clinical significance.

![Figure 5.25: Changes in mean sodium, potassium and chloride. Remacemide (black circles), Placebo (open triangles). Units; [left] sodium (mmol/l), [middle] potassium (mmol/l), [right] chloride (mmol/l). R=recruitment, P=day before surgery, 0=immediately after surgery, 1=day after surgery, 6=6 days after surgery, 8=8 weeks after surgery.](image)

![Figure 5.26: Changes in mean urea, creatinine and bicarbonate. Remacemide (black circles), Placebo (open triangles). Units; [left] urea (mmol/l), [middle] creatinine (mmol/l), [right] bicarbonate (mmol/l). R=recruitment, P=day before surgery, 0=immediately after surgery, 1=day after surgery, 6=6 days after surgery, 8=8 weeks after surgery.](image)

![Figure 5.27: Changes in mean protein, albumin and calcium. Remacemide (black circles), Placebo (open triangles). Units; [left] protein (g/l), [middle] albumin (g/l), [right] calcium (mmol/l). R=recruitment, P=day before surgery, 0=immediately after surgery, 1=day after surgery, 6=6 days after surgery, 8=8 weeks after surgery.](image)
Figure 5.28: Changes in mean phosphate, alkaline phosphatase (ALP) and total bilirubin. Remacemide (black circles), Placebo (open triangles). Units; [left] phosphate (µmol/l), [middle] ALP (iu/l), [right] total bilirubin (µmol/l). R=recruitment, P=day before surgery, 0=immediately after surgery, 1=day after surgery, 6=6 days after surgery, 8=8 weeks after surgery.

Figure 5.29: Changes in mean gamma glutamyl transferase (GGT), aspartate transaminase (AST) and cholesterol. Remacemide (black circles), Placebo (open triangles). Units; [left] GGT (iu/l), [middle] AST (iu/l), [right] cholesterol (mmol/l). R=recruitment, P=day before surgery, 0=immediately after surgery, 1=day after surgery, 6=6 days after surgery, 8=8 weeks after surgery.

Figure 5.30: Changes in mean alanine transaminase (ALT), total creatine phosphokinase (CPK) and creatine phosphokinase MB band (CPK-MB). Remacemide (black circles), Placebo (open triangles). Units; [left] ALT (iu/l), [middle] CPK (iu/l), [right] CPK-MB (u/l). R=recruitment, P=day before surgery, 0=immediately after surgery, 1=day after surgery, 6=6 days after surgery, 8=8 weeks after surgery.
A detailed statistical analysis of urine dipstick testing results was not performed.

For the 138 patients with complete biochemical and TCD data, correlations between the maximal changes, from preoperative baseline, in serum biochemical test results in the first week after surgery and (1) total cerebral microembolic event count, (2) number of bypass grafts performed, and (3) duration of CPB are shown in Table 5.68.
Table 5.68: Spearman correlation coefficients (r=rho) and p-values for relationships between changes in early postoperative biochemical values from preoperative baseline and: cerebral microembolic events (MEE), number of bypass grafts performed, and duration of cardiopulmonary bypass (CPB).

<table>
<thead>
<tr>
<th>Measure</th>
<th>MEE</th>
<th>Grafts</th>
<th>CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>$r=-0.0468$, $p=0.59$</td>
<td>$r=0.2916$, $p&lt;0.01$</td>
<td>$r=0.2703$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Creatinine</td>
<td>$r=-0.0633$, $p=0.46$</td>
<td>$r=0.1500$, $p=0.08$</td>
<td>$r=0.1781$, $p=0.04$</td>
</tr>
<tr>
<td>Protein</td>
<td>$r=0.1674$, $p=0.05$</td>
<td>$r=0.1496$, $p=0.08$</td>
<td>$r=0.0597$, $p=0.49$</td>
</tr>
<tr>
<td>Albumin</td>
<td>$r=0.1959$, $p=0.02$</td>
<td>$r=0.1483$, $p=0.08$</td>
<td>$r=0.0556$, $p=0.52$</td>
</tr>
<tr>
<td>ALP</td>
<td>$r=-0.0386$, $p=0.65$</td>
<td>$r=0.0800$, $p=0.35$</td>
<td>$r=0.1010$, $p=0.24$</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>$r=-0.0605$, $p=0.48$</td>
<td>$r=0.0609$, $p=0.48$</td>
<td>$r=0.0960$, $p=0.26$</td>
</tr>
<tr>
<td>GGT</td>
<td>$r=-0.0393$, $p=0.65$</td>
<td>$r=0.1314$, $p=0.12$</td>
<td>$r=0.0833$, $p=0.33$</td>
</tr>
<tr>
<td>AST</td>
<td>$r=0.0967$, $p=0.26$</td>
<td>$r=0.1699$, $p=0.05$</td>
<td>$r=0.2600$, $p&lt;0.01$</td>
</tr>
<tr>
<td>ALT</td>
<td>$r=-0.0174$, $p=0.84$</td>
<td>$r=0.1496$, $p=0.08$</td>
<td>$r=0.1477$, $p=0.08$</td>
</tr>
<tr>
<td>CPK</td>
<td>$r=0.1306$, $p=0.13$</td>
<td>$r=0.2930$, $p&lt;0.01$</td>
<td>$r=0.4386$, $p&lt;0.01$</td>
</tr>
<tr>
<td>CPK-MB</td>
<td>$r=0.0175$, $p=0.84$</td>
<td>$r=0.2964$, $p&lt;0.01$</td>
<td>$r=0.5273$, $p&lt;0.01$</td>
</tr>
</tbody>
</table>

Significant correlations were found for: changes in protein and albumin, and cerebral microembolic events, changes in urea and cardiac enzymes (AST, CPK, CPK-MB), with the number of bypass grafts performed, and changes in urea, creatinine and cardiac enzymes, with duration of CPB. Renal and gastrointestinal microembolisation may, in part, explain the changes in serum proteins, urea and creatinine.

5.14. Cerebrovenous lactate levels

Samples of jugular venous blood were obtained in 32 patients (13 in the remacemide group). The post-induction sample for one of the remacemide-treated patients was lost in transit. The results are summarised in Table 5.69. There were no statistically significant inter-group differences at any of the four sampling points.

Table 5.69: Mean ±SD jugular venous lactate levels (mmol/l) in the 32 patients in whom a retrograde jugular venous cannula was sited.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>p (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>1.153 ±0.330 (12)</td>
<td>1.097 ±0.387 (19)</td>
<td>0.69</td>
</tr>
<tr>
<td>CPB+15 min</td>
<td>2.067 ±0.662 (13)</td>
<td>2.233 ±0.545 (19)</td>
<td>0.44</td>
</tr>
<tr>
<td>CPB warming</td>
<td>1.854 ±0.666 (13)</td>
<td>1.969 ±0.575 (19)</td>
<td>0.61</td>
</tr>
<tr>
<td>Post CPB</td>
<td>1.722 ±0.667 (13)</td>
<td>1.837 ±0.562 (19)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

The clinical significance of isolated measures of lactate in cerebrovenous blood is unknown. The advent of continuous optical methods of measuring of jugular venous oxygen saturation rendered this aspect of the study obsolete and further sampling was discontinued. No further analysis was performed.
5.15. Summary

Between November 1992 and July 1994 a total of 200 patients were enrolled from approxi­mately 400 suitable cases referred to the Middlesex Hospital. Of these patients, 29 were ex­cluded at baseline (Table 5.1). The remaining 171 patients were randomized to receive either placebo or remacemide. The characteristics of the patients in the two groups were similar (Table 5.2). A further 12 patients were withdrawn from the study after randomization (Table 5.2).

Compliance with medication was good and, with the exception of dizziness – which was sig­nificant more common in the remacemide group (Table 5.5), adverse events were similar in both groups. Treatment with remacemide appeared to have no significant impact on routine perioperative biochemical and haematological variables (Figures 5.25 – 5.32). Preoperative mood and levels of anxiety were similar in both groups (Tables 5.9, 5.10). Patients in the placebo group scored higher than the remacedmide group on preoperative tests of general intelli­gence (Table 5.8).

Intraoperative variables (i.e. duration of surgery, CPB duration, myocardial ischaemic time, arterial pressure, temperature, pump flow rate and cerebral blood flow velocity) were similar in both groups (Tables 5.11, 5.12, 5.14 and Figure 5.1). Cerebral microembolic events were detected during surgery in all of the 140 patients studied with transcranial Doppler sonography. Although the remacemide group appeared to have a greater cerebral microembolic load (Figure 5.3) the difference between the treatment groups was not statistically significant. Micro­embolic events tended to be more numerous in patients undergoing multiple bypass grafts – presumably as a result of more frequent application of the aortic cross-clamp (Table 5.17).

Exposure to remacemide and ARL12495XX – its active desglycine metabolite – in this study was, on average, greater than that reported in the previous dose-ranging safety and tolerability study (Tables 3.8, 3.9, 5.15). The influences of surgery and cardiopulmonary bypass; and incomplete knowledge of the plasma concentrations required for neuroprotection in humans makes it hard to be sure that neuroprotective concentrations of remacemide/ARL12495XX were achieved and maintained during and immediately after surgery.

In all, 156 patients underwent technically successful neuropsychological assessment prior to hospital discharge and at follow-up 6-12 weeks after surgery (Table 5.18). For each the neuropsychological test used, test performance at 6 days after surgery was a statistically significant predictor of test performance at 8 week after surgery. Test performance typically deterio­rated at 6 days after surgery and improvement at 8 weeks after surgery (i.e. Rey AVLT, BDT, HTT, DRT). In a number of tests however, test performance was inferior to baseline at both 6 days and 8 weeks after surgery (NVRM, TMA, TMB). The LCT, CRT test and SDR test showed improved improvement at 6 days and deterioration at 8 weeks. Prospectively defined meth­
ods of analysis revealed a non-significant trend in favour of supporting the hypothesis of remacemide neuroprotection (Tables 5.60, 5.65). Neuropsychological deficits at 8 weeks after surgery appeared to be related to the number of bypass grafts performed and cerebral microembolic load (Table 5.64).

Exhaustive post hoc analysis, using two categorical definitions of neuropsychological deficit and significant improvement in test performance, suggested no significant treatment effect (Tables 5.61, 5.62, 5.63). An analysis of standardized (z) scores, however, revealed evidence suggestive of a treatment effect in favour of the hypothesis (Table 5.66).
Chapter 6

Discussion
6.1. Discussion

The work presented in this thesis evolved from the hypothesis that the neuropsychological impairment seen in many patients after coronary artery bypass surgery (CABS) is due to per-operative cerebral ischaemic damage related to amino acid excitotoxicity, and therefore might be ameliorated by the administration of a neuroprotective glutamate antagonist. The initial chapters review the historical, pathophysiological and methodological background to the design and execution of a randomised-controlled trial of the NMDA receptor antagonist pro-drug remacemide in 171 patients undergoing CABS. Using the prospectively determined method of data analysis there was a non-significant trend toward fewer neuropsychological deficits in patients treated with remacemide. A post hoc data analysis, however, suggested evidence of neuroprotection, tending to support the original hypothesis. This is believed to be the first successful trial of its kind.

During the course of the last half of the twentieth century cardiac surgery has grown from infancy to maturity. Procedures once considered 'miraculous' are now routinely performed in countless hospitals around the world. Patient registries on both sides of the Atlantic confirm that the mortality and morbidity associated with cardiac surgery continues to decline. (Figures 1.1 & 1.2) This has been achieved despite a rise in the average age of the cardiac surgical population and increased severity of cardiac disease at the time of surgery.

Despite improvements in many fields, neurological injury remains a significant cause of morbidity and mortality following cardiac surgery. [Roach, 1996; Wolman, 1999] The problem of neurological complications was discussed in the first chapter of this thesis. The historical overview, the discussion of methodological issues in assessment and the review of the incidence, nature and aetiology of neurological injury following cardiac surgery, as presented in Chapter 1, have recently been published elsewhere. [Arrowsmith, 1999b; 2000] From this discussion it is clear that advanced patient age, atherosclerosis of the proximal aorta, symptomatic cerebrovascular disease, diabetes mellitus and combined and/or open-chamber procedures are significant risk factors for adverse neurological outcome.

In the second chapter of this thesis the physiology and pharmacology of cerebral blood flow and the pathophysiology of neuronal injury were discussed. From the subsequent descriptions of excitatory amino acid neurotransmission and the cellular mechanisms underlying neuronal ischaemia it was argued that agents that interfere with these complex mechanisms might be neuroprotective. (Table 2.5) The evidence from in vitro and animal studies suggests that the neuroprotective effects of excitatory amino acid receptor antagonists – such as aptiganel, remacemide, selfotel, eliprodil and dextrophan – might be of use in humans. Because of the
central role of amino acids excitotoxicity in neuronal injury it was considered logical to study the neuroprotective effects of an amino acid antagonist in patients undergoing CABS. Enthusiasm for these agents was tempered, however, by a discussion of the failure of several agents to progress beyond phase III in stroke trials despite encouraging pre-clinical and clinical phase II studies. Reasons for this failure include; lack of efficacy (e.g. tirilazad [Johnston, 1998], selfotel [Davis, 1997], eliprodil), adverse side effects (e.g. dextrorphan [Schmitt, 1997], selfotel [Davis, 1997]) and/or inconclusive or irreproducible results (e.g. lubeluzole [Morgenstern, 1997], siag soils [SASS Investigators, 1994; Argentino, 1989]).

The pharmacology of remacemide and its active metabolites was presented in the third chapter of this thesis. Animal studies have shown that remacemide is well tolerated, is an effective anticonvulsant [Porter, 1984] and is neuroprotective in a variety of models of cerebral ischaemia. [Palmer, 1991; Harris, 1992; Palmer, 1995]. (Tables 3.1, 3.2, 3.3, 3.4 & 3.5) It was therefore chosen for a neuroprotective trial in patients undergoing CABS.

The choice of neuropsychological tests used in this study was based on previous experience with their sensitivity [Newman, 1995a], their acceptance in the literature and their compliance with the recommendations of consensus methodological conferences. [Murkin, 1995b; 1997] The number and type of tests used were thought to cover a wide range of cognitive domains and represent a compromise between sensitivity and patient tolerability. Although a more exhaustive and lengthy test battery might have improved sensitivity this would almost certainly been at the expense of increased subject dropout and lower compliance with follow-up assessments. [Stump, 1995; Borowicz, 1996] Neuropsychological assessments were conducted in accordance with consensus statements published after completion of this study. [Murkin, 1995b; 1997] Assessments were conducted by trained staff in a quiet room well away from the surgical ward. Whenever possible, computerised versions of tests were used to reduce examiner bias. When available, parallel forms were administered to limit the effects of learning between assessments, although it was expected that some learning would occur. Indeed, as stated, it was thought that learning would be more obvious in the neuroprotected group and blunted or absent in the control group.

The timing of neuropsychological assessments was based on previous experience and practicability. In most studies preoperative testing has been performed on the day before surgery – a time of emotional turmoil for many patients. [Borowicz, 1996] The advent of ‘same-day’ admission for cardiac surgery virtually precludes this approach. In this study, combining preoperative assessment with a routine pre-admission hospital attendance 1-2 weeks before surgery was convenient for both the patients and the investigators and potentially reduced adverse psychological influences on test results.

The choice of the sixth postoperative day for administration of the first postoperative neuropsychological assessment was made for a number of reasons. Firstly, the majority of patients
were discharged from hospital on the seventh postoperative day. Secondly, postoperative administration of remacemide – which may have influenced test performance by virtue of its psychotomimetic effects – ceased on the fifth postoperative day. Thirdly, most patients were ambulant, did not require supplemental oxygen, were not taking narcotic analgesics and, therefore, were able to leave the surgical ward.

The decision to perform the second postoperative neuropsychological assessment eight weeks after surgery was made so that follow-up could be combined with a routine visit to the cardiac surgical outpatient clinic. It was believed that the influence of other disease processes on cognitive function at this time would be minimal.

The scoring, analysis and interpretation of neuropsychological tests has been the subject of considerable debate and remains a problematic area. [Blumenthal, 1995; Stump, 1995; Borowicz, 1996; Mahanna, 1996; Arrowsmith, 1998] In this study, no penalty factor was added to the scores of individual test performances to account for incorrect or inaccurate responses. In determining whether or not a patient had sustained a cognitive deficit (using categorical methods) each test was considered to have the same ‘weight’ regardless of the sensitivity of that test to neurological injury. Similarly, no account was made for the fact that changes in performances in some groups of tests are significantly correlated. The use of a weighting system to adjust the relative contribution of tests according to their domain, degree of interdependence and resistance to neurological injury has been suggested [Stump, 1995; McKhann, 1997a] and might have been an improvement.

The a priori decision to use a categorical definition of neuropsychological deficit based on a standard deviation decline from preoperative score was based on previous experience with this method. This method of analysis was that most frequently used in the studies published between 1982 and 1994. [Mahanna, 1996] The method does, however, have the disadvantage that an individual’s change in performance is compared with the group norm. Furthermore, when analysing scores that are low relative to the baseline group mean, a proportionately larger decline in performance would be required for the change to be classified as a deficit. For these reasons other groups have advocated the use of a fixed change in test performance (i.e. >20%). [Stump, 1995] Neither method, however, takes into account any improvement in postoperative test performance and both are subject to the phenomenon of regression toward the mean – shown to strongly influence the analysis of cognitive function tests. [Browne, 1999] As shown in section 5.11 (summarised in Table 6.1) a decline in test performance of 1 SD represented an absolute percentage change in test performance ranging from as low as 6% in the NVRM test to over 100% in the DRT and TMB tests. This wide variation suggests that analysis Method #1 (i.e. ±1 SD) would tend to show a ceiling effect (i.e. overestimate deficit) in the NVRM, SDR, HTT, Rey AVLT and HTT tests, and show a floor effect (i.e. underestimate deficit) in the remaining tests. Put simply; small changes in performance in one test (e.g. NVRM or
SDR) may have been classified as a deficit whereas large changes in another (e.g. DRT or TMB). Conversely, Method #2 (i.e. ±20%) would tend to underestimate deficit in the NVRM, SDR and HTT tests.

<table>
<thead>
<tr>
<th>Test</th>
<th>Placebo</th>
<th>Remacemide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% change</td>
<td>range</td>
</tr>
<tr>
<td>NVRM</td>
<td>10.15 ±0.79</td>
<td>8.46 - 11.79</td>
</tr>
<tr>
<td>SDR</td>
<td>13.53 ±2.99</td>
<td>5.53 - 19.31</td>
</tr>
<tr>
<td>Rey AVLT</td>
<td>22.30 ±4.85</td>
<td>14.35 - 36.96</td>
</tr>
<tr>
<td>WAIS BDT</td>
<td>30.38 ±9.99</td>
<td>15.61 - 66.35</td>
</tr>
<tr>
<td>CRT</td>
<td>31.35 ±6.11</td>
<td>15.78 - 48.16</td>
</tr>
<tr>
<td>TMA</td>
<td>38.78 ±12.62</td>
<td>17.00 - 71.55</td>
</tr>
<tr>
<td>DRT</td>
<td>46.27 ±16.11</td>
<td>16.17 - 101.77</td>
</tr>
<tr>
<td>TMB</td>
<td>47.57 ±18.13</td>
<td>16.07 - 115.60</td>
</tr>
</tbody>
</table>

Table 6.1: Summary of mean ±SD and ranges of absolute percentage changes in postoperative neuropsychological test performance that equate to a change of 1 standard deviation from the preoperative group mean test performance.

It has been argued that studies of interventions in cardiac surgery designed to improve neuropsychological outcome that include two or more patient groups should use all the data by comparing the change in performance between the groups. [Newman, 1995a] This not only enables an examination to be made of each of the tests, as some may be more sensitive to changes than others, but crucially, also allows the potential effects of learning to be considered. [McKhann, 1997a] Improvements with repetition in neuropsychological tests are frequently reported as constituting an unwanted phenomenon. As a consequence many neuropsychological tests have either been designed to prevent this phenomenon from occurring [Stump, 1995] or corrections are made to account for such practice effects. As previous mentioned, the publication of a number of articles during the course of this study and following its completion, prompted a post hoc analysis. An analysis of a continuous, standardised measure of changes in test score (z score) was undertaken to examine the learning effect phenomenon. Learning is considered to be a sensitive measure of cognition and an increased capacity to learn in the remacemide group would therefore be considered a reflection of neuroprotection. [Arrowsmith, 1998] Of the methods of data analysis presented in this thesis, the author considers this latter method to be the most appropriate.

