Closed-loop Control of Anaesthesia

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ABSTRACT

One of the most challenging problems in modern Anaesthesia is measuring anaesthetic depth. Before the advent of muscle relaxant drugs, anaesthetists relied on respiratory patterns and movement in response to painful stimuli to titrate anaesthetic concentrations and ensure that their patients were adequately anaesthetised. The introduction of muscle relaxation rendered traditional signs of anaesthetic depth unusable and, as a result, a small percentage of the general surgical population experience conscious awareness with or without pain under general anaesthesia.

Several attempts have been made to develop an objective monitor that would work with all anaesthetic agents and be adequately reliable and robust for use in the operating theatre environment. Most of these attempts failed, the main reason being that no satisfactory measuring parameter could be identified. The most promising area of research has been centred around Auditory Evoked Potentials in determining anaesthetic depth.

This thesis describes the development of a novel technique, using Auditory Evoked Potentials to extract a single numerical index which unequivocally measures depth of anaesthesia. In order to prove this index, it has been used as an input signal to a closed-loop control system. This system has been successfully employed to deliver an intravenous anaesthetic to a large number of patients completely automatically.

Further refinements to both software and hardware and additional clinical studies, using various anaesthetic agents, are required. It is proposed that this technique will lead to the development of a commercial depth of anaesthesia monitor.

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> *"The conscientious and overworked anesthetist, while rendering invaluable service to the community, fails to appreciate that his ultimate professional status cannot be guaranteed by service alone. Without vision and research, the professions die."*
>
> *Prof. W.T. Salter, Yale, 1950.*

1.1 INTRODUCTION

Monitoring anaesthetic depth presents a number of difficulties. The two most valuable clinical signs, movement and respiration, are lost as soon as neuromuscular blockade is established. Several instrumental methods have been used, however, none of them has proved to be reliable enough to be used in all clinical situations by the non-expert. As a result, no objective method of measuring anaesthetic depth exists to date. This arguably represents the "holy grail" of modern anaesthesia.

The impetus for the establishment of such a method is not provided only by occasional reports of intraoperative patient awareness. There exists a great commercial interest for the development of a monitor, which, when connected to the patient, can provide the anaesthetist with a measure of the depth of anaesthesia quickly and accurately.

An important issue involves the absence of a "gold standard" against which to compare results. Any monitor of anaesthetic depth must be able to provide sufficient information to enable satisfactory general anaesthesia in spontaneously breathing patients. The best method to prove that a certain

parameter truly measures depth of anaesthesia is to use it as the input in a closed-loop anaesthesia (CLAN) system. If this system can provide adequate anaesthesia in a large number of spontaneously breathing patients, then that parameter actually reflects anaesthetic depth. Therefore, the primary use of closed-loop anaesthesia would be to validate any anaesthetic depth index and prove its accuracy and reliability.

Moreover, a CLAN system should be an excellent tool for clinical research. It can be used to compare relative potencies of different anaesthetic agents, to determine general anaesthetic drug requirements and to assess the effects of local blocks, muscle relaxants, premedication, age and other factors on the overall requirements for anaesthesia. All these studies can be conducted in an objective and unbiased manner, since human intervention in the course of a closed-loop anaesthetic is minimal. It appears, therefore, that a CLAN system is highly desirable.

1.2 THESIS OBJECTIVES

The objectives of this PhD project were:

- To develop an Auditory Evoked Potential (AEP) system, equipped with suitable high quality amplifiers and capable of processing the electroencephalogram (EEG) and extracting the AEPs in real time.
- To implement digital signal processing techniques in order to enhance the derived AEPs, analyse their main characteristics and extract a single numerical parameter that would reflect the changes occurring in the AEPs during general anaesthesia.
- To use this parameter as the input signal in a closed-loop anaesthesia (CLAN) system.

The project was carried out in collaboration between the Bioengineering Unit, University of Strathclyde and the Department of Anaesthesia, University of Glasgow. All clinical and most engineering work were conducted in Glasgow Royal Infirmary.

1.3 THESIS STRUCTURE

Chapter 2 examines the advent of modern anaesthesia, the introduction of muscle relaxation and the phenomenon of unnoticed awareness and recall of intraoperative events.

Chapter 3 contains an extensive review of all known clinical and instrumental methods of determining depth of anaesthesia. Emphasis is given to various derivatives of the EEG.

Chapter 4 gives a general description of evoked potentials and discusses the effects of general anaesthetics on the AEP.

The development of an AEP system and the calculation of an index (Auditory Evoked Potential Index, AEPidx) which reflects the effects of general anaesthetics on the AEP, is presented in Chapter 5.

Chapter 6 reviews medical applications of closed-loop control and describes a closed-loop anaesthesia (CLAN) system.

Chapter 7 contains three clinical studies relating to the CLAN system.

Conclusions are drawn and recommendations for future developments are given in Chapter 8.

Appendix A contains a summary of the effects of various anaesthetics on the AEP.

The implementation of a Finite Impulse Response digital filter in Pascal and Assembly is given in Appendixes B and C, respectively.

Appendix D contains all publications relating to the CLAN system. All text, data and figures have been transcribed *verbatim* from the original papers.

2. ANAESTHESIA AND AWARENESS

2.1 *INTRODUCTION*

For almost 2000 years the prevalent concept of disease was the Galenical approach. Disease was considered to be the result of a disturbance of the four cardinal humours: blood, phlegm, yellow and black bile. The body was healthy and strong when in balance but showed weakness and signs of illness when upset. It was only in the 18th century that it was learned that organic lesions were responsible for disease. Consequently, it became the purpose of diagnostics to perceive anatomical changes in the living patient. The surgeon, by excising an ulcer or a tumour or by draining an abscess, was removing the disorder and correcting the organ. However, without doubt, surgery could not develop freely before the two bonds that enslaved it were removed: *infection* and *pain*.

The history of pain relief is essentially the history of anaesthesia. It was known in ancient times that some natural extracts had analgesic and hypnotic properties. However, no information is available to describe their properties and assess their effects objectively.

In the first century A.D., the Greek philosopher Dioscourides studied some of the pharmacological properties of the plant *mandragora*. He was the first who used the Greek word ΑΝΑΙΣΘΗΣΙΑ (anaesthesia) to describe its narcotic effects on humans. The word appeared again in *Encyclopaedia Britannica* in 1771, where it was interpreted as a "privation of the senses".

Fundamental observations on the physiology of the cardiovascular and respiratory systems led to the exploitation of gases and vapours and their experimental inhalation. In 1774, Joseph Priestley liberated oxygen by heating mercuric oxide. He also produced nitrous oxide (N_2O) from nitric

oxide. Antoine Lavoisier observed that precipitation occurs when expired air passes through lime water and suggested that it contained a gas that was later called carbon dioxide (CO_2). He also found that only one fifth of the air in the atmosphere is oxygen. The rest of it is mainly nitrogen, a gas without colour, taste or smell that is irrespirable and cannot sustain life.

Nitrous oxide was initially used only for entertainment purposes. In 1799, Humphry Davy recognised its analgesic properties. He called the agent "laughing gas" because of its popular side effect and suggested that it might be used during minor surgical operations. Henry Hill Hickman, a general practitioner in Shifnal, a village in the English countryside, used an unlikely agent, carbon dioxide, to asphyxiate animals to a state of unconsciousness and perform surgical operations on them. He gave several demonstrations, however, scientists in England and France remained unconvinced and his ideas were never accepted (Sykes, 1960).

In the United States, Crawford Long, a general practitioner in Jefferson, Georgia, persuaded a young patient to inhale ether while a growth was excised from the back of his neck. The first report about this venture appeared several years later, in 1848, in the Southern Medical and Surgical Journal, delayed by influential physicians.

Within two years of this first surgical anaesthetic, in 1844, Horace Wells, a dentist in Hartford, Connecticut, started to use nitrous oxide as an analgesic for dental extractions. In January 1845, he gave a demonstration before a group of medical students at the Massachusetts General Hospital. However, the demonstration failed dramatically, as a student cried out in pain when his tooth was pulled out. Obviously, the induction period was too short and the gas reservoir too small to provide sufficient anaesthesia. The surgeon of the hospital and one-time dean of Harvard Medical School, John Collins Warren, described the failed attempt as "humbug".

Nearly two years later, in 1846, William Morton, Wells' former student and partner, successfully repeated the experiment in the same hospital by using

the vapours of ether. Dr Warren performed the operation and was so impressed that he said, "Gentlemen, this is no humbug". The Massachusetts General Hospital considered the event as the first scientific demonstration in public (rather than discovery) of inhalational anaesthesia.

Oliver Wendell Holmes, professor of anatomy and *literateur extraordinair*, used the Greek word *anaesthesia* to describe the new phenomenon that made surgery without pain possible. The news of this important medical discovery crossed the Atlantic and ether was adopted in Britain and other European countries within months (Sykes, 1960). John Snow, general practitioner and clinical investigator, became the first British physician anaesthetist. In 1847, he published a text "On the inhalation of the vapour of ether" including reports of actual cases and a detailed description of the typical signs and stages of ether anaesthesia. Robinson had already written a text on ether and Plomley had published some description of the stages of anaesthesia, but Snow's statements were conclusive. In 1847, Walter Channing, professor of midwifery and medical jurisprudence at Harvard, wrote a "Treatise on etherization in childbirth", which contained the results of a survey about the important issue of safety. Soon, other substances, like chloroform (discovered in 1831), were introduced as anaesthetics. And in 1858, Snow published a second document "On chloroform and other anaesthetics".

For several decades, there was no monitoring and recording of the patient's condition during surgical procedures. Anaesthetic drugs were usually administered by medical students. The risks and side effects of the anaesthetics used, were not fully understood and oxygen was not readily available until the early 1900s. As a result, mortality and morbidity during anaesthesia were very high (Sykes, 1960).

In 1896, Harvey Cushing started to record systematically some cardiovascular and respiratory measurements on "ether charts". Blood

pressure was also included, after Riva Rocci described his method. Most modern anaesthetic records are comparable to these early ether charts.