The size of the study population was based on the 30% incidence of neuropsychological deficits at 2-12 months after CABS reported in previous studies. [Sotaniemi, 1981; Newman, 1987; Shaw 1987b; Venn, 1988] On this basis a sample size of 180 (90 in each group) would have been adequate to detect a 20% or more absolute improvement in treated patients.
The observation that cognitive dysfunction after CABS is related to intraoperative cerebral microembolic load [Pugsley, 1994] prompted the inclusion of cerebral embolus detection in this study. As in previous studies, cerebral microembolic load was estimated with unilateral transcranial Doppler sonography as bilateral TCD monitoring equipment was not then readily available. Commercially available equipment as used in this study cannot be used to determine the nature of emboli including those produced by cardiotomy suction, the use of which was not restricted in this study. Nevertheless, the technique was considered adequate to seek evidence of any significant imbalance in embolic load in the trial groups. As reported in previous investigators [Padayachee, 1987; van der Linden, 1991a; Pugsley, 1994;], cerebral microembolic events were detected in all patients studied. Unlike the findings of van der Linden and Pugsley, the vast majority of microembolic events were detected soon after the onset of CPB. (Figure 5.3)

Of the 200 patients originally enrolled into the study, 29 (14.5%) were withdrawn prior to randomisation. Overall, compliance with the study protocol by both patients and investigators was extremely good. Only four patients were withdrawn from the final efficacy analyses on the basis of test medication protocol violations. It is certain that the value of many previously reported investigations [Mahanna, 1996] has been considerably reduced because of low patient follow-up rates. Whilst geographical and financial constraints are often cited as the reason, the obvious concern is that it is those patients with cognitive dysfunction who decline follow-up. The follow-up rates achieved in this study are substantially higher than those reported in other series, and gives confidence that the results obtained are representative of the study population. Technically satisfactory neuropsychological assessments were obtained in 156/171 (91%) patients one week after surgery and in 154/171 (90%) patients between the 6th and 12th week after surgery. Thus it is believed that combining the second postoperative assessment with a routine surgical outpatient clinical attendance was a crucial factor. Providing meals and refreshments for both patients and escorts as well as reimbursing travelling expenses undoubtedly encouraged compliance – an example to future investigators.

This study has demonstrated the safety and tolerability of remacemide hydrochloride (600 mg daily) in 84 patients undergoing CABS. Although CNS side effects were more common in patients exposed to remacemide, these were invariably mild and transient. This study gives no indication that treatment with remacemide had any adverse effect on either the surgical procedure or cardiac outcome. Furthermore, remacemide appears to have no more influence on routine perioperative biochemical and haematological indices than placebo. (Figures 5.25 – 5.32) A comparison of the data obtained in this study with data obtained in a previous dose-escalating and tolerability study indicates that exposure to ARL12495XX was, on average, higher in this study.
However, in light of the pharmacokinetic profile revealed in the preliminary study (see 3.4.1) the level of exposure to both remacemide and ARL12495XX during and immediately after surgery is a cause for concern. It is clear that the combined effects of intraoperative haemodilution, hypothermia, and haemorrhage almost certainly resulted in a significant reduction in plasma levels of both remacemide and ARL12495XX. Given that an unacceptable level of adverse events associated with doses of remacemide exceeding 600 mg/day in human volunteers, it would not have been reasonable to increase intraoperative exposure by an increase in preoperative oral dose. Had an intravenous preparation of remacemide been available for study, it might have been possible to achieve and maintain high concentrations of remacemide throughout the duration of surgery and into the early postoperative period. The intravenous administration of a bolus dose followed by a continuous infusion after the induction of anaesthesia would ensure that patients were not subjected to psychotomimetic side-effects (e.g. dizziness) while conscious. This approach assumes that concentrations of ARL12495XX (the active metabolite) reach a sufficient level during the period of neuronal vulnerability - i.e. before aortic cannulation and the onset of cardiopulmonary bypass.

The lack of validated ‘target’ plasma concentrations for remacemide and ARL12495XX in this study was a serious problem. In comparison with preclinical neuroprotection studies (see 3.3.5) it is clear that the doses of remacemide administered were significantly lower in the present study (4.7 - 11.1 mg/kg versus 7.5 - 25 mg/kg). As there are no human neuroprotection data and no data correlating plasma and brain levels of remacemide or ARL12495XX, it is not known whether adequate (i.e. neuroprotective) CNS concentrations of either remacemide or ARL12495XX were ever achieved, much less maintained.

With the exception of one patient who died of multi-system organ failure, no patient sustained any clinically apparent stroke or transient ischaemic attack in the perioperative period. Subtle, transient neurological dysfunction may have been overlooked because formal neurological assessment (e.g. visual acuity, visual fields, motor power, limb co-ordination, primitive reflex etc.) was not a component of the study protocol. On the basis of the Newcastle study [Shaw, 1985] (Table 1.1), one might predict that around 3 patients would have sustained a stroke, 40 patients would have a detectable visual field defect and 67 patients would have had demonstrable primitive reflexes. Using the McSPI/IREF risk index, the range of possible scores was 14 to 121 corresponding with a CNS injury risk ranging from <0.1% to >11%. [Newman, 1996a; Arrowsmith 2000] The exclusion of patients over 75 years of age and patients with existing neurological disease undoubtedy resulted in a study population that was at lower risk of neurological complications. It is unlikely that a significant number of the patients studied had severe aortic atheroma, although this could not be assessed as neither transoesophageal nor epiaortic ultrasound were available to the investigators. The low operative mortality (2/171 = 1.2%) tends to support the notion that this group of patients had a
lower risk of complications than an unselected group. For this reason it may be difficult to apply the results of this study to 'high-risk' CABS patients or, indeed, to patients undergoing valve or combined procedures. Had a scoring system such as the Parsonnet score [Parsonnet, 1989] been used to predict operative mortality some comparison with those patients who were not enrolled into the study could have been made.

Using the prospectively defined method of analysis (i.e. >1 SD fall in test performance from baseline) the number of patients found to have a neuropsychological deficit in this study was unexpectedly low and, significantly, below that estimated for the purposes of calculating sample size. The reasons for this probably include the rigid inclusion criteria and standardised surgical and anaesthetic technique. The enrolment criteria intentionally excluded patients with known risk factors for adverse neurological outcome – age greater than 75 years, pre-existing neurological disease, unstable cardiac symptoms, previous cardiac surgery, and alcohol abuse. [Roach, 1996] As previously mentioned, no patient over 75 years of age was enrolled and the average age of all patients studied was 58.9 years. While this is similar to the average age reported in some studies [Nussmeier, 1986; Nevin, 1987; Stephan, 1992; Newman, 1994; Grieco, 1996; Mahanna, 1996] it is significantly lower than that reported, more recently, in others. [Gold, 1995; Roach, 1996] The influence of patient age on mortality and adverse neurological outcome following CABS has already been stressed. [Cosgrove, 1984; Roach, 1996] The higher mean IQ in the placebo group (Table 5.8) could have resulted in neuropsychological test performances in this group that were marginally better than might be expected, with a 'protective' effect on postoperative changes.

Improvements in anaesthetic, perfusion and surgical practice may also, in part, explain the apparent improvement in neuropsychological outcome, since earlier studies. [Sotaniemi, 1981; Newman, 1987; Shaw 1987b; Venn, 1988] The use of a 40 μm arterial line filter in the extracorporeal circuit was not the standard of care at the Middlesex Hospital at the time this study was conceived. Although it was known that an arterial line filter could significantly reduce the number of microemboli delivered to the cerebral circulation by a bubble oxygenator [Pugsley, 1989] the same could not be said of the membrane oxygenator used in this study. During the course of this study, arterial line filtration was adopted as a standard of care and the use of these devices has become increasingly common in the UK. Although an initial study suggested no benefit [Aris 1986], a randomised trial conducted by the Oxford group provides evidence that arterial line filtration reduces cerebral injury in patients undergoing CABS. [Taggart, 1997a]

Although a greater proportion of patients with neuropsychological deficits were found in the control group (12% versus 9%), this difference was not statistically significant. A trial with a considerably larger study population may well have been sufficiently powered to determine whether this small inter-group difference was significant. A single-centre study design, how-
ever, would have resulted in an increase in the duration of the study. It would then been difficult to account for the confounding influences of changes in staff and operative techniques over time. In contrast, a multi-centre study design would allow completion of a much larger study within a reasonable time-span. Such a design would, however, introduce differences in anaesthetic and surgical techniques, in postoperative care, and in neurological and neuropsychological assessment.

Subsidiary analyses – using a second definition of deficit (-20% change in score), categorical definitions (+1 SD and +20% change in score) of significant improvement and the presence of any improvement or any deterioration in test performance – were subsequently performed. Patients in the remacemide group were found to have smaller deteriorations in performance in 4/10 tests (NVRM, BDT, HTT, DRT) 6 days after surgery (Tables 5.26, 5.38, 5.42, & 5.58) and greater improvements in performance in 5/10 tests (AVLT, TMB, HTT, SDR, DRT) at 8 weeks after surgery. (Tables 5.23, 5.34, 5.42, 5.50 & 5.58) This finding was supported by an analysis using standardised scores. Using this latter method, patients in the remacemide group were shown to have superior performances in 8/10 tests at 8 weeks after surgery. These differences were statistically significant in 3/10 tests. (Table 6.66) The remacemide group showed significantly improved performance on a composite measure of neuropsychological outcome (p=0.014).

Subjective (patient) self-assessment of cognitive function was included in the study protocol on the grounds that an earlier study had found that subjective reports of postoperative cognitive dysfunction do not reflect actual changes in cognition but rather mood and anxiety [Newman, 1989] In addition, the inclusion of a subjective outcome measure might have revealed that remacemide induced a subjective alteration in cognitive function that could not be detected by formal neuropsychological testing, and that patients with poor neuropsychological test performances actually report subjective improvements in cognitive function. The majority of patients reported either an improvement or no change in cognitive function at 8 weeks after surgery. There were no statistically significant differences between the remacemide and placebo groups. A more detailed analysis of individual test score changes and subjective reports was not conducted. A quality of life assessment – including such endpoints as exercise tolerance, return to employment and resumption of sexual activity – might have been a useful addition. Any differences in neuropsychological outcome attributable to gender could not be tested because of the small number of females (17/171; 10%) enrolled in the study. (Table 5.67)

There were no statistically significant differences in depression scores and both trait and state anxiety scores between the remacemide and placebo groups at any assessment. The incidence of new depression following CABS in this study was low (6%) in comparison with the findings of McKhann et al, who reported incidences of new depression 1 month and 1 year after CABS of 13% and 9%, respectively. [McKhann, 1997b] The most significant predictor of postopera-
tive depression (defined as BDI score >10) at both 6 days and 8 weeks after surgery was preoperative depression. This finding supports that of previous work that concludes that CABS neither causes nor cures depression. [Timberlake, 1997; McKhann, 1997b]

Evidence of a neuroprotective effect for remacemide has thus been obtained utilising a method of analysis of the results of neuropsychological tests based on changes in standardised scores that take account of improvement as well as deterioration. This observation supports the use of this method of statistical analysis and further suggests that excitotoxic pathways may play a part in cardiac surgery associated neurological injury. It is believed that a significant and quite unforeseen fall in the background (placebo group) incidence of cognitive decline coupled with the insensitivity of the categorical definition of deterioration resulted in a failure to demonstrate a statistically significant reduction in cognitive deficits using the primary methods of analysis (i.e. Methods #1 and #2), despite the very high follow-up rate.

6.2. Summary

Using an analysis of standardised neuropsychological test scores, evidence of remacemide neuroprotection has been demonstrated in a study of 171 patients undergoing CABS. The investigators believe that this finding supports the notion that excitotoxic mechanisms play at least some part in the neurological injury associated with cardiac surgery performed with cardiopulmonary bypass. The authors of the published account of this study [Arrowsmith, 1998] believe it to be the first of its kind.

This study has also demonstrated the limitations of categorical definitions of neuropsychological deficit or improvement and the utility of the analysis of continuous, standardised test scores in comparing the neuropsychological performance between treatment groups.

This study has confirmed the previously reported association between cerebral microembolic load during cardiopulmonary bypass and postoperative neuropsychological deficits.

This study has confirmed the previously reported finding that new depression following coronary artery bypass graft surgery is uncommon and that preoperative depression is a significant predictor of postoperative depression.

6.3. Future directions

At the time of writing, more than five years have passed since the first patient in this study underwent surgery. A five-year follow-up study of these patients has recently been started. In addition to further neuropsychological testing, it is hoped that patients will undergo qual-
ity of life assessments and determination of their APOE phenotype. The completed study will be the longest pharmacological neuroprotection study reported in cardiac surgery. This will hopefully answer the question as to whether neuroprotection at the time of surgery has persistent benefits over the long term. At present the manufacturer is not pursuing a licence for the use of remacemide in this indication although phase III studies in refractory epilepsy continue.

The theoretical superiority of AMPA receptor antagonists (i.e. efficacy in global cerebral ischaemia and absence of psychotomimetic side effects) make this class of drug more likely to proceed beyond phase III studies. As has already been demonstrated with a number of agents, success in the laboratory does not always translate to success in clinical trials, but trials of an AMPA antagonist in CABS are clearly warranted.

Since this study was commenced, and in the time between completion of the study and writing this report there have been a number of advances. Based on this and other work the author is currently investigating the possible neuroprotective effects of high-dose magnesium sulphate (100-150mg/kg) in cardiac surgery. To this end a dose-ranging / safety study has been undertaken and plans for a small pilot study near completion. Theoretically magnesium could influence opening of glutamate-gated ion channels without the side effects of some of the pharmacological antagonists.

The detection of cerebral microemboli in one patient associated with the first few inflations of an intra aortic balloon pump has prompted further investigation. A study of cerebral haemodynamics and microembolic events in cardiology patients undergoing IABP placement on the acute coronary care unit at Duke Hospital is currently in progress.

A recent report suggesting that lignocaine (lidocaine) is neuroprotective in cardiac surgical patients when given in antidysrhythmic doses for a period of 48 hours starting at induction of anaesthesia opens a new avenue for investigation. [Mitchell, 1999] Like lignocaine, anticonvulsant drugs (such as remacemide) act as sodium channel blockers and may reduce cytoplasmic swelling and inhibit neuronal and glial glutamate release. It will not be long before further studies aiming to reproduce these findings are published.

The under representation of females in studies of neurological and cognitive outcome in cardiac surgery has hampered investigation of gender-related differences. Recent evidence, suggesting that oestrogens are neuroprotective in animal models of cerebral ischaemia, opens yet another avenue for investigation. [Hum, 2000]

The success of remacemide in this study of cerebral ischaemia in CABS raises the hope that it or analogous compounds will also improve neuroprotective in patients with acute stroke. The possibility of pre-treatment in the CABS situation represents an ‘ideal’ test bed for neu-
roprotection that cannot be achieved in routine stroke though differences in pathophysiological mechanisms of damage may reduce the relevance of this model.

A few years ago the Russian President, Boris Yeltsin, underwent coronary artery bypass graft surgery. The apparent decline in his cognitive function has once again brought both the subtle and not so subtle neurological consequences of cardiac surgery back into the public arena. The announcement that former U.S. President Ronald Reagan has early Alzheimer's disease increased public awareness of neurodegenerative diseases that are thought to have their basis in abnormalities in excitatory amino acid neurotransmission. Rising consumption of putative 'over the counter' neuroprotectants, such as vitamin E, may be a barometer of intense public interest in this area. The explosion of interest in this field looks certain to continue.
Bibliography


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Appendices
INFORMED CONSENT FORM

Middlesex Hospital, Mortimer Street, London W1N 8AA
Tel: 071 436 1755 (direct line) or 071 636 8333 Ext 4308

Purpose of Research

You are being asked to take part in a research study under the direction of Mr W B Pugsley, Mr C Pattison and Dr J E Arrowsmith. This is to assess the effects of a new medicine, called remacemide, on patients such as yourself who are undergoing heart surgery. Studies in animals have suggested that remacemide may help prevent some of the subtle changes in memory or concentration that sometimes occur after this operation. The study that you are being asked to join in is the second in heart patients. A preliminary study has not revealed any significant problems and other types of patients have received the drug without undue problems. Up to 240 heart operation patients will be involved in this study. In order that a proper assessment of the effects of remacemide may be made, some individuals will receive a placebo (or dummy) treatment for comparison. You have an equal chance of receiving either treatment.

Study Procedures

Your operation and your other medicines will be the same whether you join in the study or not. If you decide to join in, you will be given the test treatment when you visit the hospital about one week before your operation. You will take the test tablets for up to six days and you will have a card to fill in to record the time you take the tablets and any side effects you might notice. You will stop taking the test tablets just before your operation and start taking them again the next day for another five days. Apart from having a small number of extra blood samples taken while you are in hospital (four or five) and extra monitoring during and after your operation, everything else will be as the routine procedure.

To assess the effects of remacemide you will be asked to carry out a series of tests of mental performance on three occasions - 15 tests when you join the study, 13 tests six days after your operation and again eight weeks after your operation. The series of tests will take about an hour and a half on each occasion and will be done on occasions when you are attending the hospital routinely so they should not involve any extra visits to the hospital.
Alternative Treatment

There are no treatments which act in the same way as remacemide is used at the moment nor are there any other treatments for the same purpose, so participating in this study would not deprive you of anything that you would normally have.

Discomfort / Risks

The side effects that volunteers and other patients have had with remacemide have generally been mild. A proportion of patients reported mild light-headedness after the first few doses. Some have described some discomfort in the chest or stomach after swallowing the capsules. This can generally be avoided by taking a full glass of water with each dose. Occasionally blood sampling can be uncomfortable or cause bruising. Because remacemide is a new drug there is limited information on it and it must not be taken by women capable of having children.

Warnings

During the 4 days that you take the tests tablets before coming into hospital for your operation you must not drive motor vehicles, operate machinery or drink alcohol.

Benefits

As yet there is no information about whether remacemide is effective for this use, but it is possible that by taking the drug there may be some protection against some of the subtle memory or concentration losses that sometimes follow an operation of this type.

Participation and Withdrawal

You need not take part in this study if you do not want to, and you may stop at any time. Refusal to participate will not affect your normal medical treatment, or involve any penalty or loss of benefits. It may be necessary to withdraw you from the study if you do not follow the instructions of Mr W B Pugsley, Mr C Pattison and Dr J E Arrowsmith in conducting this research, or if your medical condition changes so that continuing in this study could jeopardize your health or the research.
Compensation and Availability of Treatment

If a physical injury should occur to you in this research as a result of an adverse effect from the study medication, treatment will be available. In addition, should the injury be of an enduring and disabling character, appropriate compensation will be paid to you taking into account the nature, severity and persistence of the injury and the benefit/risk ratio associated with the treatment.

Confidentiality of Records

The hospital records and the special records created during this study will be kept confidential, access being restricted to personnel, including the sponsor's representatives, involved in the study. Some of the data and results may be published, but your identity will not be disclosed. This study is sponsored by Fisons plc, Pharmaceutical Division.

To Obtain Further Information

If you have any questions about this research, or your rights, or what to do and whom to contact in the event of a research-related injury or claim, Mr W B Pugsley, Mr C Pattison and Dr J E Arrowsmith will be happy to answer questions or will direct you to someone who can provide you with more information.

I have been fully informed of the study sponsored by Fisons plc. I have been given a copy of the information sheet to keep. My questions have been answered and I agree to take part in the research study.

Patient name (please print) _______________________________

Patient Signature _______________________________ Date ________

Investigator's Signature _______________________________ Date ________

Independent Witnesses Signature _______________________________ Date ________

Occupation of Witness _______________________________

Patient number _______ / _______
APPENDIX 2  
Post-operative social and subjective assessment questionnaire

Instructions: I would like to ask you some important questions about how life may have changed for you since your operation. It is very important for our understanding of the effects of this form of surgery that you answer as honestly as possible. The information that you provide will be considered together with other patients who have had a similar procedure and will not be identified to the surgeons involved as having come from you.