2.2 ANAESTHESIA AND DEPTH OF ANAESTHESIA

Depth of anaesthesia was first outlined by Plomley in 1847. He described three stages: intoxication, excitement and deeper narcosis. A few months later, John Snow assessed and documented the effect of ether as an anaesthetic in terms of signs of depression of the central nervous system and other physiological reactions. He depicted five degrees of narcotism. The first three stages described the induction phase and the last two surgical anaesthesia. Eleven years later, he repeated his observations with chloroform. His description included respiratory signs, paralysis of the intercostal muscles, the cornea reflex and eyeball movements. In the subsequent decades his description was refined and improved by several investigators.

Snow and his successors tried to use as little anaesthesia as possible to decrease morbidity and mortality, which were high at that time, since oxygen was not easily available until the beginning of the 20th century. Premedication with sedatives or opioids was introduced in the early 1900s. Anaesthetics with faster action, like ethylene, soon became available. As a result, the excitement phase could be passed more quickly and with less potential danger to the patient.

In 1901, George Crile proposed the *anociassociation theory*, a precursor of *balanced anaesthesia*, in which intravenous agents play an important role. Two years later, Fischer and von Mering used diethyl barbiturate (barbitone) as a long-lasting hypnotic, replaced by phenobarbitone within a short time. In the following years, a wide range of short, medium and long-acting barbiturates were devised until a sulphur derivative of pentobarbitone (thiopentone) exhibited the desired qualities and was adopted world-wide. It

is remarkable that this drug has survived for so many decades and withstood the challenge of modern anaesthetic agents.

In 1937, Arthur Guedel defined the stages of ether anaesthesia in his classic paper "Inhalational anesthesia, a fundamental guide". He used physical signs involving respiration, muscle activity and ocular signs to define four stages of ether anaesthesia (Figure 2.1).

Signs of General Anaesthesia

Stage		Somatic Muscles	Respiration	Oculomotor Muscles	Lid Reflex	Pupils (Premedication) None	Pupils (Premedication) Morph.
I		Normal Tone		++++	+		
II		Uninhibited Activity		++++	+		
III	Plane 1	Slight Relaxation		++++ +++ ++ +	o		
	Plane 2	Moderate Relaxation		o	o		
	Plane 3	Marked Relaxation		o	o		
	Plane 4	Marked Relaxation		o	o		
IV		Extreme Relaxation		o	o		

Figure 2.1 The signs and stages of general anaesthesia (adapted from Guedel, 1937).

In the first, or analgesic, stage the patient is still conscious, but is well sedated and has total analgesia and amnesia. This stage is distinguished by a positive eyelash reflex and slow, regular diaphragmatic breathing.

The second stage is the excitation stage during which the patient is unconscious but may have excitement and uninhibited activity. Breathing is irregular, the eyelash reflex is still present and pupils are dilated. Guedel emphasised the seriousness of this stage which, although is usually passed quickly, has an increased danger of violent excitement, heightened reflex irritability, vomiting, laryngospasm and arrhythmias.

The third stage is the surgical stage. It is subdivided into four successive planes. During the first plane, or light anaesthesia, small surgical procedures can be performed. It is characterised by regular breathing, slight muscle relaxation and active ocular muscles. The eyelash reflex is abolished. During the second plane, the muscles become moderately relaxed and the eyeballs are immobile. Inhalation becomes briefer than exhalation and they are separated by a slight pause. In the third plane, the abdominal muscles are almost completely paralysed and breathing is mainly diaphragmatic. The fourth plane, that of very deep anaesthesia, must be avoided because most clinical signs have vanished and circulatory and ventilatory functions are depressed. Breathing is irregular, the intercostal muscles are completely paralysed and pupils are dilated.

From this fourth plane of the third stage the patient can pass easily to the fourth, or toxic, stage, where all vital functions have disappeared. All muscles are relaxed, pupils are widely dilated and respiratory arrest and cardiovascular collapse follow, leading to the patient's death.

Artusio (1954; 1955) systematically studied the attributes of Guedel's first (analgesic) stage of ether anaesthesia and subdivided it into three planes based upon differences in the level of amnesia and analgesia. In the first plane, the patient had no amnesia or analgesia. He was able to think, distinguish colours and focus his eyes. In the second plane, the patient had

complete amnesia and limited analgesia. He moved on painful stimulation and indicated that he was uncomfortable. In the third plane, the patient had total amnesia and analgesia, but was relaxed and responsive to commands. Reflex activity was minimal and no increase in cardiac irritability was observed.

No vomiting was seen in the transition from unconsciousness to consciousness. Artusio proposed that vomiting occurs primarily because of the action of irritant vapours, mucous or foreign bodies. He also observed that once the patient was anaesthetised past the delirium stage (stage 2) he could be brought back and forth between stage 3 and plane 3 of stage 1 without re-entering stage 2. He suggested that stage 2 does not exist as a separate entity but is related to fear of the first loss of consciousness.

The stages of ether anaesthesia, as defined by Guedel and others, were based on a series of respiratory patterns, eye signs and other clinical characteristics, which were specific for each stage. With small modifications they were also applied to other inhalational anaesthetics such as chloroform and cyclopropane. The principles described in Guedel's scheme set the standard for determining depth of anaesthesia and are still used with modern anaesthetic agents.

Woodbridge (1957) examined the wide range of effects that anaesthetic drugs had on the human body. He noticed that the state called "general anaesthesia" is actually a very complicated sequence of events, during which several functions of the nervous system are depressed:

- Block of afferent impulses (analgesia).
- Block of motor functions (relaxation).
- Reduction of autonomic reflexes (respiratory, circulatory and gastrointestinal reflexes).
- Mental block (sedation, sleep and unconsciousness).

These were called the *components of anaesthesia*. Different drug combinations could be used to achieve the desired effect. Woodbridge

included signs of insufficient depth of anaesthesia, but he made no other effort to define methods of evaluating those components.

Adequate depth of anaesthesia was thus described as a sufficient degree of blocking of each of these functions to prevent short or long term physical and psychological damage to the patient and to achieve suitable conditions for the surgeon and the anaesthetist to perform their duties.

A single potent anaesthetic like ether can provide all four aspects of anaesthesia. However, each of the drugs used in modern balanced anaesthesia, produces a certain amount of depression in one of these components. It also has several side effects, which are a complicating factor. For example, most opioid analgesics also have some hypnotic action and some hypnotics, when given in adequate doses, can produce muscle relaxation.

Pinsker (1986) described anaesthesia as a *broad descriptive term*, similar to the idea of "sickness", in that the underlying mechanism is not one but several. Sickness has been divided into separate components, each one of them treated with different drugs. In a similar way, Pinsker suggested that anaesthesia has three elements: paralysis, unconsciousness and attenuation of the stress response. Any drug or combination of drugs, that can produce these three components in a reversible controlled fashion, could be used as an anaesthetic.

The first of the three components, paralysis, is defined as "the absence of movement or skeletal muscle tone in the operative field". It can be achieved by neural blockade, muscle relaxants, head trauma and many centrally acting drugs.

Unconsciousness cannot be defined adequately. It includes amnesia and hypnosis, but because of the lack of an objective monitor, drugs affecting consciousness are administered without monitoring their effects on the brain. The only objective criterion is the absence of recall of the intraoperative events by the patient.

Attenuation of the stress response is also not well defined, because of limited knowledge of the nature of stress. As a result, only the components of the stress response that can be measured are purposefully controlled during general anaesthesia. There is no administration of anaesthetics based on hormonal or metabolic responses.

Pinsker states that analgesia is not necessary for anaesthesia. As long as the stress response is controlled, it does not matter what agents are used. The best anaesthesia for each individual patient can be achieved by considering the risks and benefits of each drug's contribution to the three components of anaesthesia.

In the same year, Jones and Konieczko considered anaesthesia to be a continuous spectrum. They classified the effects of increasing anaesthetic drug concentrations on the brain into four progressive stages:

Stage 1: Conscious awareness without amnesia.

Stage 2: Conscious awareness with amnesia.

Stage 3: Subconscious awareness with amnesia.

Stage 4: No awareness.

The first stage is termed by most anaesthetists *recall*. The patient remembers intraoperative events with or without prompting. In stages 2 and 3 the brain responds (immediately or at a later time) to verbal instructions or suggestions but without spontaneous recall. Stage 4 appears to be the "normal" state in the properly anaesthetised patient, but in practice, it might exist only in patients who have received very high anaesthetic doses.

Similar concepts are described in two editorials by Griffiths and Jones (1990) and by Jessop and Jones (1991). The authors claim that all available evidence suggests that anaesthetic drugs affect predominantly short term or working memory, although transfer into a recall from long term memory may also be impaired. They conclude that in order to be able to detect awareness, knowledge about the neurophysiological mechanisms of consciousness is required.

In contrast to the above, Prys-Roberts (1987) defined general anaesthesia as the drug-induced state which ensures the sensory suppression of noxious stimuli and thus the perception of pain. A synonym to anaesthesia is hypnosis as it implies a pharmacologically induced sleep. Anaesthesia is an *all-or-none phenomenon*, since loss of consciousness is a threshold event.

Analgesia, muscle relaxation and suppression of autonomic activity are discrete pharmacological effects which can be achieved independently by specific drugs and should be considered as desirable *supplements* to the state of anaesthesia, as a means to enable surgery to be performed and *not* as components of anaesthesia.

Prys-Roberts believes that depth of anaesthesia is hard to define because anaesthetists have approached the issue in terms of the pharmacological properties of the available drugs rather than the patient's needs during surgical procedures.

He defined noxious stimuli as mechanical, chemical, thermal or radiation factors causing potential or actual cell damage. Surgery produces a series of such stimuli during and after an operation.

Pain is the conscious perception of noxious stimuli. In addition to that, noxious stimulation induces a number of somatic and autonomic reflexes and evokes a metabolic and endocrine response well into the post-operative period.

Prys-Roberts introduced the concept of a *ranked order* of reflex responses to surgery. Suppression of perception and recall of pain can be achieved with relatively low concentrations of anaesthetics. Somatic motor responses require higher concentrations and breathing responses even higher.