<table>
<thead>
<tr>
<th>SINCE YOUR OPERATION ARE YOU:</th>
<th>More</th>
<th>No Change</th>
<th>Less</th>
</tr>
</thead>
<tbody>
<tr>
<td>More or less alert and thinking more or less clearly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forgetting things, for example, things that happened recently, where you put things or keeping appointments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have more or less minor accidents, for example, dropping things, tripping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reacting more or less quickly to things that are said or done</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having more or less difficulty in solving problems and learning new things</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having more or less difficulty making decisions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Able to keep your attention to a task for more or less time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Making more or less mistakes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having more or less difficulty in doing things which involve thought or concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**APPENDIX 3**

**Beck Depression Inventory**

**Instructions:** On this questionnaire are groups of statements. Please read each group carefully and then pick out the one statement from each group which best describes the way you have been feeling in the PAST WEEK, INCLUDING TODAY. Circle the number beside the statement you picked.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I do not feel sad.</td>
<td>I feel sad.</td>
<td>I am sad all of the time and I can't snap out of it.</td>
</tr>
<tr>
<td></td>
<td>I feel so sad or unhappy that I can't stand it.</td>
<td>I am so sad or unhappy that I can't stand it.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I am not particularly discouraged about the future.</td>
<td>I feel discouraged about the future.</td>
<td>I feel I have nothing to look forward to.</td>
</tr>
<tr>
<td></td>
<td>I feel that the future is hopeless and that things cannot improve.</td>
<td>I feel that the future is hopeless and that things cannot improve.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I do not feel a failure.</td>
<td>I feel I have failed more than the average person.</td>
<td>As I look back on my life all I can see is a lot of failure.</td>
</tr>
<tr>
<td></td>
<td>I feel I am a complete failure as a person.</td>
<td>I feel I am a complete failure as a person.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I get as much satisfaction out of things as I used to.</td>
<td>I don't enjoy things the way I used to.</td>
<td>I don't get real satisfaction out of anything anymore.</td>
</tr>
<tr>
<td></td>
<td>I am dissatisfied or bored with everything.</td>
<td>I am dissatisfied or bored with everything.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I don't feel particularly guilty.</td>
<td>I feel guilty a good part of the time.</td>
<td>I feel guilty most of the time.</td>
</tr>
<tr>
<td></td>
<td>I feel guilty all of the time.</td>
<td>I feel guilty all of the time.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>I don't feel I am being punished.</td>
<td>I feel I may be punished.</td>
<td>I expect to be punished.</td>
</tr>
<tr>
<td></td>
<td>I feel I am being punished.</td>
<td>I feel I am being punished.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>I don't feel I am any worse than anybody else.</td>
<td>I am disappointed in myself.</td>
<td>I am disgusted with myself.</td>
</tr>
<tr>
<td></td>
<td>I hate myself.</td>
<td>I hate myself.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>I don't feel I am any worse than anybody else.</td>
<td>I am critical of myself for my weaknesses or mistakes.</td>
<td>I blame myself all the time for my faults.</td>
</tr>
<tr>
<td></td>
<td>I blame myself for everything bad that happens.</td>
<td>I blame myself for everything bad that happens.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>I don't have any thoughts of killing myself.</td>
<td>I have thoughts of killing myself but I would not carry them out.</td>
<td>I would like to kill myself.</td>
</tr>
<tr>
<td></td>
<td>I would kill myself if I had the chance.</td>
<td>I would kill myself if I had the chance.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>I don't cry any more than usual.</td>
<td>I cry more now than I used to.</td>
<td>I cry all the time now.</td>
</tr>
<tr>
<td></td>
<td>I used to be able to cry but now I can't even though I want to.</td>
<td>I used to be able to cry but now I can't even though I want to.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>I am no more irritated than I am normally.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>I get annoyed or irritated more easily now than I used to.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I feel irritated all the time now.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I don’t get irritated at all by the things that used to irritate me.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>I have not lost interest in other people.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>I am less interested in other people than I used to be.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I have lost most of my interest in other people.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I have lost all of my interest in other people.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>I make decisions as well as I ever could.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>I put off making decisions more than I used to.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I have greater difficulty in making decisions that I used to.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I can’t make decisions at all anymore.</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>I don’t feel I look any worse than I used to.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>I am worried that I am looking old or unattractive.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I feel that there are permanent changes in my appearance that make me look unattractive.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I believe I look ugly.</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>I can work about as well as before.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>It takes an extra effort to get started in the morning.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I have to push myself very hard to do anything.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I can’t do any work at all.</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>I can’t sleep as well as usual.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>I get tired more easily than I used to.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I get tired from doing almost anything.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I am too tired to do anything.</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>0</td>
<td>I don’t get more tired than I used to.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>I get tired more easily than I used to.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I get tired from doing almost anything.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I am too tired to do anything.</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>My appetite is no worse than usual.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>My appetite is not as good as it used to be.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>My appetite is much worse now.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I have no appetite at all anymore.</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>0</td>
<td>I haven’t lost much weight, if any, lately.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>I have lost more than 5lbs.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I have lost more than 10lbs.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I have lost more than 15lbs.</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>I am no more worried about my health than usual.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>I am worried about physical problems such as aches, pain, upset stomach or constipation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I am very worried about physical problems and it’s hard to think of much else.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I am so worried about my physical problems that I cannot think about anything else.</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>I have not noticed any recent change in my interest in sex.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>I am less interested in sex than I used to be.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I am much less interested in sex now.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I have lost interest in sex completely.</td>
<td></td>
</tr>
</tbody>
</table>
SELF-EVALUATION QUESTIONNAIRE

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel right now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

<table>
<thead>
<tr>
<th>Statement</th>
<th>NOT AT ALL</th>
<th>SOMEWHAT</th>
<th>MODERATELY SO</th>
<th>VERY MUCH SO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: I feel calm</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2: I feel secure</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3: I am tense</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4: I am regretful</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5: I feel at ease</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6: I feel upset</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7: I am presently worrying over possible misfortunes</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8: I feel rested</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9: I feel anxious</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10: I feel comfortable</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11: I feel self-confident</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12: I feel nervous</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13: I am jittery</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14: I feel &quot;high strung&quot;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15: I am relaxed</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16: I feel content</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17: I am worried</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18: I feel over-excited and &quot;rattled&quot;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19: I feel joyful</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20: I feel pleasant</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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SELF-EVALUATION QUESTIONNAIRE

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you generally feel. There is no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

<table>
<thead>
<tr>
<th>Statement</th>
<th>ALMOST NEVER</th>
<th>SOMETIMES</th>
<th>OFTEN</th>
<th>ALMOST ALWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 I feel pleasant</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22 I tire quickly</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23 I feel like crying</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24 I wish I could be as happy as others seem to be</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25 I am losing out on things because I can't make up my mind soon enough</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26 I feel rested</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27 I am &quot;calm, cool, and collected&quot;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28 I feel that difficulties are piling up so that I cannot overcome them</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>29 I worry to much over something that really doesn't matter</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>30 I am happy</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>31 I am inclined to take things hard</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32 I lack self-confidence</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33 I feel secure</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34 I try to avoid facing a crisis or difficulty</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35 I feel blue</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36 I am content</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37 Some unimportant thought runs through my mind and bothers me</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38 I take disappointments so keenly that I can't put them out of my mind</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39 I am a steady person</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40 I get in a state of tension or turmoil as I think over my recent concerns and interests</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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Rey Auditory-Verbal Learning (AVLT) Test

This is a test of immediate memory span which provides a learning curve and may reveal learning strategies. Performance is influenced by patient age and socioeconomic status. The test consists of seven ‘trials’ - five presentations with recall of a 15-word list, one presentation with recall of a second 15-word list, and recall without presentation of the first 15-word list.

The examiner first reads a list of 15 words at the rate of one per second giving the following instructions: “I am going to read a list of words. Listen carefully, for when I stop you are to say back as many words as you can remember. It doesn’t matter in what order you repeat them. Just try to remember as many as you can.”

The examiner writes down the words that the patient recalls in the order recalled. When the patient indicates he can recall no more words the examiner rereads the word list giving a second set of instructions: “Now I’m going to read the same list again, and once again when I stop I want you to tell me as many words as you can remember, including words you said the first time. It doesn’t matter in what order you say them. Just say as many words as you can remember whether or not you said them before.”

The word list is reread for the third, fourth and fifth trials using the second set of instructions. On completion of the fifth trial the examiner reads the second word list giving the fol-
Now I'm going to read a second list of words. This time, again, you are to say back as many words of this second list as you can remember. Again, the order in which you say the words does not matter. Just try to remember as many as you can.”

Following this trial the examiner asks the patient to recall as many words from the first list as he can. The score for each trial is the number of words correctly recalled. A drop in recall by more than three words from trial 5 to trial 7 reflects a retention or retrieval problem.

**Non Verbal Recognition Memory (NVRM) Test**

In this computerised test the patient is first presented with a random 6x7 square checkerboard pattern and then presented with three different checkerboard patterns, one of which is identical to the first pattern. The patient is then asked to select the pattern first presented by moving a small handset to the appropriately labelled area (labelled 1, 2 and 3) on a pressure sensitive graphics tablet, and pressing a small button on the handset.

![Sample 6x7 checkerboard patterns used in the non verbal recognition memory test.](image)

A sheet of paper with three, separate large square areas labelled 1, 2 and 3 is mounted on the graphics tablet. The examiner says; “This task looks at your memory for shapes and designs. A shape, rather like a crossword pattern, will appear on the screen and remain there for 10 seconds. During this time you have to try to memorise it. The design will then disappear and three smaller shapes will take its place. They will be numbered 1, 2 and 3, as on your sheet. What you have to do, is to decide which of the three is the same as the large one you have just seen. When you have decided place the hand set over the number you think it is and press the yellow button. Do this as quickly as you can. The shapes will then disappear and a beep will sound to indicate to you that another shape is coming up. Please make sure that you are looking at the screen. There are some practice trials for you to begin with.”

The test is repeated for a total of twenty presentations.
Trail Making Tests (TMA, TMB)

This is a test of visual conceptual and visuomotor tracking. As with other tests involving motor speed and attention, it is highly vulnerable to the effects of cerebral damage. As with other tests in which response speed contributes significantly to the score, there is a normal slowing with increasing age. It is given in two parts, A and B (see below). The subject is instructed to draw lines to connect 25 consecutively numbered circles (i.e. 1-2-3-4... 24-25) on one work sheet (Part A) and then connect the same number of consecutively numbered and lettered circles (i.e. 1-A-2-B ... 12-L-13) on the second work sheet by alternating between the two sequences (Part B).

For each of the two tests, the patient is first asked to complete a smaller, practice test. The examiner says; "This test is in two parts. This is the practice part of the test. The idea is to join the numbers in the circles in ascending order and going to the centre of each of the circles without lifting the pen from the paper. So, draw a line from 1 to 2 to 3 and so on, until you reach the end".

The subject is encouraged to connect the circles as quickly as possible without lifting the pen from the paper. The examiner points out any errors as they occur so that the subject always completes the test without errors. The scores are the times required to complete each part of the test. This simplified scoring system does, however, tend to reduce the reliability of the test. The final times include the time taken for the examiner to notice an error time (reaction time), the time taken for the examiner to point out the error, and the time taken for the subject to correct the error.

In this study, the trail making test sheets were mounted on a pressure sensitive graphics tablet and timing of the test was performed by a microcomputer.
The Hand Tapping Test (HTT)

This is a test of manual dexterity formerly known as the Finger Oscillation Test. It consists of a tapping key with a device for recording the number of taps. Each hand makes five 10-second trials with brief rest periods between trials. The score for each hand is the average for each five trials. Scores tend to be higher in the dominant or preferred hand. Advancing age and anxiety (in women) tend to depress the score.

WAIS-R Block Design Subtest (BDT)

This is a construction test in which the patient is asked to construct a series of up to 9 patterns of increasing complexity using between 4 or 9 blocks (cubes) coloured red on two sides, white on two sides, and red/white on two sides. (see below) The patient works from either a block model (constructed by the examiner) for Design 1, and from printed cards for Designs 2-9.

Design 1: The examiner takes four blocks and shows them to the patient saying; “You see these block? They are all alike. On some sides they are all red; on some, all white; and on some, half red and half white. I am going to put them together to make a design. Watch me.” The examiner then slowly arranges the four blocks into the first design. Leaving the model intact, the examiner gives the patient four other blocks saying: “Now make one just like this.” If the patient completes the design within 60 seconds the examiner proceeds to Design 2. If the patient fails the examiner says: “Watch me again” and constructs the design using the patient’s blocks. Leaving the examiners model intact, the examiner then scrambles the patient’s blocks and says: “Now you try it again and be sure to make it just like mine.” The examiner proceeds to Design 2 whether or not the patient completes the trial within 60 seconds.

Design 2: The blocks that served as the examiner’s model for Design 1 are replaced by the card marked ‘2’. The examiner says: “This time we are going to put the blocks together to make them look like this picture. Watch me first.” The examiner then slowly constructs the design as says: “You see, the top of these blocks look the same as this picture.” After scrambling the blocks the examiner then says: “Now look at this picture and make one just like it with these blocks. If the patient completes the design within 60 seconds the examiner proceeds to Design
3. If the patient fails the examiner says: “Watch me again” and constructs the design using the patient's blocks. The examiner then scrambles the patient's blocks and says: “Now try it again.” The examiner proceeds to Design 3 whether or not the patient completes the trial within 60 seconds.

Designs 3-5: The examiner scrambles the blocks and successively shows the patient the cards for Designs 3 through 5 saying; “Now make one like this. Try to work as quickly as you can. Tell me when you have finished.” When the patient has finished the design or at the end of 60 seconds the blocks are scrambled and the next card presented with the same instructions.

Designs 6-9: The examiner gives the patient all 9 blocks, and then successively presents the cards for Designs 6 through 9 saying: “Now make one like this, using nine blocks. Be sure to tell me when you have finished.” When the patient has finished the design or at the end of 120 seconds the blocks are scrambled and the next card presented with the same instructions.

The test is discontinued after three consecutive failures. A two-trial test (Designs 1 and 2) is considered failed only if both trials are failed.

The test is scored as follows; Designs 1 and 2: Two points for passing on the first trial; One point for passing on the second trial. Designs 3-9: Four points for each design successfully completed within the time limit, plus a maximum of 3 bonus points per design for quick, perfect performance. The maximum score for the test is 51 points.

Two Choice Reaction Time (CRT) Test

This computerised test, the letters “A” and “B” are randomly displayed in series on the screen. The patient is asked to press one of two keys on the keyboard, corresponding to the displayed letters, as soon as he sees the letter on the screen.

The examiner says; “On the keyboard there are two labelled keys, one marked ‘A’ and one marked ‘B’. In this task an ‘A’ or a ‘B’ will appear on the screen and you have to press the appropriate key, so if an ‘A’ appears press the ‘A’ button, if the ‘B’ appears press the ‘B’ button. Place your hands so that the index finger of your left hand is over the key labelled ‘A’ and the index finger of your right hand is over the key labelled ‘B’. When you hear the beep it is time for you to watch the screen. There is a practice session first.”
At the end of the practice session, during which the patient is given an indication of whether or not they pressed the correct key, the examiner says; “That is the end of the practice trial. The actual task is exactly the same except this time the screen will not tell you if you are correct or not. Work as quickly as you can.”

Each letter is randomly presented on 20 occasions. The reaction time recorded is the interval between presentation of the letter on the screen and depression of the keyboard key.

Displaced Reaction Time (DRT) test

A sheet of paper is mounted over the graphics tablet.

\[
\begin{array}{cccccccccc}
A & B & C & D & E & F & G & H & I & J \\
\end{array}
\]

Displaced reaction time test template for graphics tablet

The examiner says; “In this task a white square will appear in the centre on the screen, below it will be written PRESS YELLOW BUTTON, at this point press the yellow button. The square will then turn yellow and anyone of the ten letters, here on the sheet in front of you, will appear in any of the four corners of the screen. Directly you see the letter I want you to press the yellow button, then move the handset across the paper so that it is over the letter you have just seen, and press the yellow button again. Please make sure that the cross on the handset is within the square containing the letter you have chosen. Then return the handset to the square with the ‘X’ in it. When you are ready to start each trial press the yellow button. We will have a practice session first.”

The examiner shows the patient how to perform the test for two presentations and then invites the patient to do the same. When the practice session is over the examiner begins the test saying; “Try to work as quickly and as accurately as possible.”

In all there are a total of 20 presentations (each letter shown twice).
Symbol Digit Replacement (SDR) test

For most patients this is a test of psychomotor performance that is relatively unaffected by intellectual prowess, memory, or learning. Motor persistence, sustained attention, response speed, and visuomotor coordination are all required to perform this test.

The patient is given a series of symbols labelled '1' to '9' and then randomly presented with the nine symbols on a total of 50 occasions. Using the keyboard, the patient is asked to select the number corresponding to the symbol displayed (i.e symbol-digit replacement).

The examiner says; “Here is a row of symbols in the top and underneath a row of numbers one to nine. Each symbol has it’s own corresponding number. Here, at the both of the screen, we have a row of symbols, all jumbled up. Some appear more than once but the numbers are missing. What I want you to do is decide which numbers should go into the empty boxes.

The examiner demonstrates the first three symbol-digit substitutions saying; “To do this just press the number on the keyboard that you think fits into the box. As you see the box will turn yellow when you have made your choice, but there is no feedback as to whether you are right or wrong. This is a practice trial so finish the next two rows to get the idea.”

The box turns yellow to blank out the patient’s response so that time is not wasted by the patient going back to check if previous responses were correct. At the end of the practice session the examiner says; “Now the task for real, it is exactly the same with the same symbols and numbers. This test is timed so work as quickly and as accurately as you can.”
**Letter Cancellation Test (LCT)**

This 'paper and pencil' test requires visual selectivity at fast speed on a repetitive motor response task. It assesses several functions, particularly the capacity for sustained attention. Visual scanning and activation and inhibition of rapid responses are also necessary for successful performance. Lowered scores may reflect general response slowing and inattentiveness associated with diffuse brain damage or acute brain syndromes.

In this test the patient is asked to read through a page of random letters (18 rows of 20 letters) and draw a line (or cancel) every occurrence of one particular letter - usually 'B' or 'P'. In this investigation the test was administered by computer; the page of letters was mounted on a pressure sensitive graphics tablet.

The examiner says; "Here is a page of letters. I'd like you to go through it, line by line, going from left to right as though you are reading and draw a line through every letter 'B'. Do this as quickly and accurately as you can. Press your pen on the 'X' Mark in the centre of the page, then when I tell you to begin take your pen up to the top row and start. When you have finished press your pen on the stop corner".

Example of page of letters used in the Letter Cancellation Test. The page used in this investigation had 18 rows of letters with 20 letters in each.
WAIS-Revised Picture Complete Subtest

In this test a series of 20 cards printed with incomplete pictures of human features, familiar objects, or scenes, arranged in order of difficulty are presented to the patient. The test is consistently resilient to the effects of brain damage.

Before presenting the first card the examiner says: "I am going to show you some pictures in which there is some important part missing. Look at each picture and tell me what is missing." The first card is presented with the instruction: "Now look at this picture. What important part is missing?" If the patient gives a correct response successive cards are presented with the instruction: "Now what is missing in this picture?" (or no instruction if the patient understands the task). If the response to the first or second card is incorrect the examiner demonstrates the missing item, otherwise the examiner makes no comment.

A maximum exposure of 20 seconds is allowed for each card. If the patient does not indicate the missing part within 20 seconds the item is scored as a failure and the next card is presented. If the patient responds incorrectly the next card is presented even if the full 20 seconds have not elapsed. The test is discontinued after 5 consecutive failures. Each correct response scores one point giving a maximum possible score of 20.
WAIS-Revised Vocabulary Subtest

In this test of vocabulary the patient is asked to explain the meaning of a series of words of increasing complexity. (See below) The examiner places the word list in front of the patient and gives the following instructions: “I want you to tell me the meanings of some words. Let’s start with Winter; what does winter mean?”