Autonomic responses are classified into pseudomotor, haemodynamic and hormonal. Pseudomotor responses (sweating) are easily suppressed by low concentrations of anaesthetics. Haemodynamic responses occur even with concentrations high enough to preclude sensory, motor and breathing responses. Hormonal responses are the most difficult to suppress by general

anaesthetics. They can be partially suppressed by opioids and regional or beta-adrenoceptor blockade.

However, Prys-Roberts did not attempt to explain reported incidents of awareness, without any haemodynamic or autonomic signs, which contradict his model. He concluded stating that a reliable monitor of depth of anaesthesia which will *guarantee* lack of awareness is highly desirable. His approach to depth of anaesthesia, which emphasises the type of noxious stimuli and the specific category of drugs that abolishes that response, is the concept most commonly used in current clinical practice.

2.3 THE INTRODUCTION OF MUSCLE RELAXATION

In 1942, Griffith and Johnson introduced small doses of the muscle relaxant *d*-tubocurarine (an alkaloid produced from a South American plant) for use during surgical procedures. Its properties had been known since it was brought to Europe by Sir Walter Raleigh in 1584. Claude Bernard, physiologist and novelist, studied its properties and described the effects on the conscious patient with great accuracy (Blacher, 1975; Payne, 1994). He concluded as follows:

> *"Can you imagine a more dreadful agony than that of a mind conscious of the loss of control over those organs designed to serve it and finding itself fully alive entombed in a corpse?"*

Curare had already been used to treat spasticity and modify convulsions induced during psychotherapy of depression. Cullen and Papper had already experimented with the new drug, but regarded its effects to be too intruding to be used in the anaesthetic practice of those days. It is not known what motivated Griffith to inject the new drug without prior experimentation during an operation under cyclopropane anaesthesia.

The subsequent generalised use of curare had extensive consequences. As a result of muscle paralysis, respiration was assisted when necessary.

Tracheal intubation became every day practice, followed by further studies on the physiology of the respiratory system, the development of mechanical ventilators (Frumin, 1957) and the introduction of recovery rooms.

Fully controlled ventilation soon became widely available allowing larger doses of curare. Anaesthetists realised that they could combine high concentrations of muscle relaxants and artificial ventilation with low doses of anaesthetics to reduce the risk of cardiovascular and respiratory depression, caused by the toxicity of the anaesthetic drugs, and improve the speed of recovery.

However, the use of muscle relaxation abolished the two most valuable indicators of depth of anaesthesia: respiratory rate and volume, and movement to surgical stimulation. As a result, Guedel's scheme could no longer be used to assess the level of anaesthesia. This was even more pronounced with the introduction of *balanced anaesthesia*, a term proposed by J.S. Lundy (1926) to describe the use of short-acting intravenous barbiturates in conjunction with general or regional anaesthesia, where a combination of analgesics, hypnotics and muscle relaxants was used.

An editorial in Lancet (1945) discussed the problems associated with the use of muscle relaxants in anaesthesia. The author stressed the fact that traditional signs of anaesthesia are of little value in curarised patients and the anaesthetist must ensure unconsciousness or "the worst imaginings of the novelist may come true".

2.4 Awareness During Surgery: Its Detection And Incidence

Although anticipated nearly a century earlier, reports of unnoticed patient awareness during surgical operations soon began to appear in the literature. Winterbottom (1950) was the first anaesthetist who described the case of a female patient who was aware during abdominal surgery. She was paralysed and ventilated with a mixture of oxygen and nitrous oxide. Small doses of

thiopentone were given throughout the operation. This technique was very common at that time. However, after the operation, the patient complained of waking up during the operation and feeling an excruciating pain in her abdomen. She wanted to indicate her suffering, but she was unable to move. Winterbottom's letter caused a great controversy (Apperly, 1950; Coplans, 1950; Dawkins, 1950; Durrans, 1950; Goldman, 1950; Gray, 1950; Phillips, 1950; Russell, 1950; Wells, 1950; Wilson, 1950), with scientists suggesting other regimens that would provide more effective general anaesthesia, but it was soon followed by new accounts of patient awareness during surgery.

In 1951, Mushin reported another case of a middle-aged female patient who expressed her strong disapproval of the anaesthetist's comments during her operation. Apparently, she had been conscious but unable to communicate. Mushin "was inclined to believe that this occurrence is more common than we think". He also noted that "with the present-day large doses of relaxants, little objective evidence is available for the anaesthetist to determine the presence or absence of unconsciousness".

Since then, a large number of case reports has been published and the importance of the problem became fully recognised (Alment, 1959; Rosen, 1959; Anon. 1962; Bookallil, 1967; Bahl and Wadwa, 1968; Gillis, 1968; Ayre, 1969; Russell, 1969; Sia, 1969; Smith and McNeil, 1969; Alexander, 1971; Shackleton, 1974; Tantisira and McKenzie, 1974; Archer, 1976; Messer, 1976; Michael, 1976; Silbergleit, 1976; Cundy, 1978; Hutter and Tomlin, 1978; Baraka and Muallem, 1979; Russell, 1979; Guerra, 1980; Hill, 1980; Mummaneni *et al,* 1980; Hilgenberg, 1981; Mark and Greenberg, 1983; Lamberty and Lerman, 1984; MacLeod, 1984; Macmillan and Breeze, 1985; Evans, 1987b; Puri *et al,* 1987).

Such reports still occur in the literature (Brahams, 1989; Rupreht, 1989; Brahams, 1990; Henshaw, 1990; Slinger *et al,* 1990; Brahams, 1992; Kelly and Roy, 1992; McCrirrick *et al,* 1992; Beards, 1993). Sometimes, cases of

alleged awareness are resolved easily when followed up by an anaesthetist not previously involved in the patient's care (Hough and van Hasselt, 1993).

In the vast majority of cases of intraoperative awareness, the patient was paralysed and ventilated. However, there are rare reports of patients who were aware although breathing spontaneously (Ruben, 1953; Graff and Phillips, 1959; Saucier *et al,* 1983). It must be noted that some muscle relaxant (probably *d*-tubocurarine), in the first case, and relatively low doses of succinylcholine, in the last two cases, were used (500 mg over a period of three hours and 120 mg for intubation, respectively). This might have affected the patients' responses. There is no report of intraoperative awareness of patients who received no muscle relaxation at all.

In an editorial in the *British Journal of Anaesthesia* (1979) an anonymous, medically-qualified lady outlined her own experience of awareness during caesarean section under general anaesthesia. She described the unimaginable torture that she suffered, how she was "lying there intubated, covered in green towels, my abdomen split open, strange people delving inside me, blood, swabs on the rack, etc. ... The closest parallel I can think of is of being in a coffin, having been buried alive. ... If you imagine the effect of a too hot pan moved from the cooker on to a plastic surface, then that is what that pain was doing to my non-existent body. Searing, melting, pressing me into the table, with the nasty reminder of a dentist's drill".

Similar descriptions can often be found in the medical press (Anon. 1980a; Evans, 1987a; Brahams, 1990; Grunshaw, 1990; Brahams, 1992; Moerman *et al,* 1993). Most of these patients considered the event to be the worst experience of their life, especially those who suffered pain.

Four decades of editorials dealt with patient awareness during surgery and emphasised all aspects of the problem. Nearly all of them concluded that an objective monitor of depth of anaesthesia is highly desirable, but not yet available (Anon. 1959; Anon. 1961; Cobb, 1961; Anon. 1967; Anon. 1968; Anon. 1969; Lowenstein, 1971; Anon. 1973; Anon. 1974b; Anon. 1976;

Anon. 1978; Lunn, 1978; Anon. 1980b; Saunders, 1981; Wilson, 1982; Anon. 1986; Jones and Konieczko, 1986; Crawford, 1988; Plourde, 1991; Brighouse and Norman, 1992; Cormack, 1993; Newton, 1993).

2.4.1 Spontaneous recall

Recall is defined as the retention in memory and recollection (either spontaneous or prompted) of an event that took place under general anaesthesia. *Awareness* is defined as the responsiveness to auditory stimuli without recall of the stimulus (Desiderio and Thorne, 1990). Wilson and colleagues (1975) defined awareness as "the ability of a patient to recall, with or without prompting, any event during anaesthesia". They used the term "wakefulness" instead of "awareness" (which is taken as equivalent to "recall") but this terminology may create some confusion (Ghoneim and Block, 1990).

Breckenridge and colleagues (1983) defined a number of related concepts:

- *Dreaming* is "a train of thoughts or images passing through the mind which the patient believed occurred between induction of anaesthesia and return to consciousness".
- *Hallucinations* are "apparent perceptions, visual, auditory or tactile, of non-existent objects or stimuli".
- A further state of awareness which could be described as *unconscious recall*.

These terms are sometimes interchanged in the literature. Certain authors define hallucinations as distorted perception of *real* events and use the term "illusions" for entirely fictional ones (Hanning and Aitkenhead, 1994). The American Psychiatric Association defines illusions as misinterpretations of *real*, external sensory experiences and hallucinations as *false* sensory perceptions in the absence of external sensory experiences.

Dreams are usually not related to the operation. Nevertheless, their frequency was found to be higher in patients who received light anaesthesia

(Harris *et al,* 1971) or certain drugs, like ketamine (Krestow, 1974). Hallucinations are usually caused by specific drugs with psychotropic action. Some patients attribute memories of events to the intraoperative period, although the actual events occurred immediately after the operation. Obviously, it is crucial to differentiate between true recall and dreams or hallucinations.

In prospective studies, various auditory stimuli (words, noises, music, etc.) are presented during surgery. In retrospective studies, the investigators rely on the patient recalling intraoperative events. In both cases, the preferred method of assessing recall is the *structured interview*. When the patients recover consciousness, they are asked questions like:

> *"What is the last thing you remember before going off to sleep?"*
>
> *"What is the first thing you remember after your operation?"*
>
> *"Do you remember anything in between?"*

However, it must be noted that this method is not the most sensitive one (Goldmann, 1988; Millar, 1989). Several drugs used routinely for premedication and/or anaesthesia have a strong amnesic effect. Patients who appear awake and responsive may have no subsequent recollection of events (Lambrechts and Parkhouse, 1961).