The response to each item is scored 2, 1 or 0 according to the complexity and veracity of the response given. It is usual to start with item 4 (Winter) giving full credit for the first three items unless the subject is known to have poor verbal ability. In instances where it is difficult to score the response or to determine whether the subject does or does not know the meaning of a word the subject is asked to explain further: “Tell me more about it” or “Explain what you mean”. The test is discontinued after five consecutive failures (responses scored 0). The result is a score in the range 0 to 70.

Possible responses (dictionary, thesaurus based) are as follows;

**Bed** Place to sleep, foundation, area of garden; **Ship** large boat, space craft, send; **Penny** coin; **Winter** coldest month; **Breakfast** morning meal; **Repair** reconstruction, atone for, fix; **Fabric** cloth, substance; **Assemble** bring together, put together; **Enormous** gigantic, atrocious; **Conceal** cover, hide; **Sentence** judgment, convict, jail, grammatical construction; **Consume** eat, use up, ingest, utilise, squander; **Regulate** adjust, govern, control, manage, direct; **Terminate** finish, limit, abolish, end, stop; **Commence** begin, start, issue; **Domestic** Household, native, home-made, servant; **Tranquil** calm, still, sedate, placid; **Ponder** think about, meditate, consider, reflect on; **Designate** name, allocate, appoint, indicate, earmark, commission; **Reluctant** aversive, unwilling, diffident; **Obstruct** bar, hinder, inhibit, impede; **Sanctuary** church, retreat, refugee, shelter; **Compassion** thoughtfulness, courtesy, regard, solicitude; **Evasive** shifty, false, ambiguous, elusive; **Remorse** grief, anguish, sorrow, distress; **Perimeter** boundary, confines, limits; **Generate** make, breed, spawn, produce, create; **Matchless** peerless, unique, alone, unequalled; **Fortitude** perseverance, tenacity, resolve; **Tangible** touchable, perceptible, substantial; **Plagiarize** piracy, copying, forgery; **Ominous** doomed, dismal, danger-
ous, hopeless; **Encumber** hinder, load, burden; **Audacious** courageous, brazen, bold, daring; **Tirade** harangue, malediction, diatribe.

**National Adult Reading Test (NART)**

In this test the examiner presents the patient with a list of 50 short words of irregular pronunciation. The examiner asks the patient to slowly and carefully read the list. Point to each row in turn, the examiner says; “I would like you to read these words out to me. First down this row, then down this one. If you do not know a word just go to the next.”

<table>
<thead>
<tr>
<th>Word</th>
<th>Pronunciation</th>
<th>Word</th>
<th>Pronunciation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHORD</td>
<td>kôrd</td>
<td>SUPERFLIOUS</td>
<td>soo-pur’floo-as</td>
</tr>
<tr>
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<td>ak</td>
<td>SIMILE</td>
<td>sim’l-il</td>
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<tr>
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<td>dep’o</td>
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<td>kwod’roo-ped</td>
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<td>chel’ist</td>
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<td>ka’pn</td>
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<td>zel’at</td>
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<td>di-ni</td>
<td>DRACHM</td>
<td>dram</td>
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<td>e’on</td>
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<td>pla-se’bo</td>
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<td>ABSTEMIOUS</td>
<td>ab-ste’mi-as</td>
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<td>rar’-i-fi</td>
<td>DETENTE</td>
<td>da-tat</td>
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<td>IDYLL</td>
<td>id’il</td>
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<td>PUA PERAL</td>
<td>pu-ur’par-al</td>
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<td>kat’a-koom</td>
<td>AVER</td>
<td>a-vur</td>
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<td>kald</td>
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<td>tim</td>
<td>TOPIARY</td>
<td>to’pi-a-ri</td>
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<td>HEIR</td>
<td>ar</td>
<td>LEVIATHAN</td>
<td>le-vi’a-than</td>
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<td>RADIX</td>
<td>ra-diks</td>
<td>BEATIFY</td>
<td>bi-at’i-fi</td>
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<td>sing’ka-pe</td>
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<td>list</td>
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<td>la’bil</td>
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<td>gowi</td>
<td>CAMPANILE</td>
<td>kam-pan-e’la</td>
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256
<table>
<thead>
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<th>TIME</th>
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<tbody>
<tr>
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### Chronic Ill Health Definitions

**Hepatic**: Biopsy proven cirrhosis, portal hypertension, previous hepatic failure.

**Cardiovascular**: NYHA Class IV.

**Respiratory**: Chronic hypoxia, hypercapnia, severe exercise limitation, \(2^\circ\) polycythaemia, pulmonary HT.

**Renal**: Chronic dialysis.

**Immunocompromised**: Disease or drugs.

### Notes

- **Temp**: Use core temperature where possible.
- **HR**: Use ventricular rate.
- **PaO2**: If FiO2 < 0.5 use admission and worst PaO2 data. If FiO2 > 0.5 use admission and widest AaDO2 data which can be approximated by lowest PaO2/FiO2 ratio. Use pH and PaCO2 data from the same set of arterial blood gases.
- **HCO3**: Use bicarbonate if no arterial gases available.
- **Acute renal failure**: Defined as creatinine > 128 and urine output < 400ml/24 hours or persistently < 17 ml/hr for an adult not on dialysis.
- **Add APACHE II score for creatinine if acute renal failure present**.

### Table

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Add APACHE II score for creatinine if acute renal failure present.

### CHP

- Chronic health points (Add 2 for elective postoperative patients)

### Ages

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**Temp**: Use core temperature where possible.

**MAP**: Use ventricular rate.

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**HCO3**: Use bicarbonate if no arterial gases available.

**Acute renal failure**: Defined as creatinine > 128 and urine output < 400ml/24 hours or persistently < 17 ml/hr for an adult not on dialysis.


Neuroprotection of the Brain During Cardiopulmonary Bypass
A Randomized Trial of Remacemide During Coronary Artery Bypass in 171 Patients

J.E. Arrowsmith, MRCP(UK), FRCA; M.J.G. Harrison, DM, FRCP; S.P. Newman, DPhil, Dip Psych; J. Stygall, BSc, MSc; N. Timberlake, BA, BSc; W.B. Pugsley, FRCS(Ed)

Background and Purpose—Neuropsychological impairment may follow coronary artery bypass surgery as a result of peroperative cerebral microembolism. The hypothesis that remacemide, an NMDA receptor antagonist, would provide protection against such ischemic damage has been tested in a randomized trial.

Methods—One hundred seventy-one patients undergoing coronary artery bypass surgery by a single cardiothoracic surgical team were randomized to receive remacemide (up to 150 mg every 6 hours) or placebo from 4 days before to 5 days after their bypass procedure. Peroperative monitoring included an estimate of the number of microembolic events detected by transcranial Doppler ultrasonography of the middle cerebral artery. A battery of 9 neuropsychological tests was administered before and 8 weeks after surgery.

Results—The proportion of patients showing a decline in performance of 1 SD or more in 2 or more tests was reduced in the treated group (9% versus 12%), but this was not statistically significant. On the other hand, overall postoperative change (reflecting learning ability in addition to reduced deficits) was more favorable in the remacemide group, which demonstrated significantly greater improvement in a global z score ($P=0.028$) and changes in 3 individual tests ($P<0.05$). The 2 patient groups were well matched, including for the burden of microembolic events.

Conclusions—This is the first study to show statistically significant drug-based neuroprotection during cardiac surgery. In addition to offering improvement in cerebral outcome for such at-risk patients, it supports the hypothesis that drugs acting on the excitotoxic mechanism of ischemic cerebral damage can be effective in humans. (Stroke. 1998;29:2357-2362.)

Key Words: bypass surgery ■ neuroprotective agents ■ neuropsychological tests ■ ultrasonography, Doppler

In experimental animal models it is possible to investigate the mechanism of cell loss due to cerebral ischemia and devise strategies of neuroprotection.1 Most fruitful to date, at least in the animal models, has been the hypothesis that maturation of infarction involves the release of excessive amounts of glutamate with an increase in intracellular calcium levels via NMDA and AMPA receptor–mediated channels. In the cat, NMDA receptor antagonists reduce the volume of infarction produced by middle cerebral artery occlusion by 50%.2 The treatment effect is greatest if the drug is administered before ischemia is induced.

Very large clinical trials are needed to investigate whether such success is mirrored in stroke patients, principally because of the heterogeneity of both the pathology and natural history of stroke cases. It is therefore useful to seek other clinical situations in which cerebral ischemia has predictable consequences and perhaps in which the ideal circumstance of pretreatment is possible. For some years we4 and others5 have been investigating the evidence that cerebral ischemia occurs during cardiopulmonary bypass surgery (CPB), occasionally owing to hemodynamic crises but usually to microembolism. The deleterious change in performance of a battery of cognitive tests detected postoperatively proved to be related to the number of microembolic events recorded peroperatively by transcranial Doppler ultrasonography and to be reduced by strategies to prevent such events by the addition of extra arterial line filters6 or by the replacement of bubble by membrane oxygenators.7 We therefore piloted this "model" in 1991 and in 1992 planned a prospective, double-blind, randomized trial of an NMDA receptor antagonist.

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From the Departments of Anaesthesiology (J.E.A.), Neurology (M.J.G.H.), Psychiatry and Behavioural Sciences (S.P.N., J.S., N.T.), and Cardiothoracic Surgery (W.B.P.), University College London Hospital and Medical School, London, UK.


Correspondence to Prof M.J.G. Harrison, The Middlesex Hospital, Mortimer St, London W1N 8AA, UK.

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Stroke is available at http://www.strokeaha.org

2357
Remacemide [(±)-2-amino-N-(methyl-1,2-diphenylethyl)acetamide] hydrochloride was part of a screening program for novel antiepileptic drugs. It was chosen for clinical trial because it had been found to inhibit convulsions induced by NMDA and reduce cerebral damage in animal models of focal ischemia, properties shared with dizocilpine (MK-801). Its modest NMDA antagonism is apparently due to an active desglycinated metabolite. Maximal neuroprotection occurred in the animal studies when the drug was administered before the onset of cerebral ischemia.

We planned to test remacemide in a consecutive series of 180 patients undergoing coronary artery bypass surgery (CABS), using repeated cognitive assessments as the end point indicative of the effects of ischemia. We hypothesized that neuroprotection would be revealed by a reduction in the number of patients achieving a predefined threshold of impairment. As an ancillary end point, we hypothesized that a neuroprotectant would be associated with an overall net improvement (or arguably, more favorable net change) in scores, reflecting relative preservation of learning ability and relative reduction of deficits in the group receiving the active drug. This strategy has been developed independently by Jonas et al and has recently been set out in some detail.

Subjects and Methods

We considered all patients (except females with childbearing potential) aged between 18 and 75 years who were referred to a single cardiothoracic surgical team for elective, primary coronary revascularization. Patients were excluded from the study for the following reasons: (1) a history of neurological (including previous transient ischemic attacks, stroke, seizures, and "blackouts"), psychiatric, gastrointestinal (specifically, peptic ulceration and hemorrhage), hepatic, renal, or hematological disorder; (2) evidence within the previous 2 years of drug abuse (prescribed or nonprescribed) or alcohol abuse (>14 U/wk for women and >21 U/wk for men, with temperature correction) was used throughout.

The cross-clamp fibrillation technique for myocardial protection was used in all cases. Distal coronary anastomoses were fashioned with the proximal aorta cross-clamped and the heart in electrically induced fibrillation. Proximal (aortosaphenous) anastomoses were made with the aorta unclamped and the heart beating.

All patients were routinely reviewed in the Cardiothoracic Surgery Outpatient Clinic 8 weeks after surgery. This time was selected as being sufficiently distant from surgery to produce stable results unconfounded by acute aspects of surgery and anesthesia. In addition to a physical examination and routine investigations, patients underwent a further neuropsychological evaluation, and the results of this assessment form the end point for the study. Retesting in the first few days after surgery reveals a higher prevalence of disturbance, but this is a period when some patients are still on narcotic medication for pain and may have other metabolic disturbance, and the results are difficult to interpret. Those at 2 months are stable and compare well with those at 1 year.

End-Point Assessment

Patients underwent a battery of neuropsychological tests before surgery (before commencing study medication) and 8 weeks after surgery. The Vocabulary and Picture Completion subtests of the Wechsler Adult Intelligence Scale—Revised, the National Adult Reading Test, and the Spielberger Trait Anxiety Inventory were only administered preoperatively; all other tests (Table 1) were administered at each neuropsychological evaluation. The individual tests were chosen because of our previous experience with their sensitivity and their acceptance in the literature, including the results of consensus neuropsychological conferences. Where available, parallel forms were administered to limit the effects of learning between the 2 time points, although it was expected that some learning would occur. Indeed, as stated, it was hypothesized that learning would be more obvious in the presence of a neuroprotectant drug and blunted or absent due to peroperative ischemia in its absence.

Deficit

The definition of neuropsychological deficits in the field of cardiac surgery has been the subject of much discussion. We have previously published a conventional definition and have applied it in this study. A standard deviation (SD) unit for each test is computed from all the preoperative scores. A deficit is a spectral test when a patient’s postoperative score has dropped by ≥1 SD from their
Before randomization, 29 patients were excluded on the basis of consecutive series over a 2-year period from 1992 to 1994. Two hundred consenting patients were randomized from a total of patients in the study. From these standard scores a difference score was calculated for each subject by subtracting the postoperative standard score from the preoperative standard score to reflect the directional data were reversed so that all scores using the SD of the preoperative group performance of all subjects on active treatment had a fatal stroke, and another died of a gastrointestinal hemorrhage. Neither death was considered attributable to either remacemide or study participation. One patient in the placebo group suffered a fatal myocardial infarction. The most common reported side effects are shown in Table 3, with an excess of dizziness, drowsiness, and ataxia attributable to remacemide.

Biochemical, hematologic, and clotting screen data both before and after surgery showed no differences attributable to the use of remacemide. Perioperative nasopharyngeal temperatures and pump flow rates and perioperative and postoperative blood pressures and pulse rates showed no differences between groups. The ECG monitoring revealed that most patients remained in sinus rhythm, again with no difference between groups.

Twelve patients were lost to study follow-up before the 8-week assessment because of death or adverse event (4 in each group), delay in surgery that interrupted medication (1 in each group), and refusal to participate in the assessment (1 in placebo). There were 3 deaths. One patient on active treatment had a fatal stroke, and another died of a gastrointestinal hemorrhage. Neither death was considered attributable to either remacemide or study participation. One patient in the placebo group suffered a fatal myocardial infarction. The most common reported side effects are shown in Table 3, with an excess of dizziness, drowsiness, and ataxia attributable to remacemide.

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**Results**

Two hundred consenting patients were randomized from a consecutive series over a 2-year period from 1992 to 1994. Before randomization, 29 patients were excluded on the basis of abnormal laboratory baseline values, withdrawal of consent, the discovery of a history of disallowed medication or gastrointestinal disorder, or delay or difficulty in completing preoperative assessments. The remaining 171 patients were operated on according to protocol, with 87 receiving remacemide and 84 placebo. The groups were well matched in terms of age, height, weight, duration of CPB, and duration of surgery (Table 2).

Twelve patients were lost to study follow-up before the 8-week assessment because of death or adverse event (4 in each group), delay in surgery that interrupted medication (1 in the active group, 2 in placebo), and refusal to participate in the assessment (1 in placebo). There were 3 deaths. One patient on active treatment had a fatal stroke, and another died of a gastrointestinal hemorrhage. Neither death was considered attributable to either remacemide or study participation. One patient in the placebo group suffered a fatal myocardial infarction. The most common reported side effects are shown in Table 3, with an excess of dizziness, drowsiness, and ataxia attributable to remacemide.

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**TABLE 1. Neuropsychological Tests Administered Preoperatively and Postoperatively**

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<tr>
<td>WAS Vocabulary Subtest</td>
<td>Preoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAS Picture Completion Subtest</td>
<td>Preoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Adult Reading Test</td>
<td>Preoperative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WAS indicates Wechsler Adult Intelligence Scale.

TABLE 2. Baseline Patient Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Remacemide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (M/F)</td>
<td>87 (78/9)</td>
<td>84 (72/12)</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.5±0.9</td>
<td>59.4±0.9</td>
</tr>
<tr>
<td></td>
<td>[35-74]</td>
<td>[36-74]</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171.9±0.9</td>
<td>171.3±0.9</td>
</tr>
<tr>
<td></td>
<td>[150-188]</td>
<td>[155-189]</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.2±1.5</td>
<td>79.8±1.4</td>
</tr>
<tr>
<td></td>
<td>[54.1-127.2]</td>
<td>[51.9-109.8]</td>
</tr>
<tr>
<td>Surgery time, min</td>
<td>193±5 (n=84)</td>
<td>191±5 (n=79) *</td>
</tr>
<tr>
<td></td>
<td>[83-223]</td>
<td>[83-354]</td>
</tr>
<tr>
<td>Bypass time, min</td>
<td>81±3 (n=84)</td>
<td>80±3 (n=79) *</td>
</tr>
<tr>
<td></td>
<td>[25-184]</td>
<td>[21-174]</td>
</tr>
</tbody>
</table>

Data are mean±SEM, with ranges in brackets. Data incomplete in *5 cases and Y3 cases.

**TABLE 3. Side Effects During Treatment**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Remacemide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Ataxia</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>
TABLE 4. MEANS, SDs, and t-Tests of the Raw Preoperative Test Scores

<table>
<thead>
<tr>
<th>Test</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>t</th>
<th>P (2-Tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block Design</td>
<td>9.27 (2.46)</td>
<td>9.47 (2.83)</td>
<td>-0.50</td>
<td>0.617</td>
</tr>
<tr>
<td>Choice Reaction</td>
<td>0.62 (0.22)</td>
<td>0.61 (0.14)</td>
<td>0.92</td>
<td>0.360</td>
</tr>
<tr>
<td>Displaced Reaction</td>
<td>0.86 (0.35)</td>
<td>0.86 (0.35)</td>
<td>0.02</td>
<td>0.986</td>
</tr>
<tr>
<td>Letter Cancellation</td>
<td>93.73 (18.93)</td>
<td>96.83 (25.91)</td>
<td>-0.87</td>
<td>0.386</td>
</tr>
<tr>
<td>Nonverbal Memory</td>
<td>332.61 (39.39)</td>
<td>332.18 (26.20)</td>
<td>0.08</td>
<td>0.935</td>
</tr>
<tr>
<td>Rey</td>
<td>54.94 (13.01)</td>
<td>56.27 (11.54)</td>
<td>-0.68</td>
<td>0.495</td>
</tr>
<tr>
<td>Symbol Digit</td>
<td>177.55 (43.82)</td>
<td>177.71 (64.81)</td>
<td>-0.02</td>
<td>0.984</td>
</tr>
<tr>
<td>Tapping</td>
<td>60.00 (11.85)</td>
<td>62.09 (10.13)</td>
<td>-1.19</td>
<td>0.235</td>
</tr>
<tr>
<td>Trails A</td>
<td>40.57 (13.39)</td>
<td>39.83 (14.12)</td>
<td>0.34</td>
<td>0.736</td>
</tr>
<tr>
<td>Trails B</td>
<td>91.42 (35.45)</td>
<td>88.87 (36.96)</td>
<td>0.45</td>
<td>0.656</td>
</tr>
<tr>
<td>New Adult Reading Test</td>
<td>29.72 (9.68)</td>
<td>30.94 (10.02)</td>
<td>-0.62</td>
<td>0.535</td>
</tr>
<tr>
<td>WAS Vocabulary Subtest</td>
<td>47.38 (12.45)</td>
<td>49.65 (12.23)</td>
<td>-1.19</td>
<td>0.234</td>
</tr>
<tr>
<td>WAS Picture Completion Subtest</td>
<td>16.33 (2.67)</td>
<td>16.17 (2.83)</td>
<td>0.08</td>
<td>0.938</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>7.34 (5.15)</td>
<td>7.51 (5.14)</td>
<td>-0.21</td>
<td>0.833</td>
</tr>
<tr>
<td>Spielberger Trait Anxiety Inventory</td>
<td>38.00 (9.59)</td>
<td>38.61 (8.39)</td>
<td>-0.44</td>
<td>0.660</td>
</tr>
<tr>
<td>Spielberger State Anxiety Inventory</td>
<td>36.52 (10.59)</td>
<td>38.33 (9.94)</td>
<td>-1.20</td>
<td>0.233</td>
</tr>
</tbody>
</table>

Values in parentheses are SDs.