Major literature reviews (Mainzer, Jr. 1979; Breckenridge and Aitkenhead, 1983; Jones, 1994) have cited a 1 to 2 percent incidence of intraoperative awareness with recall in the general population during anaesthesia.

2.4.1.1 Awareness with recall in the general population

Ruben (1953) studied 40 patients anaesthetised only with N_2O and muscle relaxant. He found 1 patient (2.5%) who thought that he could remember part of the operation. It is interesting to note that this patient was breathing spontaneously for most of the time but he showed no response to surgery.

His blood pressure and heart rate remained unchanged throughout the procedure. This was observed in all subjects, even when they were moving to painful stimulation.

Frumin (1957) reported 9 cases of awareness with recall in a total of 171 operations (5.3%). Three of those patients experienced pain (1.8%).

Rosen (1959) studied 58 patients anaesthetised with N_2O. He failed to find a range of N_2O concentrations that would *ensure* anaesthesia. Twenty-nine patients could perform simple tasks during the investigation, but almost half of them (25% of the total) had total amnesia for the proceedings as a whole.

In a prospective study of 656 patients, Hutchinson (1960) reported 8 cases of awareness. From those patients, 417 were paralysed and 239 were breathing spontaneously. All patients that had been aware, had been given oxygen, N_2O and muscle relaxants (incidence of 1.9%). Three of those patients (0.7%) experienced pain. No spontaneously breathing patient had any memory of intraoperative events.

McIntyre (1966) presented a tape-recorded story during the operation, but found no recall of it when his patients were questioned in a postoperative interview.

Faithfull (1969) reported 5 cases of awareness in a total of 1328 operations (0.38%). In a subgroup of 133 patients, receiving N_2O and muscle relaxant, the incidence of awareness was 2.3%. The rest of the patients received thiopentone, N_2O and halothane or only thiopentone.

Powell and Gingrich (1969) anaesthetised 19 patients at an altitude of 1.6 km above sea level. All patients were anaesthetised with 70% N_2O and muscle relaxant and hyperventilated. No other anaesthetic agents were used. They found 1 patient who could remember parts of the operation.

Terrell and colleagues (1969) were unable to find any recall in a group of 37 patients (12 of them served as controls) either during a postoperative interview or under hypnosis. The authors ruled out the possibility that

patients under surgical anaesthesia can hear and later recall sounds presented to them intraoperatively.

Brice and colleagues (1970) used light N_2O anaesthesia without narcotic premedication or analgesic supplements to investigate the incidence of awareness and dreaming in 57 patients. One patient reported that he was conscious and in pain during an interview immediately after the operation, but did not repeat his description when interviewed later in the ward. Dreaming was reported in 25 patients (43.8%).

Wilson and colleagues (1970) attempted to perform the same type of study, using volunteers. They found no evidence of recall or dreams during anaesthesia.

Harris and colleagues (1971) studied the effect of morphine premedication and the addition of two volatile agents on dreaming during general anaesthesia. In a total of 120 patients divided into four groups, they found no cases of awareness, but the incidence of dreaming was significantly higher (57%) in the group that was anaesthetised only with N_2O, compared to morphine premedication (23%), 0.3% to 0.5% halothane (0%) and 0.1% to 0.3% methoxyflurane (23%).

Garfield and colleagues (1972) found 3 cases of awareness and 8 of dreaming in a total of 24 patients anaesthetised with ketamine, but none in 24 patients anaesthetised with halothane. In a prospective study, Scott (1972) failed to confirm the occurrence of recall of intraoperative events.

Browne and Catton (1973a) reported that 3 patients (in a total of 56) anaesthetised with N_2O had some recall of the music played during the operation. Dreaming occurred in 4 patients. No awareness or dreaming was reported in a second group of 56 patients anaesthetised with Innovar (fentanyl-droperidol). The authors noted that "in spite of the appearance of muscle movement and signs of light anaesthesia, the incidence of awareness in these patients is very small". They concluded that there is "no

practical means of measuring depth of anaesthesia when relaxants are used".

The same authors (Browne and Catton, 1973b) studied 120 patients. Anaesthesia was induced with thiopentone and fentanyl-droperidol and maintained by 60% N_2O. Two patients had recall (1.7%) and another 2 experienced dreams during the surgical procedure. The remainder could not recall anything at all, although 37 patients (30.8%) moved arms, legs or head or had other signs of light anaesthesia.

In a study of awareness in 202 children, McKie and Thorp (1973) found dreams in 12 (5.9%) and awareness in 10 (5%) cases. Vaughan and Stephen (1974) used ketamine and N_2O in 174 patients for major surgery. They found no recall, but 13 of their patients experienced dreams or hallucinations. However, only 1 of those patients had dreams during surgery.

Eisenberg and colleagues (1974) reported no recall of surgery in a group of 60 patients anaesthetised with diazepam and morphine. Nine patients (15%) reported dreaming. In a prospective study of 490 patients, Wilson and colleagues (1975) found awareness in 4 cases (0.8%), dreams in 38 patients (7.8%) and hallucinations in 12 (2.4%).

Eisele and colleagues (1976) used galvanic skin responses to determine a light plane of anaesthesia, at which time they believed that sensory input might be perceived. At that time their patients were given a sound stimulus. However, none of the 50 patients, who were studied, could recall it during a postoperative interview.

During a study of 48 patients designed to test the presence or absence of implicit memory, Dubovsky and Trustman (1976), found 1 patient (belonging to a sub-group of 12 obstetric cases) who was aware during her operation.

In a prospective study of 138 patients anaesthetised with N_2O and neuromuscular blockade, Agarwal and Sikh (1977) failed to demonstrate any evidence of awareness during surgery. No data regarding dreams were collected.

Utting and colleagues (1979) reviewed the records of the anaesthetic accidents reported to the Medical Defence Union during the eight years from 1970 to 1977. They found 11 cases of awareness in a total of 602 accidents.
Cormack (1979) reported 2 cases of awareness in a total of 1000 operations. He used a new test, the "Time to Correct Response" (TCR), in order to identify patients who were potentially aware during their operation. After antagonising the relaxant, nitrous oxide is turned off and the lungs are ventilated with oxygen. The patient is asked to open their mouth every 15 seconds until a response is obtained. If the time to obtain this response is less than 30 seconds, then the patient might have been aware during the final stages of the operation.
Heneghan and colleagues (1981) reported 1 patient who was aware in a group of 40 patients undergoing dental surgery under general anaesthesia.
Purdell-Lewis and colleagues (1981) found 8.1% incidence of dreaming and 1% of awareness in 99 patients anaesthetised with N_2O and fentanyl. Half of the patients were exposed to music throughout the operation. None definitely remembered it, but 4 of them (7.5%) thought they heard music.
Clifton (1984) interviewed 100 patients postoperatively. He found 1 patient who thought that she was "vaguely aware" and 5 patients who had dreams during their operations. Six patients said that their main preoperative worry was about awareness during their operation.
In a letter to the editor of *Anesthesia and Analgesia*, Russell (1985) reported that 11 patients anaesthetised with thiopentone, fentanyl and N_2O moved to command (using a modification of the Isolated Forearm Technique). Despite that, only 1 patient had factual recall and another 5 had dreams. The author studied only 25 patients. He found so many aware and responsive patients that he felt obliged to terminate the investigation on moral and ethical grounds.
In two similar prospective studies, a group from Liverpool (Hobbs *et al,* 1988; O'Sullivan *et al,* 1988) found dreams in 23 of 120 (19.2%) and 14 of 144

(9.7%) paediatric patients, respectively. No awareness was reported. The authors found statistically significant differences in the incidence of dreaming between subgroups treated with different muscle relaxation techniques. They speculated that increased muscle spindle discharge associated with depolarising muscle relaxants may cause cerebral arousal and increased incidence of dreaming.

In a large prospective study of 5926 general anaesthetics, Pedersen and Johansen (1989) found 8 cases of awareness with recall (0.14%). This relatively low incidence was attributed to the fact that only patients, who spontaneously reported that they were aware during anaesthesia, were included in the study. It was suggested (Jelicic and Bonke, 1989) that if they had used a structured interview, they would have found more cases of intraoperative awareness.

McCleane and Cooper (1990) found no cases of awareness in 207 dental patients using a structured interview.

Desiderio and Thorne (1990) studied 11 female patients anaesthetised with midazolam and alfentanil. They reported no cases of awareness or dreams. However, the small number of subjects, that participated in the study, does not allow any definitive conclusions.

Liu and colleagues (1991) interviewed 1000 patients after their operation and asked specific questions about awareness and dreams. Three hundred and sixteen of those patients were breathing spontaneously throughout the procedure, 92 received suxamethonium only for intubation and 592 were paralysed and ventilated. Only 2 patients (0.2%) could recall events after the induction of anaesthesia, but before the start of surgery. Both of them were paralysed during their period of awareness. A further 9 patients (0.9%) had dreams during their operation.

Sandin and Norstrom (1993) were able to identify 5 cases of awareness with recall in approximately 2500 patients anaesthetised with propofol and

alfentanil or fentanyl. They concluded that all cases were caused by lack of experience and could have been prevented.

2.4.1.2 Awareness with recall in high risk groups

In some clinical situations, the amount of anaesthetic drug given to the patient is minimal. This is done deliberately in order to protect the patient from the depressant side effects that most general anaesthetics have on the cardiorespiratory system. Obviously, the likelihood of intraoperative awareness and recall is much higher than that in the general population.