*This score was calculated with the Choice Reaction Time Test performance included. When analyzed with this test excluded, the difference between the 2 groups remained significant (P<0.036).
conventional definition of deficit outlined above, 7 patients in
the remacemide group (9%) and 9 in the placebo group (12%)
had deficits on 2 or more tests at follow-up, a 33% but
nonsignificant reduction (Fisher's exact test, \(P=0.6\)).

The results of comparisons of the difference in \(\pm\) score
performance of the 2 groups indicated that all but 2 of the
tests showed more favorable mean change in the remacemide
group. Where appropriate, transformed scores were used in
the analysis.

The remacemide group (Table 5) showed significantly
greater improvement in performance on the composite mea-
sure of neuropsychological performance (total \(z\) score;
\(P=0.028\)). Further analysis of the individual subtests indi-
cated that in 3 of the neuropsychological tests the remace-
mide group showed significantly superior performance over
the control group (Table 5). In these cases the results suggest
both a better preservation of learning and fewer or less-severe
deficits in the remacemide group.

Discussion
The number of patients showing a neuropsychological deficit
in this study was very low and below that estimated for the
purposes of calculating sample size. The reasons for this
change may lie in the continued improvements in surgical
techniques surrounding such issues as minimal manipulation
of the aorta and complete de-airing of the ventricle. There
were no obvious nonsurgical factors that may have accounted
for this low incidence. Although a greater proportion of
patients with deficits was found in the control group (12% versus 9%), this difference was not significant. This method
of handling the data is, however, considered to be insensitive,
because it applies a conventional but arbitrary cut-off and
ignores any improvements in performance.\(^1\)

We have argued elsewhere\(^2\) that studies of interventions in
cardiac surgery designed to improve outcome that include 2
or more patient groups should use all the data by comparing
the change in performance between the 2 groups. This not
only enables an examination to be made of each of the tests,
as some may be more sensitive to change than others, but,
crucially, also allows the potential effects of learning to be
considered. Although the number of subjects recruited was
for a binary analysis, it would be expected to be adequate for
an analysis that uses all the data.

As a planned ancillary analysis in this study, therefore, we
analyzed the change scores once they had been standardized
to the preoperative SD. This technique enables the overall test
performance to be calculated from the cumulative change
scores. The findings indicated that the overall change in
neuropsychological performance from before to after surgery
was superior in the remacemide group. Significantly greater
improvement was found in 3 of the 9 neuropsychological
tests. In these cases the results suggest both a better preser-
vation of learning and fewer or less-severe deficits in the
remacemide group.

Improvements with repetition in neuropsychological tests are
frequently reported as constituting an unwanted phenomen-
on, and tests are either designed to prevent this phenomena
from occurring\(^3\) or corrections are made to account for such
practice effects.\(^4\) In other contexts,\(^5\) the ability to learn or
demonstrate so-called practice effects has been considered a
reflection of improved capacity in individuals impaired in
such ability before intervention. In the context of this study,
postoperative (postinsult) learning, as indirectly adduced
from the \(z\) score changes after preoperative (preinsult)
priming, was greater in patients who received the neuroprotective
agent. Learning is a sensitive measure of cognition, and the
increased capacity for learning in the remacemide group may
therefore be considered a reflection of the protection ac-
corded the nervous system by this agent during bypass. The
anticipated improvement in scores due to learning is thus
interrupted and blunted by the ischemic insult but preserved
by an effective neuroprotectant.

The plasma levels achieved during this study are very similar
to those seen with antiepileptic use of remacemide but lower
than those found during intravenous infusion in animal models
of neuroprotection, which may therefore have limited efficacy.

Consequently, we believe this to be the first report of
statistically significant pharmacological neuroprotection in
this clinical context. Grieco et al\(^6\) recently reported a pilot
study using GM1 ganglioside in 18 patients undergoing
bypass surgery, with 11 patients on placebo. No statistically
significant differences were detectable, and a sample size of
150 was estimated to be needed to confirm or reject a
nonstatistically significant treatment benefit. They, too, fa-
vored a strategy of calculating change scores for all tests to
incorporate both potential improvement in performance
through preservation of learning as well as potential deterio-
rations in performance as a result of the procedure. The
approach reported here and that of Grieco et al\(^6\) differed in
their calculation of change scores, although both expressed
change scores on the basis of preoperative SDs.

To date, only preliminary reports of studies of neuropro-
tective agents in acute stroke have appeared, although many
are ongoing. The excitotoxic hypothesis of neuronal damage
in cerebral ischemia is supported by our data and the trends in
some of these stroke studies. For example, post hoc analysis
of patients under the age of 70, with only mild or moderate
strokes and treated with lubeluzole, shows a benefit in both
mortality and the chances of attaining independence as
judged by a Barthel Index score.\(^8\) Lubeluzole inhibits gu-
tamine rise and glutamine-stimulated rises in cyclic
guanosine monophosphate- and nitric oxide-related neuro-
toxicity.\(^9\) As suggested in the introduction and supported by
the results of this study, the circumstances of CPB appear to
offer a practical test bed for putative neuroprotective agents.
The pathophysiology of massive focal infarction in an em-
bulic stroke and the more diffuse microembolic damage
combined with disordered blood flow during CABS are
clearly different, so it could not be assumed that efficacy in
one context was transferable to the other without a trial in
stroke patients.

Finally, the effect of remacemide in this context highlights
the possibility of further reducing the morbidity of CABS.
The side-effect profile suggested some central nervous sys-
tem influences, but these were minor and transient and were
never a reason for stopping trial medication. There was no
evidence that remacemide had adverse effects on the surgical
procedure. The use of membrane rather than bubble oxygen-
Neuroprotection During Cardiopulmonary Bypass

ators and other changes in surgical anesthetic and perfusion practice, including the choice of filters, has already been associated with a decline in the incidence of neuropsychological sequelae. This study suggests neuroprotective drugs that operate through the excitotoxic pathway may further protect patients undergoing this common procedure.

Acknowledgments

We are pleased to record our gratitude to Fisons UK Ltd for funding the study and providing supplies of remacemide, and to Drs John Hutchison, Frances Willetts, and David Hodder of that company for their help. Dr Arrowsmith held a Lord Amulree traveling studentship grant from University College London during the course of the study. The database was kept by the investigators, who were also responsible for the computations and statistics reported here. We would also like to thank Tan Shah, the study coordinator.

References

Neurologic Risk Assessment, Monitoring, and Outcome in Cardiac Surgery

Joseph E. Arrowsmith, MBBS, MRCP (UK), FRCA, Hilary R. Grocott, MD, FRCPC, and Mark F. Newman, MD

NEUROLOGIC INJURY after cardiac surgery encompasses a wide spectrum of clinical entities ranging from the rare, fatal cerebral catastrophe to considerably more common psychiatric, neuropyschologic, and behavioral changes. A major neurologic complication after otherwise successful surgery represents a devastating outcome for both the patient and the immediate family. The social and economic impact of unemployment and the requirement for long-term rehabilitation or institutional care are significant. Despite steady increases in average patient age as well as the prevalence and severity of other risk factors thought to contribute to adverse neurologic outcome in the cardiac surgical population, the incidence of these complications has fallen.

Because most patients undergoing cardiac surgery in the 1990s can reasonably expect to survive without significant long-term neurologic impairment, justifying the indiscriminate use of putative pharmacologic neuroprotectants or recommending the universal adoption of novel neuroprotective strategies that may significantly increase operating room time and cost is difficult. A more effective strategy is to reserve specific preventive or therapeutic interventions for patients who are at the greatest risk for neurologic or neuropsychologic dysfunction. Alternatively, minimally invasive or noninvasive monitors of cerebral function could be used in high-risk patients to detect intraoperative cerebral dysfunction and allow early deployment of potentially beneficial interventions. The purpose of this review is to assist in determining which patients are at increased risk for perioperative neurologic or neuropsychologic injury, thus improving the opportunity for intervention or the appropriate use of advanced neurologic monitoring techniques.

IDENTIFYING RISK FACTORS FOR ADVERSE NEUROLOGIC OUTCOME

Considerable effort has been expended in determining which factors can be used to help assess overall surgical risk and identify patients at high risk for significant perioperative neurologic injury. In defining these predictors, the most frequently reported measures of adverse neurologic outcome after cardiac surgery are stroke and neuropsychologic (or cognitive) dysfunction. Although similar, the risk factors for stroke are not exactly the same as those for cognitive dysfunction.

The low incidence of perioperative stroke dictates that investigators seeking to identify risk factors or measure the efficacy of interventions require large study populations to be adequately powered to identify differences. Neuropsychologic dysfunction, with an incidence at least one order of magnitude greater than stroke, offers the potential advantage of investigation with a smaller, more manageable sample size. Cognitive function testing is, however, time-consuming, with less widespread agreement on which tests should be used, when they should be administered, and how they should be interpreted. Furthermore, low compliance with follow-up assessments has confounded a number of investigations.

Risk Factors for Neuropsychologic Dysfunction

Investigations of the risk factors for perioperative central nervous system dysfunction have delineated that the risk factors for stroke are similar in some regards but not the same as those for nonfocal encephalopathy and neuropsychologic morbidity. The factors thought to contribute to neuropsychologic morbidity include patient age and gender, cerebrovascular disease, diabetes mellitus, cerebral microembolism, duration of cardiopulmonary bypass (CPB), temperature, and acid-base management. The relationship between risk and neuropsychologic outcome has been the most broadly studied with age.

Age. As with stroke, age represents one of the primary risk factors for perioperative neuropsychologic dysfunction. Although the elderly are at increased risk for relative decreases, they also tend to begin at a lower level of cognitive functioning, which together result in postoperative functional levels that may significantly impinge on their autonomy. Although the increased susceptibility to stroke with aging appears to be directly
associated with the degree of aortic atherosclerosis, the association between aortic atherosclerosis and encephalopathy or subtle neurophysiologic changes is notably absent, leaving the mechanism of aging-related cognitive decline in question and likely multifactorial.2

Genetic predisposition. Researchers have discovered a genetic association between late-onset Alzheimer’s disease and the apolipoprotein E (APOE, gene; apoE, protein) ε4 gene. This finding has triggered further studies demonstrating an important role for apoE in the determination of neurologic injury and recovery after a variety of acute ischemic insults, including intracerebral hemorrhage,9 closed head injury,10,11 acute stroke,12 and dementia pugilistica.13 Most important to the current discussion is a report documenting preliminary evidence of an association of APOE4 with neurocognitive decline after cardiac surgery.14 The hypothesis is that the biochemical products coded by this gene are not available to protect and repair the neurons of the central nervous system during cardiac surgery, resulting in deficits of memory, attention, and concentration. This hypothesis is supported by several studies in cerebral ischemia models. For example, genetically engineered mice lacking normal apoE3 had poorer functional recovery and increased infarct size after both focal and global ischemia.15,16 Potential mechanisms for the association of apoE4 with acute neurologic injury include modulation of the inflammatory response. ApoE in vivo modulates the release of nitric oxide and tumor necrosis factor (TNF)-α.17,18 This activity may compound the autonomic dysregulation that was reported in the elderly. Preliminary data associating APOE4 with cognitive impairment after cardiac surgery support this hypothesis. The different potential mechanisms of apoE function in neuronal injury and recovery are not mutually exclusive, and it is likely that apoE modulates the central nervous system injury response at several functional levels.

Cerebral embolization. Both gaseous and particulate emboli have long been implicated in the etiology of neurophysiologic dysfunction after cardiac surgery. Histologic,19 ophthalmologic,20 and ultrasonographic21,22 studies suggest that cerebral microembolization occurs in all patients subjected to CPB. A correlation between intraoperative cerebral microembolic load and postoperative neurophysiologic dysfunction has been demonstrated.24,25 It is not clear, however, which types of microemboli are most injurious to the brain. Current technology does not permit the accurate identification or differentiation of cerebral microemboli in real time.

Ophthalmologic26 and ultrasound27 studies suggest that membrane oxygenators generate fewer microemboli than bubble oxygenators. The use of arterial line filters has been shown both to reduce cerebral microembolic load22 and to improve neurophysiologic outcome.24 The observation, in an animal study, that the use of cardiotoxic suction was associated with increased cerebral microembolization suggests that blood aspirated from the surgical field is a major source of microemboli.28

The use of biologically compatible materials, such as heparin-bonded or prostaglandin-bonded plastics, in extracorporeal circuits offers a number of potential advantages, including reduced contact activation,29-31 reduced platelet deposition,32 reduced formation of thromboemboli,33 and decreased systemic anticoagulation requirements.34,35 In a prospective, randomized study of 234 patients undergoing primary coronary revascularization, a heparin-bonded circuit in conjunction with a low-dose heparin regimen (to achieve an activated clotting time [ACT] of >280 seconds) was compared with a non-heparin-bonded circuit and full heparinization (ACT > 480 seconds). The use of a heparin-bonded circuit was found to be safe and effective, resulting in significant reductions in homologous transfusion, duration of ventilation, duration of intensive care, postoperative complications, and hospital stay.34 A later study by the same group concluded that the choice of heparinization regimen (ACT > 250 v ACT > 480) used with a heparin-bonded circuit had no significant influence on neurologic outcome. Cerebral microemboli (detected by transcranial Doppler) and adverse neurologic and neuropsychologic outcomes were similar in both groups.35

Perfusion pressure and flow. During CPB, cerebral blood flow (CBF) is determined by the complex interaction of factors such as mean arterial pressure (MAP), pump flow rate, cerebral metabolic rate, blood gas management strategy, and hematocrit. Prolonged periods of profound arterial hypotension and cerebral hypoperfusion during CPB eventually lead to cerebral injury. Which factor is most important—pressure or flow?

In the presence of a constant arterial carbon dioxide content, CBF during CPB is said to remain virtually constant over a wide range of arterial pressures. In reality, MAP, in the range 50 to 75 mmHg, does appear to have a small but consistent effect on CBF during both hypothermic and normothermic CPB.3,36 The observed relationship between jugular venous oxygen saturation and cerebral perfusion pressure during constant flow hypothermic CPB appears to support this finding.37

The common practice of maintaining a perfusion pressure of approximately 50 mmHg during hypothermic CPB appears to be based not on any objective evidence, but rather on the fact that most patients appear to tolerate a degree of intentional hypotension that would not be permitted during noncardiac surgery.38,39 To address the issue of perfusion pressure, Gold et al40 prospectively studied outcome in 248 cardiac surgical patients randomly assigned to either lower (50 to 60 mmHg) or higher (80 to 100 mmHg) pressure perfusion. There were no statistically significant differences in the incidence of cardiac, neurologic, or neurocognitive complications 6 months after surgery. The overall incidence of combined cardiac and neurologic complications, however, was significantly lower in the high-pressure group (4.8% v 12.9%, p = 0.026). The higher prevalence and severity of aortic atheromatous disease in patients in the low-pressure group may account for the observed differences in outcome.41

During hypothermic CPB, it is customary to calculate systemic or arterial flow rate using temperature and body surface area and to make adjustments based on blood gas analysis. Does pump flow, in the clinical range (ie, 1.6 to 2.4 L/min/m²), during CPB have any influence on CBF? A number of early studies reached different conclusions.42-44 Evidence from a baboon model of hypothermic CPB suggests that CBF is governed solely by arterial pressure and that, at constant MAP, changes in pump flow have no influence on CBF.44 A clinical study comparing the influence of standard pump flow rates with high flow rates on neurologic or neuropsychologic outcome has not been attempted.
Temperature. In many centers, hypothermia remains the
mainstay of organ protection during CPB. With decreasing
temperature, the tight coupling between cerebral metabolic rate
and CBF is gradually lost such that CBF exceeds metabolic
requirements. Despite its advantages and continued popularity,
hypothermia is not entirely benign. Disadvantages include
clinically significant coagulopathy, rare cases of acute pancreati-
and the need for rewarming at the end of the surgical
procedure. Rapid or excessive rewarming may have deleterious
effects on many organs, including the brain and spinal cord. The
common practice of monitoring nasopharyngeal temperature
during CPB may significantly underestimate brain temperature
during rewarming.47

The significant deoxygenation of jugular venous blood
observed during rewarming from moderate hypothermia sug-
jects inadequate cerebral oxygen delivery.48 Furthermore, post-
operative neuropsychologic morbidity appears to be a function
of the magnitude of cerebral arteriovenous oxygen difference
during rewarming.49

Widespread interest in so-called warm heart or normothermic
procedures has generated considerable concern about cerebral
protection during CPB and adverse neurologic outcome.50 Early
studies in this area had small but significant methodologic
problems and reached opposing conclusions.51-54 The deliberate
exclusion of elderly and other high-risk patients from these
studies makes it difficult to apply the findings to the cardiac
surgical population as a whole. Two studies suggest that
normothermic techniques do increase neurologic morbidity.

Mors et al50 compared neurologic and neuropsychologic
outcome in 138 patients randomly assigned to receive either
continuous retrograde normothermic blood cardioplegia during
normothermic CPB or intermittent cold crystalloid cardioplegia
during hypothermic CPB. Although there were no significant
differences in neuropsychologic outcome, the seven patients
who developed new focal neurologic deficits all came from the
normothermic group. In the prospective study reported by
Regragui et al,52 the incidence of neuropsychologic deficit was
found to be significantly higher in patients subjected to normo-
thermic CPB than those perfused at 32°C. Perfusion at 28°C had
no additional benefit.

Acid-base management. Maintenance of normocapnia
throughout a cardiac surgical procedure, using alpha-stat blood
gas management, appears to preserve pressure-flow autoregula-
tion of CBF. Inadvertent hyperventilation before the onset of
CPB, the use of pH-stat blood gas management57,58 and
hemodilution during CPB have been shown to worsen neuropsychologic outcome. A number of factors are thought to contribute to the worsened outcome observed in pH-stat–managed patients—failure of autoregula-
tion of CBF at low perfusion pressures, intracranial steal,
cerebral acidosis during rewarming, and increased delivery of
microemboli to the cerebral circulation. The relative importance
of these factors remains unclear.

Hyperglycemia. It has long been known that diabetics have
a worse outcome from stroke. It has emerged more recently that
diabetics are also at increased risk of neurologic morbidity after
cardiac surgery.2 The undoubtedly higher incidence of hypertens-
tion, renal dysfunction, and generalized vascular disease in
these patients almost certainly contributes to their increased
neurologic risk. What is not clear, however, is whether hypergly-
cemia per se plays a major role. The observation that insulin-
dependent diabetics have impaired cerebral autoregulation—
characterized by increased cerebral oxygen extraction—during
CPB59 may explain increased cerebral vulnerability.

The addition of glucose-containing priming solutions to the
extracorporeal circuit remains a contentious issue. Compared
with electrolyte solutions, glucose solutions have been shown to
be associated with worsened neuropsychologic outcome.6 In
animal models of both focal and global cerebral ischemia,
hyperglycemia worsens neurologic outcome.60,61 Although some
investigators argue that hyperglycemia during cardiac surgery is
undesirable and should therefore be avoided, others suggest that
glucose administration may be beneficial on the grounds that
improved fluid balance is achieved.62,63

Hemodilution. The viscosity of blood, which is chiefly
determined by hematocrit, tends to increase as temperature
falls. For this reason, intentional hemodilution during CPB has
been standard practice since the introduction of hypothermia. A
hematocrit of 20% is widely considered an acceptable level of
hemodilution during moderately hypothermic CPB. In the
absence of objective supportive evidence, this practice is likely
based on the assumption that reduced oxygen carrying capabil-
ity is more than compensated for by the hypothermia-induced
reduction in metabolic rate and more favorable rheology. There
is, however, a possibility that low hematocrit during CPB might
 predispose or contribute to neurologic dysfunction.64

During the last 2 decades, a trend toward a greater degree of
hemodilution during CPB appears to coincide with growing
concern about both the availability and the safety of donor
blood supplies. Although hemodilution to a hematocrit of less
than 17% has been reported to be acceptable by a number of
groups, the safety of this practice in elderly and high-risk
patients has been questioned.65 The persistence of a low
hematocrit during rewarming could, at least in theory, expose
the brain to a greater risk of hypoxic injury. Animal evidence
suggests that during CPB there is a temperature-dependent
critical hematocrit, below which brain oxygenation and oxygen
use are decreased.66 Critical hematocrit values for humans
during hypothermic CPB have not been determined.