Awareness is probably most common during caesarean sections under general anaesthesia. Until birth, the mother is given as little general anaesthetic as possible to avoid depressing the baby. A large number of studies investigated the effects of various anaesthetic regimens on the condition of the foetus (Crawford, 1962; Johnstone and Breen, 1966; Bergstrom and Bernstein, 1968; Turner and Wilson, 1969; Moir, 1970; Galbert and Gardner, 1972; Crawford *et al,* 1973; Coleman and Downing, 1975; Famewo, 1976; Barr *et al,* 1977; Farnsworth, 1978; Kristoffersen, 1979; Haram *et al,* 1981; Dich-Nielsen and Holasek, 1982; Morgan *et al,* 1983; Abboud *et al,* 1985; Blogg *et al,* 1986; Dann *et al,* 1987; Baraka *et al,* 1989; Bogod *et al,* 1990; King *et al,* 1993; Krissel *et al,* 1994; McCrirrick *et al,* 1994). Many different drug combinations were recommended. The incidence of awareness depended on the particular anaesthetic method used. A study by Lyons and Macdonald (1991) is particularly important because it showed a dramatic reduction in the incidence of awareness (from 1.3% to 0.4%) when 1% isoflurane (0.8 MAC) replaced 0.5% halothane (0.6 MAC). Clearly, the increase of anaesthetic depth produced by the additional 0.2 MAC of volatile agent was adequate to ensure unconsciousness in the vast majority of operations and reduced awareness three-fold.

Other high risk procedures include bronchoscopy (Barr and Wong, 1973; Duncan and Barr, 1973; Hewitt and Barr, 1978; Hinds *et al,* 1978; Moore and Seymour, 1987; Thomas, 1988), difficult intubation (Davies, 1963; Khawaja,

1971; McKenna and Wilton, 1973; Dunnett, 1977), major trauma (Bogetz and Katz, 1984), cardiac operations (Mendelsohn *et al,* 1960; Maunuksela, 1977; Kim, 1978; Quintin *et al,* 1981; Hickey *et al,* 1992; Phillips *et al,* 1993) and patients in intensive care (Nicoll, 1974).

Sometimes, patients are deliberately kept conscious during part of their operation. This allows the surgeons to assess the condition of the central or peripheral nervous system and prevent permanent damage due to pressure or trauma. Those procedures include Harrington rod instrumentation (Sudhir *et al,* 1976), neurosurgery (Weiss and Schwartz, 1993) and carotid endarterectomy (Benjamin *et al,* 1993).

2.4.2 Conscious awareness with amnesia

Tunstall (1977) described the *isolated forearm technique* (IFT), which allows a lightly anaesthetised patient to respond to commands intraoperatively. This will be examined in detail in the next chapter.

2.4.3 Subconscious awareness with amnesia

This phenomenon was first demonstrated by Levinson (1965). In his classic study (which would be considered unethical with today's standards), he exposed ten patients to an intraoperative "crisis", with the anaesthetist saying that cyanosis was present and then treating it properly. The patients were anaesthetised with thiopentone, nitrous oxide, oxygen and ether. One month after the operation, the patients were hypnotised and regressed to the actual operation. Four of them were able to repeat almost exactly the words of the anaesthetist, four others remembered hearing something and only two denied hearing anything at all. All of the patients displayed marked anxiety during the hypnotic session. However, none of them could consciously recall any of the intraoperative events. An interesting observation is that the EEG recording indicated a marked response to the "crisis" and returned to normal only several minutes after the operation was resumed.

There have been other reports of recall under hypnosis, but they are restricted to intraoperative events or words which cause a great anxiety and concern to patients (Cheek, 1959; Pearson, 1961; Cheek, 1962a; Cheek, 1962b; Cheek, 1964; Cheek, 1965; Goldmann *et al,* 1987). Negative results have also been published (Terrell *et al,* 1969), as well as literature reviews (Trustman *et al,* 1977), with the recommendation for better controlled studies. Blacher (1984) attempted to duplicate Levinson's experiment using hypnosis to recover a noxious verbal stimulus presented to a patient undergoing major surgery. He reported similar findings but found it too inhumane to continue with more patients. When he tried to repeat the experiment with benign stimuli, he was unsuccessful. He speculated that "patients register stimuli only when they have a profound significance".

Sometimes, it may be easier for the brain to recognise previously acquired knowledge ("cued" recall and recognition) than recall intraoperative events explicitly. There is some evidence to support this theory (Millar and Watkinson, 1983; Stolzy *et al,* 1986; Standen *et al,* 1987; Wilson and Spiegelhalter, 1987; Jelicic *et al,* 1990; Block *et al,* 1991a; Bethune *et al,* 1992). However, there have been several other studies that proved negative (Dubovsky and Trustman, 1976; Eich *et al,* 1985; Stolzy *et al,* 1987; Cork *et al,* 1992).

Another means of detecting unconscious perception is by studying behavioural changes that occur because of positive suggestions presented verbally to the patient during anaesthesia. Two variations of this method have been described. In the first one, the suggestions regard the quality of postoperative recovery. Several investigators (Pearson, 1961; Bonke *et al,* 1986; Evans and Richardson, 1988; McLintock *et al,* 1990) found that postoperative analgesic requirements and time to discharge were both reduced significantly. Negative findings have also been reported (Abramson *et al,* 1966; Woo *et al,* 1987; Boeke *et al,* 1988; Block *et al,* 1991b; Liu *et al,* 1992). In the second variation, the patients were given suggestions for faster

recovery, but they were also instructed to touch a particular part of their body during a postoperative interview (Bennett *et al,* 1985; Goldmann *et al,* 1987; Block *et al,* 1991a). Other authors have failed to replicate those results (Eich *et al,* 1985; Jansen *et al,* 1990; Bethune *et al,* 1992). Most of those studies were shown (Bonke and Rupreht, 1986; Wilson and Spiegelhalter, 1986; Millar, 1987; Wilson and Spiegelhalter, 1987) to have serious methodological problems and ambiguous results.

In summary, the phenomenon of unconscious perception during general anaesthesia requires further investigation. Its clinical significance remains dubious and there is no indication that it should be prevented. Evidence on memory formation and information processing under general anaesthesia has been reviewed extensively (Cherkin and Harroun, 1971; Goldmann, 1988). In an excellent paper, Keith Millar (1989) analysed recent research into memory during anaesthesia and examined other aspects of the problem which are beyond the scope of this thesis.

2.4.4 Causes of awareness with recall

By definition, the fundamental reason of awareness during surgical operations is *inadequate anaesthesia* (Scott, 1991; Anderson, 1992; Payne, 1994). It is caused by the administration of insufficient drug doses, incorrect combinations of anaesthetic agents or by a technical failure (Baraka and Muallem, 1979; Lamberty and Lerman, 1984; Puri *et al,* 1987; Slinger *et al,* 1990; McCrirrick *et al,* 1992; Beards, 1993) in the delivery of those drugs. Sometimes a combination of all or some of those is responsible.

Waters (1968) examined several factors that can lead to awareness. The main cause during induction is the use of very short-acting intravenous agents. Their effect may diminish before achieving adequate concentrations of volatile agents. During maintenance, there can be problems with the ventilator or the anaesthetic machine, which may lead to awareness. Modern

anaesthetic equipment and the routine use of end-tidal gas analysers should eradicate this type of problems.

Lintin (1990) stressed that awareness during surgery was caused by "dogmatic adherence to techniques that have little basis in physiological or pharmacokinetic principle". Scott (1991) agreed that "rigid protocols" have no place in modern anaesthesia.

Sandin and Norstrom (1993) cited lack of experience as the main reason for intraoperative awareness.

2.4.5 Consequences of awareness with recall

Any patient who can remember part of their operation, has suffered considerably, especially if pain was also present. Some patients feel degraded or humiliated by this experience. Their confidence and trust in the anaesthetist, who conducted the anaesthetic, is damaged. Disbelief by relatives or nursing staff can cause further problems.

There is some evidence that intraoperative awareness with subsequent amnesia may lead to postoperative psychosis. Blacher (1975) described a syndrome of traumatic neurosis, which included generalised anxiety and irritability, insomnia, repetitive nightmares, depression and a preoccupation with death. In addition, there may be a morbid fear of hospitals, of doctors and of the need for future surgery. Some authors were sceptical and suggested that a broader explanation should be given (Larson, 1976). For example, some of Blacher's patients could have described experiences during the preoperative period or during emergence from anaesthesia. Others supported Blacher's description (Cundy, 1978; Tunstall, 1980b; Tunstall and Lowit, 1982; Moerman *et al,* 1993).

This syndrome may last for several months or, even, years. The most effective treatment is a reasonable, accurate explanation of what had happened (Cundy, 1978). Patients, who are treated sympathetically or have an adequate background to understand what happened to them, usually

recover promptly. However, psychiatric consultation might be necessary (Guerra, 1980; Cundy, 1992).

There are no data on pathophysiological changes because of intraoperative awareness. However, one can extrapolate from studies regarding the effect of endotracheal intubation or surgery (Fox *et al*, 1977; Gelman *et al,* 1984; Achola *et al,* 1988; Anand *et al,* 1988) and expect that significant haemodynamic, hormonal and metabolic responses might be elicited. Those responses could extend well into the postoperative period but specially designed studies are required to confirm this.

Legal action may be taken against the anaesthetist or the hospital. Every year, a number of compensation claims for alleged awareness are made (Brahams, 1989; Brahams, 1990; Brahams, 1992; Payne, 1994). Most of those cases are settled before they reach the courts. However, some attract significant publicity which may be devastating for the anaesthetist involved (Henshaw, 1990).

This publicity has raised the awareness of medical and nursing staff about the existence of the problem, but has caused undue anxiety to patients who are about to undergo surgery (Clifton, 1984; McCleane and Cooper, 1990). Preoperative reassurance is essential, provided that the potential anxieties of each individual patient are discussed and that no new anxieties are introduced.

2.4.6 Prevention of spontaneous recall

The most obvious way to reduce the incidence of awareness is to increase the concentration of the anaesthetic agent (Ayre, 1969; Barron, 1974; O'Sullivan, 1988; Guise, 1989; Robinson and Calder, 1989; Lintin, 1990; Matthews *et al,* 1991; Bennett, 1992; Cox, 1992; Tasch, 1992). Several guidelines have been published (Lunn and Rosen, 1990). The correct preparation of thiopentone was underlined (MacLeod, 1984) and it was

proposed that nitrous oxide should be supplemented with another potent inhalational agent (Waldron, 1971).