Risk Factors for Stroke

Previous studies attempting to predict stroke from perioper-
ative variables have been limited by several important factors:
(1) Patient sample size often is inadequate; (2) both intraopera-
tive and postoperative variables are often used, making stroke
prediction based solely on preoperative predictor variables
difficult or impossible; (3) the variables collected and examined
are not consistent across studies; and (4) conclusions often are
based on results from one center, with potential bias introduced
by the practice of a single surgeon, surgical group, or institution.
Accordingly, the investigators of the Multicenter Study of
Preoperative Ischemia (McSP) attempted to minimize the
difficulty in assessing preoperative risk of stroke from the data
of single institutions’ perioperative data by developing a
preoperative stroke risk index based on a prospective, random-
ized, multicenter population for patients undergoing coronary
ey artery bypass graft (CABG) surgery.67

To determine preoperative factors predictive of major periop-
ervative neurologic events in patients undergoing CABG surgery,
the McSPI group accomplished a prospective, multicenter, observational study, enrolling 2,417 patients at 24 academic medical centers in the United States. Patients who died intraoperatively or had concomitant cardiac procedures were excluded from analysis, resulting in a total of 2,107 for analysis. Sixty-eight patients (3.2%) developed major adverse neurologic events, defined as cerebrovascular accident, transient ischemic attack, or persistent coma. Key predictor variables were age, history of previous neurologic disease, diabetes, history of vascular disease, previous coronary artery surgery, unstable angina, and history of pulmonary disease, the coefficients for which were used to develop a preoperative stroke risk index that was validated (c-index = 0.778). Stroke risk could then be determined for each patient, calculating a patient’s risk for stroke within 95% confidence limits. Table 1 describes the stroke index calculation, allowing the clinician to predict probable risk of major neurologic outcome preoperatively for an individual patient using Fig 1.

Advancing age, vascular disease, and diabetes predict atherosclerotic disease of the aorta and cerebral vessels, implicating embolization as the likely primary cause of major neurologic deficits after CABG surgery. These data suggest either that the severity of coronary atherosclerosis predicts the severity of atherosclerosis of the aorta and cerebral vasculature or that the increased manipulation of the heart and great vessels required for the greater number of required grafts in patients with extensive coronary disease increases the risk of major central nervous system injury. Prior CABG surgery was also associated with greater risk of stroke in this population. Although repeat CABG surgery consistently produces greater overall morbidity and mortality, its association with an increased risk of stroke is variable.

Proximal aortic atheroma. In addition to the value of preoperative risk stratification, a number of investigators have demonstrated a correlation between severe atheromatous disease of the proximal aorta and postoperative death or stroke. The presence of atheroma is also associated with significantly prolonged hospitalization and greater cerebral microemboli load. Although assessment of the aorta by transesophageal echocardiography is superior to direct surgical palpation, comparisons between transesophageal echocardiography and epiaortic ultrasound conclusively show that both the presence and the severity of aortic atheromatous disease are underestimated by transesophageal echocardiography. A number of centers are currently investigating the efficacy of alterations in surgical technique based on ultrasonic evaluation of the aorta. Such alterations range from choice of an alternate cannulation site and avoidance of aortic cross-clamping to replacement of the ascending aorta under deep hypothermic cardiac arrest. Whether this approach results in improved neurologic and neuropsychologic outcome has yet to be determined in prospective, randomized trials.

Antifibrinolytic therapy. The routine, prophylactic use of lysine analogs (either e-aminocaproic acid or tranexamic acid) to reduce hemorrhage during and after cardiac surgery appears to be widespread in North America and parts of Europe. Although virtually every study conducted has shown that the serine protease inhibitors (principally aprotinin) reduce both bleeding and blood product requirements during cardiac surgery, their use has been limited by relatively high cost when compared with the lysine analogs and their potential for allergic reactions.

Does the use of an antifibrinolytic agent increase the risk of thrombotic complications and therefore the potential for neurologic morbidity? Thrombotic complications associated with the use of both types of agent have been reported. Although there is little evidence to suggest that the lysine analogs significantly contribute to neurologic complications, early studies using aprotinin conducted in the United States raised concerns about thrombotic complications.

Contrary to expectation, several reports have hinted that exposure to aprotinin may protect organs. Laboratory evidence suggests that aprotinin is protective in both cerebral and myocardial ischemia. Meta-analyses indicate that a reduc-

---

**Table 1. Calculation of the Stroke Risk Index**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(Age - 25) x 10</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>14</td>
</tr>
<tr>
<td>Diabetes mellitus (history of either type I or type II diabetes or insulin use on admission or preoperatively)</td>
<td>17</td>
</tr>
<tr>
<td>History of neurologic disease (previous stroke or transient ischemic attack)</td>
<td>18</td>
</tr>
<tr>
<td>Prior coronary artery bypass surgery</td>
<td>15</td>
</tr>
<tr>
<td>History of vascular disease (peripheral vascular disease, known carotid vascular disease, claudication, or vascular surgery)</td>
<td>18</td>
</tr>
<tr>
<td>History of pulmonary disease (emphysema, chronic bronchitis, asthma, restrictive lung disease)</td>
<td>15</td>
</tr>
</tbody>
</table>

*Points are assigned for age and positive history of the predictors listed.

---

**Fig 1. The relationship between stroke risk index and risk of adverse neurologic outcome.** For example, 100 total points predicts a risk of central nervous system (CNS) injury of 5%. (Adapted with permission from Newman MF, Wolman R, Kanchuger M, et al: Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass (McSPI) Research Group. Circulation 94:874-1180, 1996.)
ion in the observed incidence of perioperative stroke is only statistically significant in patients given high-dose aprotinin.86,87

NEUROLOGIC MONITORING

Despite significant technologic advancement in neurologic monitoring and the obvious increasing awareness of perioperative neurologic complications, neurologic monitoring has not reached the mainstream of cardiac anesthesia or surgical practice. Radiofrequency and other electromagnetic interference make the operating room a "hostile" environment in which to conduct electrophysiologic assessments. Monitoring devices may be difficult to place and maintain, and there is a lack of any reproducible evidence as to which neurologic monitoring device can be used to predict or alter neurologic outcome. An additional problem in neurologic monitoring for cardiac surgery is patient selection. Similar to the predictive powers of preoperative tests or other monitoring devices, the greatest yield and best correlation of true positives occur in patients at significant risk for the observed event. Risk stratification with use of neurologic monitoring in patients at greatest risk for neurologic injury would significantly improve the reliability (and decrease the false-positive rate) of devices when used in patients at low risk for neurologic injury.

Electroencephalography

The gold standard for the detection of central nervous system ischemia has long been electroencephalography. The development of multiple fast Fourier transformation directed processed electroencephalographs held promise for decreased complexity, increased ease of use, and therefore enhanced use. The same electrical difficulties, patient selection difficulties, necessity for technical support (particularly if multiple leads are monitored), and conflicting data on its predictive power, however, have prevented its widespread use.86-90

Transcranial Doppler

Transcranial Doppler represents a noninvasive mechanism to assess CBF velocity and emboli number during CPB nonbypass procedures. Transcranial Doppler monitors blood flow velocity and not absolute CBF, thus limiting its usefulness as a quantifier of the adequacy of cerebral oxygen delivery.81,82 Transcranial Doppler has found increased use because of advances in the use ofport-access surgical procedures or endovascular clamping, allowing assessment of flow from the aorta to the innominate artery and ensuring that the endovascular clamp has not occluded innominate artery flow.83

Despite data showing some correlation between the number of emboli and neuropsychologic outcome, transcranial Doppler remains a somewhat difficult device to place and maintain a signal. The most important role that transcranial Doppler appears to have played is in the detection and quantification of microemboli occurring during CPB.84 The ability to assess different surgical techniques and the number of cerebral emboli associated with these interventions may be an important step forward.25,90,94 Advancement in the technical ability to differentiate particulate and gaseous emboli would serve to substantially improve the ability to predict which patients are likely to suffer major neurologic injury. Advances in automatic localiza-

Juglar Bulb Monitoring

Continuous monitoring of jugular bulb saturation with oximetric devices has yielded markedly variable results in terms of both accuracy and predictive power. The authors' group showed a significant correlation between widening arteriovenous oxygen content difference or decreasing saturation during rewarming and cognitive dysfunction (Fig 2). Data from intermittent samples taken during rapid rewarming. The predictive power and accuracy of continuous monitoring have been much more difficult to assess and have come under significant fire.85 Because the technique is invasive it has, similar to the other monitors, not extended into the mainstream practice of cardiac anesthesia, with it currently being primarily limited to the assessment of closed head injury.96

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) has been promoted as a technique for neurologic monitoring for many years. The technique has been limited by the use of trends from baseline versus absolute values. These trends from baseline are often difficult data from which to make clinical decisions, thus limiting the usefulness of NIRS to clinicians. Use of internal algorithms to assess and determine better regional saturation has enhanced the utility of the devices, but questions remain as to the accuracy or the tissue from which the device is measuring.97 Data evaluating the association between declines in regional saturation during CPB and postoperative cognitive dysfunction have been promising but have not reached statistical significance in small numbers of patients.94 The monitor must be viewed as an indicator of the adequacy of global or
localized regional perfusion because the technique monitors saturation in a small region. Marked ischemia in distant regions could obviously occur with no substantial change in monitored values. If hypoperfusion plays a secondary role after embolization in determining neurologic outcome or a primary role, determination of the adequacy of global or regional perfusion could be of benefit. Additional study is needed to determine the value of NIRS because its ease of use and interpretation make it a monitor that could reach mainstream practice and possibly improve outcome.

Biochemical Markers of Cerebral Injury

The release into the circulation of proteins of neuronal, glial, and endothelial cell origin in response to injury offers, at least in theory, the potential for rapid diagnosis and early intervention with neuroprotective agents. Of the biochemical markers studied, the S100B protein has received the most interest. Although several reports have described an encouraging correlation between perioperative levels of S100B and neurologic outcome, no studies have used intraoperative measures of S100B as an outcome measure. For the time being, the measurement of biochemical markers remains a research tool.

CONCLUSION

The progression of the ability of cardiac surgery to improve overall quality of life with reduced myocardial morbidity has presented the perioperative physician with new challenges of increasing comorbidity and organ dysfunction. Despite these challenges, clinical investigation has led to a better understanding and a gradual improvement in neurologic outcome in the face of advancing risk factors. To capitalize on these gains and reduce neurologic complications of CPB and cardiac surgery, the clinician must first identify those patients at highest risk for developing neurologic complications. Advances in the understanding of patients at risk for neurologic sequelae have occurred through preoperative identification of risk factors as well as through the intraoperative use of monitoring technologies. Although an understanding of the incidence and severity of neuropsychologic sequelae remains somewhat less defined, clinicians are beginning to put together the multifactorial components contributing to this risk. Using this risk information, clinicians should be able to significantly enhance the usefulness of neurologic monitoring. In doing so, the ratio of true-positive to false-positive events should significantly improve when these devices are used on high-risk individuals.

The relatively low incidence of severe neurologic sequelae and the unpredictable nature of neuropsychologic dysfunction have made it difficult to study the usefulness of monitors or cerebroprotective strategies in patients undergoing cardiopulmonary bypass. Based on risk and neurologic monitoring, clinicians can best assess the efficacy of interventions to reduce neurobehavioral sequelae and secondarily apply them cost-effectively in helping to take the final step in unlocking the future of brain protection.

REFERENCES


61. Li PA, Krishan T, Shamloo M, Siesjo BK: Effects of preischemic hyperglycemia on brain damage incurred by rats subjected to 2.5 or 5 minutes of forebrain ischemia. Stroke 27:1593-1602, 1996
63. Metz S: Pre: Glucose priming solution should be used for coronary artery bypass. J Cardiothorac Vas Anesth 9:603-604, 1995
86. Levy JH, Ramsay JG, Murkin J: Aprotinin reduces the incidence of strokes following cardiac surgery. Circulation 94(suppl);I535, 1996
88. Levy WJ: Monitoring of the electroencephalogram during cardiopulmonary bypass: Know when to say when. Anesthesiology 76:876-877, 1992
Central nervous system complications of cardiac surgery†

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While the number of patients undergoing surgery for valvular and other types of heart disease has remained fairly constant, the number undergoing coronary revascularization procedures is increasing (Fig. 1). Because of many technological advances over the past four decades, there has been a steady decrease in the mortality and morbidity associated with these procedures. Nevertheless, neurological injury remains an important cause of postoperative morbidity and is responsible for an increasing proportion of perioperative deaths. Since the introduction of cardiopulmonary bypass (CPB) in the early 1950s, the neurological sequelae of cardiac surgery have been a major concern. Identification of risk factors for adverse neurological and neuropsychological outcomes has led to the development of physical and pharmacological neuroprotective strategies targeted at the 'at risk' population.

Neurological injury after cardiac surgery

Advances in medical care and the introduction of broader indications for surgery has meant that patients previously deemed inoperable are now considered suitable candidates for surgery. Over the past 20 yr, there has been a steady increase in the average age of patients undergoing cardiac surgery. This increase has been accompanied by a rise in both the severity of cardiac disease at the time of surgery and the reoperation rate for recurrent disease. Nevertheless, the likelihood of dying or sustaining a major complication after cardiac surgery in the late 1990s is significantly lower than that in the 1950s. Not unreasonably, most patients expect to survive cardiac surgery intact, make a good functional recovery and live longer. A significant number of patients however suffer a perioperative complication involving the central nervous system (CNS).

Adverse neurological outcome from cardiac surgery is the result of damage to the brain, spinal cord and/or peripheral nerves. CNS injury ranges in severity from subtle changes in personality, behaviour and cognitive function to fatal brain injury—the 'cerebral catastrophe' (Table 1). A major neurological complication after otherwise successful surgery represents a devastating outcome for patient and their family. The social and economic impact is enormous.

Measures of neurological outcome after cardiac surgery

A wide variety of techniques have been used to assess adverse neurological events after cardiac surgery (Table 2) with the incidence of stroke and cognitive dysfunction being the most frequently used outcome measures. Early retrospective studies in this area could only detect what they set out to look for—neurological (e.g. coma, hemiparesis, seizures, blindness) and psychological (e.g. depression, disorientation and confusion)—problems that were sufficiently obvious to be noticed and documented.

The introduction of psychometric testing, typically measures of memory, attention, visuospatial ability and motor speed, broadened the scope and power of investigations. Prospective studies not only demonstrated the value of a multimodal (i.e. neurological and neuropsychological) approach, but highlighted the need for investigators to have the appropriate training and background.

Several difficulties associated with perioperative neurocognitive testing continue to challenge the research community. There is as yet no 'gold standard' against which to compare new tests. In addition, there is neither agreement

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Many confounding factors make it difficult to attempt direct comparisons between studies that have used different methodologies. In an effort to address these problems, a consensus on the use of these tests is beginning to emerge.

**Marketers of neuronal injury**

In addition to neurocognitive testing, proteins released by the injured brain have been used to measure brain injury. After cerebral hypoxia–ischaemia, numerous substances have been shown to be released from neurons, glia, endothelium, platelets and leucocytes (Table 3). Quantification of these substances offers the potential for rapid diagnosis, making possible early interventions aimed at reducing cerebral injury. Furthermore, if the degree of elaboration of a biochemical marker can be shown to correlate with clinical (neurological and cognitive) outcome, large interventional studies could be designed that do not rely on costly and time consuming neurological and neuropsychological testing.

Although a marker of neuronal injury may provide an indication of the severity of a cerebral injury, it cannot provide information on the anatomical distribution and clinical impact of that injury. A small infarct in the internal capsule may be associated with modest release of a marker substance yet produce a disabling hemiplegia, whereas a considerably larger infarct in a frontal lobe, accompanied by massive release of marker, may produce few symptoms or physical signs.

Brain-specific creatine phosphokinase (CPK-BB) was one of the first markers to be evaluated. Marked increases in cerebrospinal fluid (CSF) concentrations were detected in dogs subjected to 60 min of CPB. Incorporation of a 40-μm arterial line filter resulted in significantly lower CSF CPK-BB concentrations compared with those in unfiltered animals. In a clinical study conducted at the Cleveland Clinic, 413 of 421 (98%) patients undergoing coronary artery bypass surgery (CABS) had increased blood concentrations of CPK-BB after surgery. There was, however, no correlation between CPK-BB concentration and the occurrence of encephalopathy or stroke.

The use of CSF adenylate kinase (CSF-AK) as a marker of cerebral injury after cardiac surgery was reported by Åberg and colleagues. A subsequent publication reported a significant correlation between CSF-AK and performance in psychometric tests. Further work characterizing CSF markers has been limited because of the methodological problems of lumbar puncture in patients who have been heparinized for CPB.

The marker that has received the most interest recently is astrogial protein S100β. The numerous functions of...
The Oxford group has also shown that intracardiac surgery (e.g. mitral line filter decreased the number of patients who had abnormal increases in $SIO_{O_{2}P}$ after surgery. The same shown that, compared with controls, the use of an arterial transcranial Doppler sonography. The Oxford group has shown that concentrations of $SIO_{O_{2}P}$ have been shown to correlate with intraoperative cerebral microemboli quantified with CPB showed no increase in $SIO_{O_{2}P}$. Peak postoperative increase in $SIO_{O_{2}P}$ than CABS. Retrospective, focusing on clinical manifestations in the time of discharge, or death caused by stroke or hypoxic coma (which were becoming increasingly uncommon) to neurological outcome; and type II—new deterioration in intellectual function, confusion, agitation, disorientation, memory or aortic valve procedures is associated with a greater postoperative increase in $S100\beta$ than CABS.

**Table 1** Potential biochemical markers of brain injury

<table>
<thead>
<tr>
<th>Source</th>
<th>Marker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glia</td>
<td>$S100\beta$, myelin basic protein (MBP), Glial fibrillary acidic protein (GFAP)</td>
</tr>
<tr>
<td>Neuroaxons</td>
<td>Neurone specific enolase (NSE), adenylate kinase (AK)</td>
</tr>
<tr>
<td>Creatine phosphokinase brain isoforn (CPK-BB)</td>
<td></td>
</tr>
<tr>
<td>Guanine nucleotide binding protein G0, calbindin-D</td>
<td></td>
</tr>
<tr>
<td>Creatine phosphokinase brain isoforn (CPK-BB)</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH), glutamate</td>
<td></td>
</tr>
<tr>
<td>Inflammatory cells</td>
<td>Interleukin-6, transforming growth factor-β</td>
</tr>
<tr>
<td>Adhesion molecules (ICAM-1, E-selectin, neural cell adhesion molecule–NCAM)</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Lactate, Cu-Zn superoxide dismutase (CuZn-SOD)</td>
</tr>
</tbody>
</table>

$S100\beta$ include promotion of axonal growth, glial proliferation, neuronal differentiation and calcium homeostasis. Increased concentrations of $S100\beta$ in both blood and CSF have been found after acute stroke, transient ischaemic attacks, head injury, intracranial haemorrhage and post-cardiac arrest coma, in addition to Alzheimer’s disease and Down’s syndrome. In acute stroke, the degree of $S100\beta$ elevation correlates well with infarct volume and neurological outcome.

Several studies have demonstrated an increase in $S100\beta$ after cardiac surgery. Westaby and colleagues reported a relationship between $S100\beta$ concentrations and age, aortic cross-clamp time and CPB duration. Patients with carotid artery stenosis had higher concentrations of $S100\beta$ than those who did not and patients who had CABS without CPB showed no increase in $S100\beta$. Peak postoperative concentrations of $S100\beta$ have been shown to correlate with intraoperative cerebral microemboli quantified with transcranial Doppler sonography. The Oxford group has shown that, compared with controls, the use of an arterial line filter decreased the number of patients who had abnormal increases in $S100\beta$ after surgery. The same group has also shown that intracardiac surgery (e.g. mitral
Table 4 Adjusted odds ratios (95% confidence intervals) for type I and type II cerebral outcomes associated with selected risk factors from the McSPI and IREF study. IABP = intra-aortic balloon pump; AP = arterial pressure; CABS = coronary artery bypass surgery (reproduced with permission from Roach and colleagues).^125

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Type I outcomes</th>
<th>Type II outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal aortic atherosclerosis</td>
<td>4.52 [2.52-8.09]</td>
<td></td>
</tr>
<tr>
<td>History of neurological disease</td>
<td>3.19 [1.65-6.15]</td>
<td></td>
</tr>
<tr>
<td>Use of IABP</td>
<td>2.60 [1.21-5.58]</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.59 [1.46-4.60]</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>2.31 [1.20-4.47]</td>
<td></td>
</tr>
<tr>
<td>History of pulmonary disease</td>
<td>2.09 [1.14-3.85]</td>
<td>2.37 [1.34-4.18]</td>
</tr>
<tr>
<td>History of unstable angina</td>
<td>1.83 [1.03-3.27]</td>
<td>1.75 [1.27-2.43]</td>
</tr>
<tr>
<td>Age (per additional decade)</td>
<td>1.75 [1.27-2.43]</td>
<td>2.20 [1.60-3.02]</td>
</tr>
<tr>
<td>Admission systolic AP &gt;180 mm Hg</td>
<td>3.47 [1.41-8.55]</td>
<td>3.47 [1.41-8.55]</td>
</tr>
<tr>
<td>History of excessive alcohol intake</td>
<td>2.64 [1.27-5.47]</td>
<td>2.64 [1.27-5.47]</td>
</tr>
<tr>
<td>Arhythmia on day of surgery</td>
<td>1.97 [1.12-3.46]</td>
<td>1.97 [1.12-3.46]</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>1.78 [1.02-3.10]</td>
<td>1.78 [1.02-3.10]</td>
</tr>
</tbody>
</table>

Table 4 Adjusted odds ratios (95% confidence intervals) for type I and type II cerebral outcomes associated with selected risk factors from the McSPI and IREF study. IABP = intra-aortic balloon pump; AP = arterial pressure; CABS = coronary artery bypass surgery (reproduced with permission from Roach and colleagues).^125

Deficit or seizure without evidence of focal injury. More than 30% of patients were 70 yr or older and there was a high prevalence of hypertension, unstable angina, cardiac failure and diabetes mellitus. In all, 129 of 2108 (6.1%) patients had an adverse neurological outcome in the perioperative period. Type I outcomes occurred in 66 of 2108 (3.1%) patients and included eight deaths as a result of cerebral injury, 55 non-fatal strokes, two TIA and one case of stupor at the time of discharge. Type II outcomes occurred in 63 of 2108 (3.0%) patients and included 55 patients with intellectual dysfunction and eight with seizures. The wide variation in institutional outcome rates for both type I (1-13.8%) and type II (0-9.3%) outcomes is cause for concern and has yet to be fully addressed.

Stepwise logistic regression analysis identified eight significant, independent predictors of type I outcomes and seven significant, independent predictors of type II outcomes (Table 4). Although similar, the predictors for the two outcome types were not identical.

Factors found not to be significant predictors were: perioperative hypotension (systolic arterial pressure <40 mm Hg during CPB or <80 mm Hg at other times for more than 10 min), intraoperative use of an apical vent to decompress the left ventricle, congestive cardiac failure on the day of surgery and a history of peripheral vascular disease. Adverse neurological outcome was associated with higher in hospital mortality, increased duration of intensive care and postoperative hospital stay, increased patient charges and increased likelihood of being discharged to an intermediate or long-term care facility.

Using data obtained from the McSPI study, the Duke group went on to develop a model to predict the development of stroke after CABS. Using preoperative patient factors, the so-called stroke index allows rapid assessment of risk (Fig. 2).

More recently, the McSPI group have reported adverse neurological outcomes in 43 of 273 (16%) patients undergoing combined intracardiac and coronary artery procedures. The authors concluded that this surgical population was at extraordinary risk of adverse cerebral outcome.
Sex

Few studies have specifically examined the influence of sex on neurological outcome after cardiac surgery. The main reason for this is that men greatly outnumber women in the adult cardiac surgical population. Data from the US Society of Thoracic Surgeons (http://www.sts.org/outcomes) for the years 1995 to 1996 suggest that operative mortality was significantly greater in females after both repeat and/or emergency CABS (4.30% vs 2.63%; P<0.0001) and primary elective CABS (2.9% vs 1.5%; P<0.0001). A recent report from the Bypass Angioplasty Revascularization Investigation (BARI) group however, suggests that the higher mortality observed in women is a product of higher risk profiles rather than increased gender susceptibility. When risk factors are controlled for, female sex was an independent predictor of improved 5-yr survival.

Laboratory evidence suggests that oestrogens have a vital role in neuronal growth, differentiation and survival. Furthermore, oestrogens also appear to play an important and specific role in cognitive function in women. The finding that oestrogen administration reverses memory deficits in women rendered hypo-oestrogenic with leuproide acetate (a gonadotrophin releasing hormone agonist) suggests that a study of oestrogen replacement in postmenopausal women undergoing cardiac surgery is warranted.

Severity of cardiac disease and cardiac function

An early study by Blachly and Kloster suggested that low postoperative cardiac output was related to the occurrence and severity of a postoperative brain syndrome or hallucinosis. Lee and colleagues reported that patients who had symptoms of cardiac disease for more than 6 months were more likely to develop neurological damage after coronary artery surgery. Poor preoperative left ventricular function and/or episodes of left ventricular failure have been reported to be associated with worse neurological outcome. Interestingly, the McSPI study found that neither congestive cardiac failure nor arrhythmia on the day of surgery were associated with adverse neurological outcome. It is possible that improvements in critical care, anti-arrhythmic therapy and support of the failing heart have reduced the impact of poor cardiac function on neurological outcome.

Cerebrovascular disease

Patients with a history of stroke or TIA are more likely to sustain a perioperative stroke. Patients with significant but asymptomatic atheromatous disease in the extracranial cerebral arteries may be at increased risk on the grounds that they will be more vulnerable to regional ischaemia during periods of hypoperfusion. Although preoperative detection of a carotid bruit is associated with a two-fold increase in absolute perioperative stroke risk after CABS, it is a poor measure of the severity of stenosis and has been shown not to correlate well with angiographic findings. The presence of carotid disease detected by Doppler sonography, the risk of stroke is increased threefold. As expected, the risk of stroke increases with the severity of carotid disease. In a follow-up study of 4047 patients examined before CABS, Brener and colleagues demonstrated that in the presence of >50% carotid stenosis, the risk of stroke increased from 1.9% to 6.3%. In 32 patients with complete carotid occlusion, the stroke rate was 15.6%.

In a study of 47 patients undergoing CABS at the Middlesex Hospital, studied with i.v. digital subtraction carotid angiography, 51% had evidence of atheroma and 17% had stenosis of at least one carotid artery in the neck. The incidence of cognitive deficit at 8 days and 8 weeks after surgery was not significantly greater in those patients with angiographically visible carotid artery disease.

A retrospective study at the Cleveland Clinic revealed that the incidence of new stroke after open-heart surgery was 13.4% in 126 patients with previous stroke. The likelihood of a new perioperative stroke was not related to the time interval between the previous stroke and surgery. Furthermore, the presence of extracranial occlusive disease appeared to be non-contributory. Patients who had had a stroke in the 3 months before surgery were more likely to have worsening of a prior deficit whereas those with a more remote history of stroke were more likely to have a stroke in a different brain region. Intraoperative hypotension was found to be more frequent in those patients with recent

![Graph showing the effect of age on the risk of stroke and mortality after coronary artery bypass surgery.](http://www.sts.org/graphics/sts/db/us98/gchart63.gif)
preoperative stroke, suggesting persistent haemodynamic vulnerability.

Current evidence suggests that asymptomatic extracranial cerebrovascular disease represents a modest increase in the risk of peripreoperative stroke, but other factors, such as embolism or hyperperfusion, are probably more important.

**Diabetes mellitus and hyperglycaemia**

For many years, the use of glucose-containing priming solutions in the extracorporeal circuit was commonplace. Although there is evidence that outcome from stroke in humans is worse in diabetics, there are no data unequivocally implicating hyperglycaemia as the cause.138 The higher incidence of hypertension, renal impairment and vascular disease may partly explain a worse outcome in diabetic patients. In a study of 70 patients conducted at the Middlesex Hospital, allocated randomly to either electrolyte or dextrose prime, neuropsychological outcome was found to be worse in the latter group.112 In a recent study using 133Xe clearance, the Duke group demonstrated that insulin-dependent diabetic patients who had impaired cerebral blood flow autoregulation, characterized by increased oxygen extraction, during CPB. Several reports have suggested that diabetes mellitus is a risk factor for poor neurological outcome after CPB.84 111 123

In recent years, there has been a re-evaluation of the use of glucose-containing priming solutions in cardiac surgery.139 On the grounds that hyperglycaemia appears to worsen neurological outcome in both focal and global cerebral ischaemia,76 101 some investigators claim that hyperglycaemia during cardiac surgery is detrimental and should be avoided.140 Others, however, suggest that glucose administration may be beneficial.88 89

In our experience, most centres avoid deliberate hyperglycaemia and treat intraoperative hyperglycaemia with insulin. The critical glucose concentration at which treatment should be instituted is unknown.

**Genetic susceptibility**

It is known that patients with similar physical characteristics, identical medical histories and cardiac disease of equivalent severity have markedly differing neurological and neuropsychological outcomes from uneventful cardiac surgery. This observation led investigators at Duke University to speculate that genetic factors may account for this variability.105 106 155 Concurrent laboratory studies, focusing on apolipoprotein E, prompted a clinical investigation.

Apolipoprotein E (APOE), a 34 kD glycosylated lipid-binding protein, is expressed as three common isoforms (ε2, ε3 or ε4) in humans. Possession of the APOEε4 allele is now known to be a risk factor for the development of late-onset and sporadic forms of Alzheimer's disease.129 130 It may also be associated with a worse outcome after subarachnoid haemorrhage3 and increased severity of chronic neurological deficits in boxers exposed to chronic head trauma.68 Interestingly, accelerated aortic atheromatous disease and early re-stenosis after coronary angioplasty, independent of serum cholesterol, may also be associated with APOEε4.82

APOE was evaluated as a predictor of postoperative cognitive dysfunction in 65 patients undergoing CABGS.155 A significant association was found between the APOEε4 allele and decline in four of nine measures of cognitive function at discharge from hospital and 6 weeks after surgery.

The notion that APOE isoforms may have a role in dictating the expression of early immediate genes after neuronal injury, and thus the balance between neuronal repair and neuronal death, is attractive but requires further investigation.

**Education level, socioeconomic status and mood**

An interesting observation is that a higher number of years of formal education appears to protect patients from cognitive decline.108 Level of educational achievement however, correlates poorly with baseline (preoperative) cognitive function test scores.

Depression is commonly reported after cardiac surgery. The use of non-standard measures of depression, however, may have overestimated its frequency. A presumed association between postoperative depression and poor performance on psychometric tests has meant that mood assessment has become an integral component of many studies. In a recent study, the Center for Epidemiological Study of Depression (CES-D) depression questionnaire and a battery of neuropsychological tests were used to assess outcome in 124 CABG patients 1 month and 1 yr after surgery.82 Depression was defined as a CES-D score >16. Only 12 (13%) patients not depressed before surgery were depressed 1 month afterwards, whereas 18 (53%) of those who were depressed before surgery were depressed at 1 month (P=0.001). One year after surgery, values were eight (9%) and 16 (47%), respectively (P=0.001). There was little or no correlation between depression and changes in cognitive function. The inference is that cardiac surgery neither causes nor cures depression.

**Cerebral microembolization**

Emboli, which may be gaseous or particulate, can be conveniently divided into 'macro' and 'micro' according to size. Macroemboli occlude flow in arteries 200 μm or greater in diameter, whereas microemboli occlude flow in small arteries, arterioles and capillaries.14 Air may reach the systemic circulation from the bypass circuit via the venous cannula, or as an inevitable consequence of left-heart surgery.149 Not surprisingly, systemic embolization is more common during valve surgery than CABGs.72 The ultimate fate of bubbles depends on their initial size, the partial pressure of gases in solution and temperature, which dictates the solubility of gases in liquids. Because of high surface tension forces, small bubbles are unstable and tend to collapse. Bubbles are more likely to
grow in size during rewarming when gas solubility decreases. Although bubbles are known to traverse the cerebral vasculature, they may cause endothelial injury. Particulate matter can also be categorized according to composition and origin. Biological particles arise from components of the circulation (aggregates of erythrocytes, leucocytes, platelets, denatured protein, fibrin) and the operative site (thrombus, fat, calcium, cellular aggregates, atheroma, valve debris, muscle fragments, hair). Non-biological particles arise from the extracorporeal circuit and cardiectomy reservoir (polyvinyl chloride, silicone rubber, antifoam, priming solutions, cardioplegia solutions) and from foreign material introduced into the operative field (fibres from swabs, glove talc, dust).

Considerable histological, angiographic and ultrasonographic evidence suggests that cerebral embolization occurs in all patients subjected to CPB. Although it is not clear which types of microemboli cause most damage to the brain, a correlation between intraoperative cerebral microembolic load and postoperative neuropsychological dysfunction has been demonstrated. The finding, in a recent animal study, that the use of cardiectomy suction was associated with histological evidence of increased cerebral microembolization suggests that blood aspirated from the surgical field can be a major source of microemboli.

Aortic atheromatous disease

Although the possibility of atheromatous cerebral embolism during aortic surgery was recognized many years ago, it is only in recent years that this problem has been revisited. The severity of aortic atheromatous disease increases sharply with age. Postmortem studies indicate a prevalence of 20% in the fifth decade increasing to 80% in the eighth decade. The prevalence of ulcerated aortic arch atheroma at autopsy has been shown to be higher (26% vs 5%) in patients with cerebrovascular disease but appears not to be correlated with the presence of extracranial internal carotid artery stenosis. Surgical manipulations of the proximal aorta, cannulation through an atheromatous plaque or 'sandblasting' of the aortic wall during perfusion may cause atheroembolism. The advent of transoesophageal echocardiography (TOE) and intraoperative aortic ultrasonography has allowed a more detailed view of the aorta during surgery and quantification of atheromatous plaques according to thickness and the presence of mobile components.

The importance of aortic atheroembolism has been highlighted by Katz and colleagues who found that the incidence of stroke was 25% in patients with a mobile plaque of the aortic arch compared with 2% in those with sessile plaque. A strong association between severe aortic atheroma and postoperative stroke or death has been confirmed by others. The successful use of intraoperative epicardial ultrasound in surgery for congenital heart lesions stimulated use of the technique in adults. Recent comparisons between intraoperative TOE and epiaortic ultrasound showed conclusively that TOE underestimated the presence and severity of aortic atherosclerosis.

Several centres are currently investigating the efficacy of alterations in surgical technique based on ultrasonic evaluation of the aorta. Such alterations include aortic cannulation at a different site, avoidance of aortic cannulation altogether, avoidance of aortic cross clamping and replacement of the ascending aorta and/or aortic arch.

Duration of cardiopulmonary bypass

The suggestion that CPB is associated with progressive, embolic cerebral microvascular obstruction suggests a relationship between duration of bypass and adverse neurological outcome. Many investigators have either observed or suggested that neurological outcome is related to the duration of bypass and difficulties. The finding that progressive cerebral vasoconstriction leads to a gradual decrease in cerebral blood flow during prolonged non-pulsatile hypothermic bypass may be an additional factor, but has not been substantiated.

It is important to note that bypass time may be prolonged by several factors which may themselves contribute to cerebral injury. A slow (meticulous) or 'delayed' surgeon may occasionally increase bypass time. It is more usual, however, that complicated surgical procedures (e.g. combined valve and CABS), complications or technical problems (e.g. haemorrhage, aortic dissection) and difficulty weaning from bypass are the main causes of prolonged bypass. It is clear that all of these factors may reflect a greater severity of cardiac disease in a population of surgical patients that have a higher incidence of adverse neurological outcomes.

Perfusion: pressure, flow and pulsation

Few would doubt that prolonged periods of profound arterial hypotension and cerebral hypoperfusion are bad for the brain and that certain areas, at the boundaries of cerebral artery territories (so-called 'watersheds'), are particularly vulnerable. The influence of systemic (arterial or 'pump') blood flow, flow character and cerebral perfusion pressure (CPP) on CBF during CPB and neurological outcome has been the subject of considerable debate. In addition to pressure and flow, actual CBF during CPB is determined by other factors including: acid–base management strategy, temperature, depth of anaesthesia, packed cell volume and oxygen saturation. During moderate hypothermia, cerebral autoregulation remains intact at a mean arterial pressure (MAP) as low as 30 mm Hg such that, in α-stat managed patients, CBF remains virtually constant within the range 30–100 mm Hg. Children appear to tolerate a MAP as low as 15 mm Hg. Recent evidence suggests that MAP in the range 51–75 mm Hg has a small effect on CBF during both hypothermic (+0.086 ml
100 g\(^{-1}\) min\(^{-1}\) mm Hg\(^{-1}\) and normothermic (+0.178 ml 100 g\(^{-1}\) min\(^{-1}\) mm Hg\(^{-1}\)) CPB.\(^{106,107}\) These findings are supported by the observation that at constant pump flow, jugular venous oxygen saturation \(\left( S_{\text{O}_2} \right) \) correlates with CPP during hypothermic, pulsatile CPB.\(^{52}\)

Although maintenance of a perfusion pressure \(\geq 50\) mm Hg during hypothermic CPB appears to be tolerated by the majority of patients, the safety of this practice has been questioned.\(^{24}\) The obvious question is, could higher perfusion pressures (i.e. \(\geq 70\) mm Hg) improve outcome?\(^{28}\) In an attempt to answer the question, Gold and colleagues prospectively compared cardiac and neurological outcome variables in 248 patients undergoing elective CABS, allocated randomly to either lower (50–60 mm Hg) or higher (80–100 mm Hg) perfusion pressures.\(^{46}\) Six months after surgery, the overall incidence of combined cardiac and neurological complications was significantly lower in the higher pressure group (4.8% vs 12.9%; \(P=0.026\) ) as was the stroke rate (2.4% vs 7.2%). There were no differences in cognitive and functional outcomes. The small study population, unusually high baseline stroke rate (7.2%) and method of data analysis makes it hard to reach any definite conclusion.\(^{70,121}\) The observed differences in outcome could have occurred by chance but may be accounted for by the greater number of patients with aortic atherosclerosis in the lower pressure group.