In caesarean sections, the use of the Isolated Forearm Technique or of a technique with rapid anaesthetic uptake and a "plateau" level of 0.8 MAC (Tunstall and Hawksworth, 1981) may be beneficial. A dramatic reduction in the incidence of awareness was found when 1% isoflurane replaced 0.5% halothane (Lyons and Macdonald, 1991).

The use of amnesic drugs has been advocated. However, their long-term effects are not clear. The cynical might add that all we need to do is wipe out patients' memories of the operation without giving them any anaesthetic at all. Obviously, this should not be the case.

The use of epidural nerve block for caesarean sections was proposed twenty five years ago (Steel, 1969) and has become a routine practice for procedures of this type.

Partial isolation of the patient from auditory stimuli (McIntyre, 1969) by using ear plugs (Hill, 1980), music or "white noise" (Grant *et al,* 1979; Moore and Seymour, 1987) has been proposed. There are strong arguments against that practice, since it is believed that it could contribute to the patient's feeling of isolation and make things worse (Guerra, 1980). In any case, conversation about prognosis or other emotionally disturbing topics should be avoided or, at least, be optimistic (Cherkin and Harroun, 1971; Anon. 1974a; Eisele *et al,* 1976; Grunshaw, 1990).

Personality (Guerra, 1980) and other patient characteristics like nervous type (Anon. 1974a), metabolic state (Simpson, 1974), or reason for surgery and emotional response to illness (Guerra, 1980), should be taken into account.

Whenever possible, general anaesthesia should be preceded by an assessment of the patient and direct questioning as to whether awareness has been experienced previously (Macmillan and Breeze, 1985).

The use of pharmacokinetic and pharmacodynamic principles can simplify the administration of anaesthetics, especially when using total intravenous

anaesthesia (TIVA), and ensure that drug concentrations in patient's blood are adequate (Glass, 1993).

Talking to the patients or theatre staff and reassuring them that no signs of awareness can be found (Stanley, 1989) is a simple form of defensive practice. It might protect the anaesthetist from accusations of negligence but it does not address the problem and will not provide much comfort to a patient who is aware of the operation.

Use of minimum doses of muscle relaxants (Jobes, 1976) may allow the patient to indicate that they are not fully anaesthetised. However, this may not always be possible. Some cases of awareness occurred, although the patient had received very low doses of muscle relaxant drugs.

A preoperative check of equipment (Guerra, 1980) can prevent awareness due to the malfunction of ventilators or anaesthetic machines. So can monitoring of inspired and expired gases (Slinger *et al,* 1990) and meticulous attention to the details (Agarwal and Sikh, 1977; Guerra, 1980) during the anaesthetic.

Some anaesthetists routinely warn patients prior to surgery that they might be aware during their operation (Coodley, 1976). However, others (Archer, 1976; Blacher, 1976) disagreed, because they believed that this could add too much anxiety to an already stressed patient.

2.4.7 What should the patient be told?

In an editorial in *Anaesthesia*, Aitkenhead (1990) examined the very sensitive issue of what the patient who experienced intraoperative awareness should be told. There is a need to educate nursing and medical staff in other disciplines so that the anaesthetist is informed if a complaint is made. The anaesthetist should routinely visit all patients postoperatively and discuss with them any complaint they might have. In case of suspected awareness, direct and indirect questioning may help ascertain that the patient was actually dreaming. However, if the patient was not dreaming and

the experience cannot be attributed to the immediate postoperative period, the anaesthetist should explain that awareness can occur without fault or negligence, apologise and try to reduce the patient's fears about awareness during subsequent operations.

A reasonable, accurate explanation of what has happened might act as a most effective treatment and legal action against the anaesthetist may be avoided.

2.5 SUMMARY

Despite 150 years of continuous progress in modern anaesthesia, the phenomenon of awareness and recall of intraoperative events remains a rare but very disturbing complication. It is caused by inadequate doses of anaesthetics and may have serious consequences for both the patient and the anaesthetist. Several preventive measures have been proposed, but none of them has eradicated the problem.

An objective monitor of depth of anaesthesia would be extremely useful in that respect. Unfortunately, no such device is yet available.

3. MEASURING DEPTH OF ANAESTHESIA

3.1 INTRODUCTION

One of the central questions in modern anaesthetic practice is the determination of the level of anaesthesia. As mentioned in the previous chapter, Guedel (1937) described the stages of ether anaesthesia according to a well-defined set of clinical signs including respiration, movement and eye reflexes. However, the introduction of muscle relaxation revolutionised many aspects of modern anaesthesia and rendered Guedel's scheme almost unusable. As a result, intraoperative awareness became a very real "complication" of general anaesthesia and provided the impetus for the development of a monitor of anaesthetic depth.

Any such monitor should provide a reliable and accurate measure of anaesthetic depth, preferably in the form of a single numerical index. The ideal index should have the following properties:

- There should be a similar value for different anaesthetic agents at equipotent doses.
- The values at induction of anaesthesia should be consistent with those measured at recovery.
- It should provide reliable, reproducible, unambiguous results easily interpreted by ordinary clinicians.
- It should respond appropriately to alterations in the level of stimulation.
- It should not be affected by hypotensive, vasoactive or other non-anaesthetic drugs commonly used in anaesthesia.

There have been numerous attempts to develop a method that would fulfil all these requirements based on both clinical and instrumental approaches.

3.2 PHARMACOLOGICAL PRINCIPLES

The essence of determining depth of anaesthesia is measuring the effect of anaesthetic drugs. Pharmacological concepts govern the relationship between drug dose and effect. *Pharmacokinetics* describe the way the drug interacts with the body through distribution and elimination. The concentration of the drug at the site of action is also determined by these principles. *Pharmacodynamics* describe the pharmacological effect of the drug. For every drug, the *dose-response curve* is defined by a combination of pharmacokinetic and pharmacodynamic elements. Measurement of depth of anaesthesia is ultimately a pharmacodynamic quantification.

Figure 3.1 represents the relationship between time, drug concentration and drug effect. When the drug is administered at a high rate, the plasma concentration reaches a maximum very quickly. The effect of the drug lags behind the concentration by a certain amount of time. This *disequilibrium* (or *hysteresis*) can be seen clearly in Figure 3.1C as the difference between the top (decreasing concentration) and bottom (increasing concentration) curves. When the drug is administered at a low rate, the plasma concentration and the drug effect reach their maximum over a longer period of time, but there is very little time difference between them. This results in the typical sigmoid curve C.

The hysteresis during rapid drug administration is a result of the concentration difference between blood and the site of action. When the drug is administered slowly, these two concentrations are allowed enough time to achieve minimum difference.

In order to separate the pharmacokinetic and pharmacodynamic components of the dose-response curve, pharmacokinetic equilibrium must be achieved. When plasma concentrations of the anaesthetic drug are constant, the pharmacokinetic component is effectively taken out of the equation. An appropriate stimulus can then be applied and the time of response measured. From that time of response, a probability curve can be

constructed using suitable mathematical methods (logistic regression, logit or probit analysis).

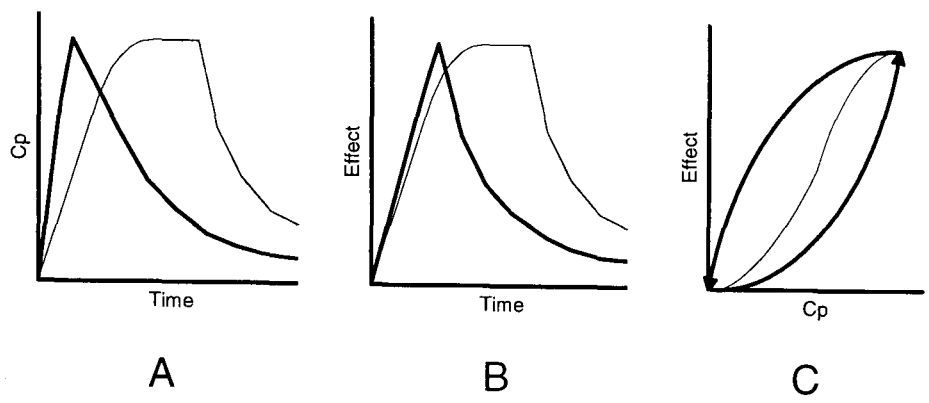

Figure 3.1 The effect of rapid (thick line) or slow (fine line) administration of an anaesthetic agent on the relationship between (A) time and plasma concentration (Cp), (B) time and effect, and (C) plasma concentration and effect (modified from Stanski, 1990).

Detailed discussion of the theory related to pharmacokinetic modelling, study design and characterisation of pharmacodynamic performance, is beyond the scope of this thesis. An excellent review by Stanski (1990) can be used as an introduction to these principles. Other contributors in Miller's *Anesthesia* (1990) provided a scholarly analysis of basic scientific principles regarding, among others, mechanisms of action, and uptake, distribution and elimination of anaesthetic drugs.

3.3 CLINICAL SIGNS

At the present times, monitoring of clinical signs is the only routine method of determining depth of anaesthesia. When no muscle relaxants are used, skeletal muscle response to surgical stimulation, and frequency and depth of respiration reflect accurately the depth of anaesthesia. If "adequate anaesthesia" is schematically illustrated as a range of acceptable responses, then its upper limit (i.e. insufficient anaesthesia) is determined by movement to surgical stimuli and the lower limit (i.e. excessive anaesthesia) by respiratory depression (Figure 3.2).

Figure 3.2 Signs relating to depth of anaesthesia in a spontaneously breathing patient.

If the patient is ventilated but not paralysed, the upper limit remains the same but the lower limit is now determined by circulatory depression (Figure 3.3).

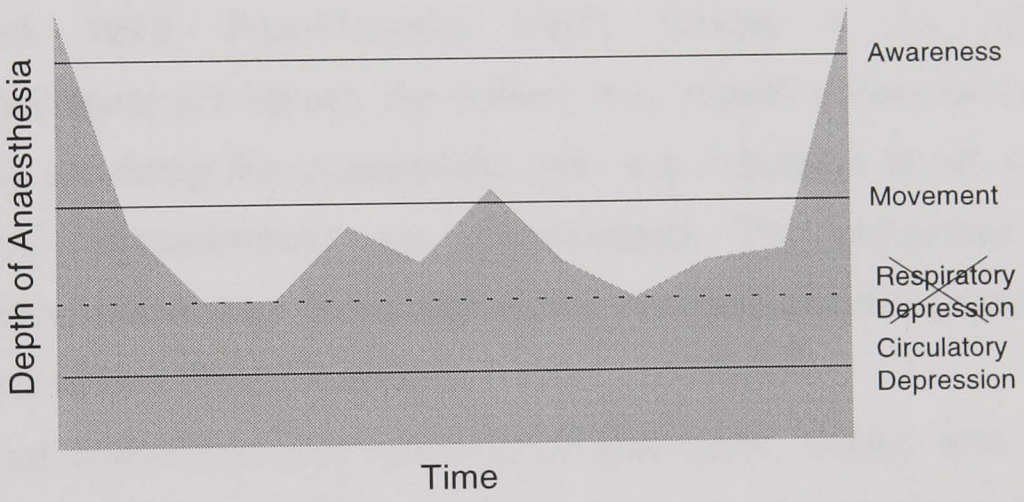

Figure 3.3 Signs relating to depth of anaesthesia in a ventilated, not paralysed patient.

When muscle relaxants are used, an indication of the depth of anaesthesia is given by the combination of cardiovascular changes, sweating and lacrimation, and pupil signs. The lower limit is still circulatory depression, but there is no clear upper limit, since the patient cannot move (Figure 3.4).

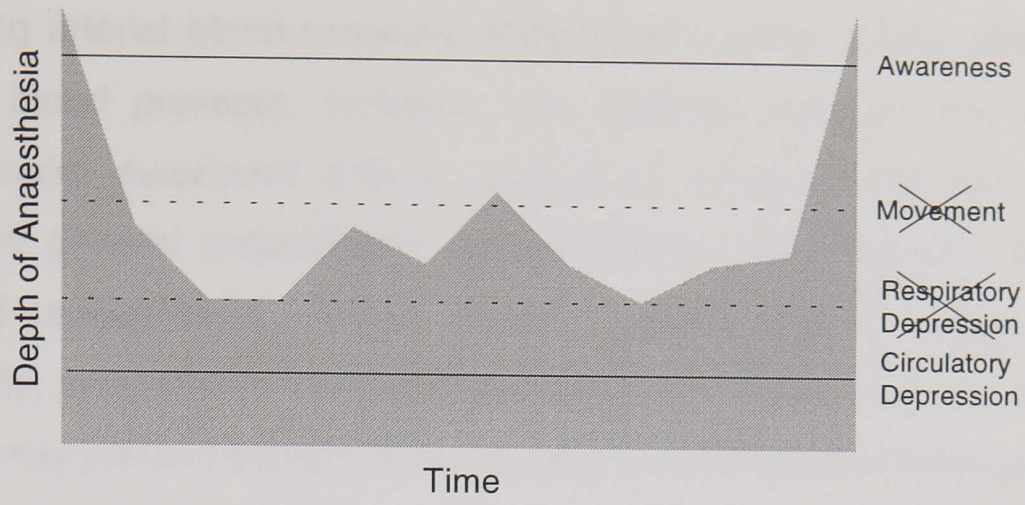

Figure 3.4 Signs relating to depth of anaesthesia in a paralysed patient.

The only available signs are those which arise from stimulation of the sympathetic nervous system. However, these are not specific and are affected by many drugs routinely used in clinical practice (Artusio, Jr. 1955; Parkhouse, 1960; Robson, 1969; Saunders, 1981; Breckenridge and Aitkenhead, 1983; Prys-Roberts, 1987). Clearly, if, for any reason, anaesthesia becomes lighter, the patient may regain consciousness without necessarily providing the anaesthetist with any indication at all, especially if high opioid concentrations are administered. The numerous cases of intraoperative awareness discussed in the previous chapter proved that this possibility is far from just theoretical.

In the most comprehensive study of clinical signs, Cullen and colleagues (1972) compared changes in a large set of clinical signs for several anaesthetic techniques. They found that interpretation of the various clinical signs had to take into account the type of anaesthesia, the particular drugs used and their pharmacological effects. No generalisations could be made about the use of clinical responses other than movement to objectively assess depth of anaesthesia.

3.3.1 Cardiovascular signs

For most inhaled and intravenous anaesthetic agents (with the exception of ketamine), increasing levels of anaesthetic depth are associated with

decreasing arterial blood pressure. Surgical and other painful stimuli tend to increase blood pressure. However, this balance between the increase in cardiovascular autonomic activity, caused by surgery, and the depression, caused by general anaesthetics, is modified by many factors, unrelated to depth of anaesthesia. These factors include blood volume, cardiac contractility, sympathetic tone, age and acid-base status (Stanski, 1990). Beta blockers may prevent hypertension caused by insufficient anaesthesia.

Heart rate also tends to decrease with increasing levels of anaesthesia. However, it is a relatively poor sign, since it is influenced by many other factors, including drugs (e.g. anticholinergics and beta blockers), blood pressure, haemorrhage and lack of fluids.

3.3.2 Sweat and tear formation

Sweating and lacrimation are indicators of light anaesthesia and can be assessed quantitatively. However, they may be present when anaesthesia is adequate. Any interference with the eye can also produce increased lacrimation and anticholinergic drugs affect both.

Maryniak (1987) evaluated the correlation between sweating and changes in heart rate in patients undergoing cystoscopy. He found a close relationship between the two and suggested that it might be used as an indicator of the degree of sympathetic activity during surgery.

3.3.3 Pupil signs

The diameter of the pupil tends to increase and is more responsive to light with lower concentrations of anaesthetics. At deeper levels of anaesthesia, pupils do not respond and become widely dilated. However, large pupils may also indicate very light anaesthesia. Various volatile and intravenous anaesthetic agents, opioids and atropine all have different and sometimes conflicting effects on pupillary signs. Therefore, it is not surprising that these signs are no longer considered to provide an accurate reflection of anaesthetic depth.

3.3.4 PRST score

Evans and his team (Evans *et al,* 1983; Evans and Davies, 1984; Evans *et al,* 1987) suggested the PRST scoring system as another clinical method of assessing adequacy of anaesthesia. This score is based on four variables: systolic blood Pressure, heart Rate, Sweating and Tear formation (Table 3.1).

Index	Condition	Score
Systolic pressure (mm Hg)	< Control + 15	0
	< Control + 30	1
	> Control + 30	2
Heart rate (beats/min)	< Control + 15	0
	< Control + 30	1
	> Control + 30	2
Sweating	Nil	0
	Skin moist to touch	1
	Visible beads of sweat	2
Tears	No excess tears in open eye	0
	Excess of tears in open eye	1
	Tears overflow from closed eye	2

Table 3.1 The system for calculation of the PRST score.

A score between 0 and 2 is allocated to each variable and the total is calculated by adding together all individual scores. A score of 0-2 suggests sufficient or excessive anaesthesia, 2-4 acceptable and that of 5-8 inadequate. However, the clinical signs of lightening anaesthesia are not specific and can also be produced by other conditions, including hypoxia and hypercarbia. Russell (1989; 1993) found this score to be a poor indicator of conscious awareness, since responses to verbal commands using the

Isolated Forearm Technique (*vide infra*) were observed even with the lowest PRST scores 0, 1 and 2.

3.4 ISOLATED FOREARM TECHNIQUE

Movement is the only universally accepted sign of inadequate anaesthesia, but, unfortunately, it is masked by muscle relaxants. To circumvent this problem, Tunstall (1977; 1979) introduced the Isolated Forearm Technique (IFT). The concept of this method is very simple: a tourniquet is placed around the arm and is inflated at pressures well above the maximum expected systolic blood pressure. The neuromuscular blocking drug is then given. Because the muscles do not receive the relaxant, the extremity is not paralysed and the patient can move the forearm to command.

This technique was first used during the initial stages of caesarean sections. It allowed the anaesthetist to assess the patient's depth of anaesthesia and ask direct questions concerning the sensation of pain or fear. The patient answered by squeezing the anaesthetist's hand.

To enable use of the IFT for long surgical procedures, Russell (1979) proposed a slight modification which allowed deflation of the tourniquet after 15-20 minutes. When this happens, the blood concentration of muscle relaxants needs to be low, otherwise the extremity will become paralysed. If the circulation is blocked for a prolonged period of time, a nerve block will occur. This may be the cause of a "locked in" syndrome, in which patients are fully aware but unable to move their arm although normal peripheral nerve activity was found (Russell, 1989). Another reason for false negative results is that there may be enough muscle relaxant in the blood to paralyse the extremity when the tourniquet is deflated (Clapham, 1981).

The IFT has been used to study the relationship of muscle movement to autonomic signs and recall of intraoperative events (Tunstall, 1980a; Wilson, 1980; Russell, 1985; Russell, 1986; Schultetus *et al,* 1986; Russell, 1989; Russell, 1993). However, despite its simplicity, the technique has never been

widely adopted. One reason is that its usefulness is limited by frequent reflex movements. Recent evidence (Antognini and Schwartz, 1993) suggests that purposeful movements in response to painful stimuli are modulated by subcortical structures, such as the spinal cord. There is also strong scepticism about its worth in determining very light levels of anaesthesia, since it has been reported that it is not related with clinical signs of light anaesthesia (Breckenridge and Aitkenhead, 1981; Breckenridge and Aitkenhead, 1983). Further studies are needed to investigate this poor correlation between IFT and clinical signs and to determine which method is the best predictor of intraoperative awareness.

3.5 THE MAC CONCEPT

The Minimum Alveolar Concentration (MAC) of a volatile anaesthetic is the concentration of the drug required to prevent movement in response to a painful stimulus in 50 percent of a test population. It was first introduced by Merkel and Eger (1963) and later refined by Eger and colleagues (1965).