During CPB, systemic flow rate is usually based on body surface area and the degree of hypothermia (typically 1.6–2.4 litre min\(^{-1}\) m\(^{-2}\) ) and adjusted according to indices of the adequacy of organ perfusion (e.g. arterial blood gases). Although it is well established that low pump flow with concomitant arterial hypotension results in decreased CBF, the independent effects of low flow and low pressure are less well characterized. In a baboon model of non-pulsatile hypothermic (28°C) CPB, Schwartz and colleagues showed that, regardless of pump flow, CBF was governed by mean arterial pressure (20–60 mm Hg). Furthermore, when mean arterial pressure was maintained constant, changes in pump flow (0.75–2.25 litre min\(^{-1}\) m\(^{-2}\) ) did not alter CBF.\(^{133}\) These findings are at odds with the results of several other studies of CBF during CPB.\(^{47,123–127,147}\)

Govier and colleagues showed no correlation between CBF and either mean arterial pressure (30–110 mm Hg) or pump flow rate (1.0–2.2 litre min\(^{-1}\) m\(^{-2}\) ) in 67 patients undergoing CABS.\(^{47}\) In contrast, Soma and colleagues reported that CBF was directly dependent on pump flow rate (40–70 ml kg\(^{-1}\) min\(^{-1}\) ).\(^{147}\) The Bowman Gray group have reported the effects of CBF of alterations in arterial pressure with administration of sodium nitroprusside\(^{126}\) and phenylephrine\(^{127}\) (measured by \(133\)Xe clearance) at constant pump flow. In \(\alpha\)-stat managed patients, changes in arterial pressure had no effect on CBF whereas in pH-stat managed patients, CBF was correlated positively with pressure. A subsequent study showed that modest changes in pump flow rate (1.75–2.25 litre min\(^{-1}\) m\(^{-2}\) ) had no influence on arterial pressure or CBF.\(^{125}\)

Non-pulsatile perfusion is associated with diminished endothelial shear stress and a reduction in endothelial nitric oxide production leading to increased vascular resistance and end-organ dysfunction.\(^{77}\) Furthermore, it is suggested that non-pulsatile flow may cause stasis of cerebral interstitial fluid\(^{167}\) and also the cerebral swelling demonstrated after hypothermic\(^{24}\) and normothermic\(^{35}\) bypass. In a canine model of extracorporeal perfusion after 15 min of cardiac arrest, non-pulsatile perfusion was associated with worse cerebral hyperaemia and lower oxygen consumption compared with pulsatile perfusion.\(^{5}\) In a prospective study of 316 patients undergoing CABS, however, Murkin and colleagues were unable to demonstrate any influence of mode of perfusion on neurobehavioural outcome.\(^{96}\)

Despite considerable research, the characteristics of 'optimal' CPB perfusion remain to be defined. Within the bounds of usual CPB conduct, pressure, flow and flow character appear to have little influence on CBF.\(^{132}\) In the absence of unequivocal evidence suggesting otherwise, there seems little reason to alter perfusion practices that are tolerated by the vast majority of patients.

### Temperature

Since the early days of cardiac surgery, systemic and regional hypothermia has been the mainstay of organ protection during CPB. Hypothermia is unique among neuroprotective modalities in that it reduces energy consumption (about 7% per °C) associated with both electrophysiological function and maintenance of cellular integrity. At modest hypothermia, autoregulation of CBF is such that CBF is tightly coupled to cerebral metabolic rate \(\text{CMR}_O_2\). With decreasing temperature, the CBF:CMR\(_O_2\) ratio increases resulting in 'luxury' brain blood flow. At temperatures of 15–20°C (deep hypothermia), pressure-flow autoregulation is lost. In animal models of cerebral ischaemia, mild hypothermia reduces neuronal adenosine triphosphate (ATP) depletion,\(^{169}\) and both delays the onset and reduces the rate of excitatory amino acid release.\(^{102}\)

Hypothermia does, however, have several distinct disadvantages, not least of which is the requirement for rewarming the patient at the end of the procedure. Placement of the arterial cannula in the ascending aorta results in cerebral perfusion with blood at a temperature close to that of blood leaving the heat-exchanger. For this reason it is easy to produce inadvertent cerebral hyperthermia during rewarming. The observation that warming from moderate hypothermic CPB is associated with jugular venous desaturation \(S_{\text{O}_2} < 50\%\) suggests that cerebral oxygen extraction during this period exceeds supply.\(^{29,34}\) In a series of 255 patients studied at Duke University, the cerebral arteriovenous oxygen difference \(\left( C_{\text{aO}_2} - C_{\text{vO}_2} \right) \) on rewarming was significantly associated with overall cognitive decline (\(P=0.0013\)).\(^{35}\)

Rapid rates of warming, using temperatures >41°C, have long been considered a potential cause of neurological injury during CPB.\(^{22}\) Hyperthermia increases CMR\(_O_2\) and
may cause protein denaturation and air embolism, in addition to tissue ischaemia. In a recent study, nasopharyngeal temperature ($T_{NP}$) monitoring was compared with continuous jugular venous temperature monitoring. Although there was a high degree of precision between the two monitoring sites, there was a marked difference in bias. This was most pronounced during rewarming when jugular venous temperature was $3.4^\circ C$ higher than $T_{NP}$. The authors concluded that $T_{NP}$ monitoring underestimated brain temperature during rewarming and speculated that as a result, the brain may be at increased risk of neurological injury. However, in an unrandomized and unblinded study of 28 CABS patients, von Knobelsdorff and colleagues suggested that the use of a ‘slow’ rewarming regimen did not attenuate reductions in $S_{I_{O_{2}}}$. An accompanying editorial raised several methodological issues and advised caution in interpreting these findings.

The finding that even mild hyperthermia ($38-39^\circ C$) increases excitotoxic neurotransmitter release during cerebral hypoxia and delays recovery of energy metabolism is cause for concern. The use of mild hyperthermia ($34^\circ C$) after CPB and in the early postoperative period has been shown not to be associated with increased bleeding, cardiac morbidity or time to tracheal extubation. Any neuroprotective effect of this strategy remains to be established in prospective, randomized studies.

In recent years, studies have suggested that normothermic cardioplegia may improve myocardial protection during heart operations. As interest in these so-called ‘warm-heart’ techniques has increased, their use has become widespread. The immediate concern was that abandonment of hypothermic perfusion during CPB would compromise cerebral protection and lead to a higher incidence of neurological morbidity.

To date, studies that have examined the effect of normothermic cardioplegia and CPB on myocardial and neurological outcome have yielded conflicting results. Singh and colleagues, the Warm Heart Investigators and McLean and colleagues reported no increase in neurological complications. Martin and colleagues, however, demonstrated a marked increase in neurological injury in patients maintained at normothermia during CPB. Directly comparing these studies is difficult because actual brain temperature was not measured and small variations in the conduct of CPB and operative technique may have had a crucial influence on temperature. This is further confounded by relatively low mean patient ages and the deliberate exclusion of patients with increased risk of perioperative stroke.

In an attempt to resolve the issue, Mora and colleagues compared neurological and neuropsychological outcomes in 138 patients allocated randomly to receive either intermittent cold oxygenated crystalloid cardioplegia during hypothermic ($\leq 28^\circ C$) bypass or continuous retrograde normothermic blood cardioplegia during normothermic ($\geq 35^\circ C$) bypass. All seven patients found to have new focal neurological deficits came from the normothermic group. One patient died as a result of cerebral infarction. In contrast, there were no significant differences in neuropsychological test performances, although the study was not sufficiently powered to detect a difference.

Hypothermic neuroprotection is consistent with the findings of Rebragui and colleagues who prospectively investigated the effect of perfusion temperature ($28^\circ C$, $32^\circ C$ or $37^\circ C$) on postoperative cognitive function in 96 adults undergoing elective CABS with CPB. Compared with patients perfused at $32^\circ C$, the incidence of cognitive deficits was significantly higher in patients perfused at $37^\circ C$ ($P = 0.021$). Cooling to $28^\circ C$ appeared to offer no additional benefit.

Despite suggestions that normothermic bypass does not increase risk, it is interesting to note that at a meeting of researchers in the field, held in Oxford at the end of 1996, the majority of participants indicated that they would rather undergo hypothermic ($32^\circ C$), rather than normothermic, bypass if they required cardiac surgery (personal communication!).

**Acid–base management**

The importance of maintaining normocapnia before the onset of CPB was highlighted by Nevin and colleagues in 1987. Three days after surgery, patients who had been inadvertently hyperventilated ($P_{aCO_{2}} \leq 4.7$ kPa) had a higher incidence of neurological (46% vs 27%) and psychometric (71% vs 40%) deficits than patients who were normocapnic ($P_{aCO_{2}} 4.7-6.0$ kPa).

The solubility of gases in a liquid, including blood, increases as temperature decreases. When arterial blood gases are analysed with a temperature correction during hypothermia, patients appear to have a respiratory alkalosis (decreased $P_{aCO_{2}}$ and increased pH). Addition of carbon dioxide to ‘normalise’ $P_{aCO_{2}}$ and maintain a pH of 7.40 is known as ‘pH-stat’ acid–base management. The use of arterial blood gases without temperature correction is known as ‘a-stat’ management.

During moderate hypothermic CPB, pressure–flow autoregulation of CBF is maintained when $\alpha$-stat blood-gas management is used but lost when pH-stat management is used. The inability to autoregulate CBF at low perfusion pressures, the possibility of ‘steal’ in patients with intracranial cerebrovascular disease and the presence of ‘acidosis’ during rewarming associated with the pH-stat strategy increase the potential for brain injury. Furthermore, the excessive CBF associated with pH-stat may substantially increase the delivery of emboli to the brain.

The influence of pH management has been assessed by several groups. In a study of 86 patients undergoing CABS, Bashein and colleagues reported that the pH management strategy had no influence on either cardiac or neurocognitive outcome.
the pH-stat strategy was associated with cerebral hyperaemia (+191% vs -18%) and a higher incidence of neurological dysfunction 7 days after surgery (P=0.036). In a study of 316 patients undergoing CABS, cognitive dysfunction at 2 months was less prevalent after 90 min of CPB in patients managed with α-stat than with the pH-stat strategy (27% vs 44%; P=0.047). Similar findings have been reported in a study of 70 patients undergoing CABS at St Thomas’ Hospital (20% vs 48.6%; P<0.05).

In patients and animals undergoing deep hypothermic cardiac arrest (DHCA) however, pH-stat management before the onset of circulation arrest appears to improve neurological outcome. Using magnetic resonance spectroscopy in an immature piglet model of DHCA, Aoki and colleagues have shown that recovery of cerebral ATP and intracellular pH in the initial 30 min of reperfusion is faster in pH-stat managed animals. In α-stat managed animals, cerebral intracellular pH decreased during early reperfusion, whereas it showed continuous recovery in pH-stat managed animals. Possible reasons for these observations include improved brain cooling by increased blood flow to subcortical areas, improved oxygen delivery and reduction of reperfusion injury, in addition to an alkaline shift in intracellular pH with hypothermia in spite of a stable blood pH.

Neuroprotective interventions

It is clear that risk factors for adverse neurological outcome fall into two categories: those that cannot be modified (i.e. age, sex, genotype and medical history) and those that may (i.e. cerebral embolism, aortic atheroma, CPB duration and cerebral perfusion). Interventions designed to reduce or prevent neurological injury during cardiac surgery can be divided into two categories: (1) physical and (2) pharmacological. Table 5 summarizes some of the physical interventions that have been used or advocated.

Pharmacological interventions

A greater understanding of the pathophysiology of neurological injury offers the hope of pharmacological neuroprotection. At present, however, there is no agreement on the need for prophylactic neuroprotectants in cardiac surgery, much less the choice of drug. With the exception of some anaesthetic drugs, many of the prototype neuroprotective agents studied in cardiac surgery were developed originally for the treatment of stroke. In many ways, cardiac surgery is a convenient model with which to test these agents—a large number of patients sustaining a cerebral injury at a predictable time. Unfortunately, disagreement over the precise nature of heart surgery related brain injury (focal vs diffuse ‘micro-focal’ vs diffuse), the confounding influences of other ‘standard’ neuroprotective strategies (hypothermia, blood-gas management, arterial line filtration, etc.) and the lack of a gold standard for assessment of neurological and cognitive outcomes, reduces its use as an experimental model.

The observation that certain barbiturates could reduce CMRO₂ led to extensive research into their neuroprotective potential. In 1986, Nußmeier, Arlund and Slogoff were first to report barbiturate neuroprotection in humans. One hundred and eighty-two patients undergoing open-ventricle procedures were randomized to either thiopental (an initial bolus followed by a continuous infusion—mean total dose 39.5 mg kg⁻¹), sufficient to maintain electroencephalographic silence throughout the period from before aortic cannulation to termination of bypass (n=89) or fentanyl (n=93). On the first postoperative day, clinical neuro-psychiatric abnormalities were found to be more common in the control group (5.6% vs 8.6%). By day 10 after operation, all neuropsychiatric dysfunction had resolved in the thieno­pental group but persisted in seven (7.5%) control patients (P<0.025). The incidence of complications was related significantly to calcification of replaced valves, aortic valve replacement, advanced age and prolonged bypass, but not to hypotension during perfusion. It is curious to note that in a later publication by the same group, the background incidence of new neurological deficit was much lower. In a similar study of patients undergoing CABS, however, no protective effect could be demonstrated. Mortality in the thieno­pental; group was, however, lower than in controls (0.7% vs 2.6%; P=0.018). More recently, a retrospective evaluation of 227 open-heart surgery patients revealed that thieno­pental (mean dose 38.1 mg kg⁻¹) had no beneficial effect on neurological outcome although mortality was significantly lower in the thieno­pental group (1.2% vs 9.6%; P=0.034).

Propofol has similar effects to thieno­pental on CMRO₂ and CBF. Although in vitro evidence suggests a direct neuroprotective action, perhaps via GABA_A receptors, it is suggested that a propofol-induced reduction in CBF reduces the delivery of microemboli to the cerebral circulation.

Calcium channel antagonists have stimulated considerable research. Of these, nimodipine, an L-type calcium channel blocker, has shown considerable promise in the management of subarachnoid haemorrhage but not acute head injury. A prospective, double-blind, randomized study of nimodipine in 400 patients undergoing valve surgery was terminated because of lack of efficacy and significant adverse events. The incidence of new neurological deficits was no different to placebo (72% vs 77%; P=0.55). In the 6-month follow-up period, mortality was significantly higher in the nimodipine group (10.7% vs 1.5%; P=0.02). Major haemorrhage was also significantly more common in the nimodipine group (13.3% vs 4.1%; P=0.04).

Prostacyclin has been used in addition to, or as a replacement for, heparin during CPB. It is known to reduce platelet aggregation during extracorporeal circulation and may therefore be neuroprotective. In 1987, Fish and
Table 5 Potentially neuroprotective physical interventions in cardiac surgery

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<th>Category</th>
<th>Intervention</th>
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<td>General considerations</td>
<td>Expeditious surgery</td>
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<td>Attention to myocardial preservation and haemostasis</td>
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<td>Maintaining cerebral perfusion</td>
<td>Avoid prolonged/profound arterial hypotension</td>
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<td>Avoid prolonged systemic hypoperfusion</td>
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<td>Avoid prolonged superior vena caval obstruction</td>
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<td>Reducing cerebral embolization</td>
<td>Consider retrograde cerebral perfusion during DHCA</td>
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<td>Adequate anticoagulation</td>
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<td>Minimize aortic manipulation/instrumentation</td>
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<td>Careful (de)canulation of the aorta</td>
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<td>Avoid venous air entrainment</td>
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<td>Use of arterial line filter</td>
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<td>Avoid CPB altogether (i.e. &quot;beating heart&quot; procedures)</td>
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<td>Use of exhaustive debridement procedures</td>
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<td>Avoid or reduce use of cardiomyotomy suction</td>
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<td>Temperature management</td>
<td>Moderate hypothermia (i.e. 32°C)</td>
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<td>Avoid rapid/excessive rewarming</td>
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<td>Acid–base management</td>
<td>Alpha-stat regimen (pH-stat during cooling before DHCA and in patients with significant aorto-pulmonary anastomoses)</td>
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<td>Other</td>
<td>Avoid hypercapnia and hypocapnia</td>
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<td>Advanced neurological monitoring</td>
<td>Jugular venous oxygen saturation</td>
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<td>Near infrared spectroscopy (NIRS)</td>
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<td>Electroencephalography (EEG)</td>
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<td>Transcranial Doppler sonography</td>
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colleagues reported the results of a randomized, double-blind study designed to evaluate the effect of prostacyclin on the incidence and severity of postoperative neuropsychological dysfunction in 100 patients undergoing CABS. Of 96 patients who completed the psychological and neurological evaluations 1 week after surgery, 74 were evaluated psychologically 2 months after surgery. There were no differences in neurological outcome or psychological test performance.

Grieco and colleagues have recently reported the results of a double-blind, placebo-controlled pilot study of GM1 ganglioside in patients undergoing cardiac surgery. Although there was a trend towards improved neurological and neuropsychological outcome in the ganglioside treated group, the differences did not reach statistical significance.

The systemic inflammatory response associated with CPB, characterized by the release of cytokines in response to activation of the coagulation, fibrinolytic and complement cascades, has been the subject of recent discussion. The bovine serine protease inhibitor, aprotinin, has been shown to significantly reduce intraoperative bleeding and transfusion requirements in a variety of settings, including cardiac surgery with CPB. Despite an early report suggesting an increased incidence in perioperative myocardial infarction there is now a suggestion, from a meta-analysis of several studies, that high-dose aprotinin may actually reduce the incidence of perioperative stroke. Whether or not this action is a result of the non-specific anti-inflammatory properties of antiproteases remains unclear. Nafamostat mesilate (FUT-175), a synthetic serine protease inhibitor, is currently under investigation in cardiac surgery. Although it is known that glucocorticoids can suppress some of the inflammatory cytokines liberated during CPB, recent laboratory evidence suggests that they may worsen neurological outcome.

Indications that free radical production increases during CPB and in cerebral ischaemia suggests a possible neuroprotective role for free radical scavengers. Desferrioxamine, which may reduce iron-catalysed free radical production, has been evaluated in 24 adult patients (12 controls, 12 treated) undergoing CPB for various cardiac operations. Desferrioxamine was given both i.v. and with the cardioplegic solution. Polymorphonuclear neutrophils (PMN) harvested from desferrioxamine-treated patients produced significantly fewer superoxide radicals than those of control patients. It was concluded that desferrioxamine-exposed PMN had decreased oxidative responsiveness. These results were thought to be consistent with the hypothesis that desferrioxamine reduces free radical-mediated amplification of the inflammatory response to CPB. Although this could be effective in reducing the harmful effects of extracorporeal circulation, no evaluation of any neuroprotective effect has been reported.

In light of experimental evidence indicating a role for excitatory amino acid neurotransmission in the pathogenesis of brain injury occurring during cardiac surgery with CPB, several compounds have reached phase II clinical trials. Of these, the competitive glutamate antagonist, remacemide hydrochloride, has been shown to improve neuropsychological outcome in a prospective, randomized, double-blind study in patients undergoing CABS. Compared with the placebo group, patients treated with remacemide showed significantly superior performance on three of 10 neuropsychological tests. Furthermore, the remacemide group had significantly greater improvement in performance on a composite measure (total z score) of neuropsychological performance ($P=0.028$).
CNS complications of cardiac surgery

Numerous drugs are currently being evaluated in stroke, epilepsy, head injury, subarachnoid haemorrhage and cardiac arrest. Putative neuroprotective drugs currently under investigation in cardiac surgery include chlorpromazine, lidocaine, nicorandil and magnesium sulphate.

Summary

The neurological complications of cardiac surgery are associated with significantly increased mortality, morbidity and resource utilization. The use of new surgical techniques, introduction of wider indications for surgery and increased public expectation has led to an increase in the average age of cardiac surgical patients and an increased incidence of repeat procedures. With these changes has come an increased risk of neurological complications.

The likelihood of perioperative stroke varies between 1% and 5% in most published series and is dependent on a multitude of risk factors. Of these, patient age, aortic atheroma, symptomatic cerebrovascular disease, diabetes mellitus and the type of surgery appear to be most important. Cognitive deterioration after cardiac surgery is far more common, affecting as many as 80% of patients a few days after surgery and persisting in one-third. Despite an increase in the age of the cardiac surgical population, the reported incidence of cognitive dysfunction after cardiac surgery seems to have fallen in recent years. Whether this is a real phenomenon or the result of changes in the use of psychometric testing and the definition of cognitive decline remains unclear.

Recognition that certain equipment, surgical practices and patient factors contribute to neurological morbidity has prompted 'neuroprotective' interventions. Some of these (e.g. arterial line filtration and α-stat management) have been shown to improve outcome. Despite these measures, a small number of patients will inevitably sustain cerebral injury during otherwise successful cardiac surgery. Although pharmacological neuroprotection may, in the future, offer some of these patients an improved outcome, it is unlikely that any single agent will prevent neurological injury. In the meantime, the CNS complications of cardiac surgery remain a fertile area of research.

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References

79 Li PA, Kristian T, Shamloo M, Siesjô BK. Effects of preischemic hyperglycemia on brain damage incurred by rats subjected to 2.5 or 5 minutes of forebrain ischemia. Stroke 1996; 27: 1592–602
85 Metz S, Pro: glucose priming solutions should be used for cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1995; 9: 601–4
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protects primary cortical neurons from glutamate toxicity. Neurosci Lett 1996; 212: 13–16