The MAC value is determined by the presence of an all-or-none movement response to a standard noxious stimulus, usually skin incision or tail clamping, in a population of humans or animals, respectively. All measurements must be performed at equilibrium, indicated by equal inspired and end-tidal concentrations of the agent. Since the metabolic rate of volatile agents is low, the partial pressure of the drug in all body parts can be considered to be equal. Thus, the measured end-tidal concentration is similar to the brain concentration. This state of equilibrium is generally achieved within 15 minutes of the end-tidal concentration being at a constant level (Stanski, 1990). It was found (Eger and Bahlman, 1971) that if the difference between the inspired and end-tidal concentrations of halothane was less than 10 percent, then the difference between the end-tidal and the arterial concentration would be minimal.

However, when Frei and colleagues (1991) investigated differences between arterial and end-tidal partial pressures of isoflurane during uptake and elimination, they concluded that clinically useful prediction of arterial pressures from end-tidal measurements is not possible.

Appropriate mathematical and statistical techniques (non-linear logistic regression and extrapolation) are used to determine the relationship between response-no response data and end-tidal concentrations and to extract curves showing the concentration at which 50 percent (or 95 percent) of the population would not move in response to the stimulus.

The MAC concept has been expanded to include other types of stimuli. MAC-awake is the concentration allowing opening of the eyes on verbal command in 50 percent of the population (Stoelting *et al,* 1970), MAC-intubation is the concentration preventing movement during laryngoscopy and endotracheal intubation in 50 percent of the population (Yakaitis *et al,* 1977) and MAC-BAR is the concentration that blocks autonomic response (=BAR) to skin incision in 50 percent of the population (Roizen *et al,* 1981).

Once the MAC value of a certain anaesthetic agent has been determined, all concentrations of this agent can be expressed as multiples of this MAC value, e.g. 1.5 MAC.

There is some indirect evidence (Stanski, 1990) that MAC values of different anaesthetics can be added. However, it is believed (Waud and Waud, 1970) that, as MAC is only one experimental point on the concentration-response curve, such curves may not be parallel for various agents. This means that multiples of MAC for different anaesthetics may not represent equal levels of CNS depression. In order to define the complete concentration-response curve, a continuous measure of anaesthetic depth is required.

MAC is influenced by several factors. It is increased in young people, alcoholics and people who suffer from hyperthermia or hyperthyroidism. It is decreased by hypoxia, hypothermia, anaemia, severe hypotension, age, pregnancy and the use of narcotics, ketamine, barbiturates and

benzodiazepines (Stanski, 1990). It appears that under controlled conditions, MAC can be a sensitive tool to compare relative potencies of inhaled anaesthetic agents.

Another major benefit of the introduction of the MAC concept into clinical practice has been the fact that attention was turned from the inspired to the equilibrated end-tidal concentration of volatile anaesthetics (Waud and Waud, 1970).

One disadvantage of the MAC concept is that it emphasises the analgesic properties of the drug and it does not necessarily give a reliable measure of its hypnotic potency. A further disadvantage is that it can be applied only to inhalational anaesthetics.

There have been some attempts to use Minimum Infusion Rate (MIR) to compare anaesthetic requirements for intravenous agents (Sear *et al,* 1983; Sear *et al,* 1984). Anaesthesia was induced with a bolus dose and then a maintenance infusion was started. After 25 minutes, surgery was allowed to start and the movement response to the initial incision was recorded. The rate of infusion was related to the percentage of patients who moved and the 50 percent Effective Dose (ED_{50}) and 95 percent Effective Dose (ED_{95}) was estimated. The method is analogous to the MAC concept, since it uses the movement response to a noxious stimulus. However, the metabolic rate of most intravenous drugs is much higher than that for inhalational agents and, consequently, it is difficult to achieve equilibrium. MIR is affected not only by the CNS requirements but also by the pharmacokinetic properties of the drug, therefore it is not capable of isolating the pharmacodynamic components of the concentration-response curve. For these reasons, MIR has now been superseded by the Effective Concentration 50 (EC_{50}), which is the plasma concentration of the anaesthetic agent at which 50 percent of patients do not respond to a painful stimulus (Davidson *et al,* 1993).

Excellent review articles have been published (Quasha *et al,* 1980), where the development and clinical applications of the MAC concept are examined in great detail. The subject is also very well presented by Stanski (1990).

3.6 ELECTROENCEPHALOGRAM (EEG)

It has been known since the last quarter of the 19th century that the brain exhibits bioelectrical activity sensitive to anaesthetic drugs. In an abstract, published in 1875 in the British Medical Journal, Caton reported the use of chloroform to investigate the origin of the electrical oscillations of the brain.
In 1926, Berger used an electronic amplifier to record the EEG from the human scalp. Few years later, Gibbs and colleagues (1937) observed that anaesthetic drugs caused changes in the electroencephalogram (EEG) and speculated that it might be used to measure those changes.
Bickford (1950; 1951b; 1951c; 1951a) and Faulconer (1952) where the first who used the EEG to monitor general anaesthesia. Since then, numerous reports have been published, demonstrating changes of the EEG during anaesthesia.

3.6.1 Unprocessed spontaneous EEG

The electroencephalogram is the summation in both time and space of excitatory and inhibitory postsynaptic cortical electrical activity. This activity is directly related to cerebral blood flow and cerebral metabolism. Recording of the raw EEG produces long tracings on paper and requires a very tedious and time-consuming analysis by experts. The signals have an amplitude of 10 to 200 μV and consist of various frequencies which are typically divided into δ (0.5-3.5 Hz), θ (3.5-7.7 Hz), α (7.7-14.3 Hz) and β (14.3-30 Hz) bands. Deepening anaesthesia produces a shift of the dominant frequencies to lower bands and ultimately an isoelectric EEG, sometimes with intermittent electrical activity (*burst suppression*).

Spontaneous EEG analysis has been used extensively to measure the effects on the brain of various anaesthetic and other drugs (Henrie *et al,* 1961; Doenicke and Kugler, 1965; Doenicke *et al,* 1966; Doenicke and Kugler, 1966; Wolfson *et al,* 1967; Goldie *et al,* 1968; Corssen *et al,* 1969; Eriksson, 1969; Clark *et al,* 1970; Courtin and Burnap, 1970; Clark *et al,* 1971; Eger *et al,* 1971; Neigh *et al,* 1971; Oyama *et al,* 1971; Torda and O'Brien, 1971; Scott and Virden, 1972; Takahashi, 1972; Clark and Rosner, 1973; Kavan and Julien, 1974; Schwartz *et al,* 1974; Smith *et al,* 1974; Rosen and Soderberg, 1975; Soderberg and Grattidge, 1975; Celesia *et al,* 1976; Rosen and Hagerdal, 1976; Sakabe *et al,* 1976; Ghoneim and Yamada, 1977; Tinker *et al,* 1977; Persson *et al,* 1978; Klein and Klein, 1979; Fariello, 1980; Oshima *et al,* 1981; Quasha *et al,* 1981; Sebel *et al,* 1981; Yamamura *et al,* 1981; Bovill *et al,* 1982; Doenicke *et al,* 1982; Bovill *et al,* 1983; Sakabe *et al,* 1983; Todd *et al,* 1984; Campkin *et al,* 1985; Todd *et al,* 1985; White *et al,* 1985).

Martin and colleagues (1959) classified the changes in the EEG associated with increasing anaesthetic concentrations, but data interpretation was very difficult and the scale constructed could not predict anaesthetic depth accurately.

Brand and colleagues (1961) found no consistent correlation between electroencephalographic effects and plasma concentrations of thiopentone.

Because of the vast amounts of information in the EEG, it soon became clear that special techniques were needed in order to process the signals and display various parameters for intraoperative use. However, certain EEG patterns, like burst suppression are still used as endpoints in pharmacokinetic and pharmacodynamic (Avram *et al,* 1993; Illievich *et al,* 1993) or other (Schwartz *et al,* 1989; Jantti *et al,* 1993) studies. Raw EEG is also used to investigate excitatory movements suspicious of seizures in patients under general anaesthesia (Yamashiro *et al,* 1985; Borgeat *et al,* 1993; Reddy *et al,* 1993)

3.6.2 Processed EEG

There have been several factors limiting the use of EEG monitoring in the operating theatre environment. Primary among them has been the large size of conventional EEG equipment and the lack of trained personnel available to interpret the traces during the procedure. This problem was ameliorated by using appropriate devices of small physical dimensions to process, compress and display the EEG in a form easy to interpret by those clinicians not specifically trained in electroencephalography.

Nevertheless, the main disadvantage of the EEG, its inherent sensitivity to the type of anaesthetic used, has not been dealt with, even in the most sophisticated of the methods described below (McDowall, 1976; Levy *et al,* 1980; Mori, 1987; Simons *et al,* 1989; Stanski, 1990).

3.6.2.1 Cerebral Function Monitor (CFM)

The Cerebral Function Monitor (CFM) recorded the EEG from a pair of electrodes and, then, amplified and filtered it. The trace varied with both the amplitude and the frequency of the input signal. Its position on the printed record gave an indication of the overall cerebral energy and its width was related to the variability of the brain activity. Adequate function of the recording system was indicated by a continuous monitoring of electrode impedance and by artefact identification and rejection.

The CFM gave only a gross indication of global cerebral activity and has been used to investigate the central effects of various anaesthetic agents (Savege *et al,* 1971; Schwartz *et al,* 1974; Dubois *et al,* 1978a; Dubois *et al,* 1978b; Prior *et al,* 1978; Maynard *et al,* 1979; Frank *et al,* 1982; Bendtsen *et al,* 1985).

3.6.2.2 Cerebral Function Analysing Monitor (CFAM)

The Cerebral Function Analysing Monitor (CFAM) is a modification of the CFM. The CFAM measured the mean, average maximum and average minimum voltages of cerebral activity in the CFM trace and, also, its

frequency content as a proportion of the total activity in each of the conventional EEG bands. It could, also, record auditory, visual and somatosensory evoked potentials (Sebel *et al,* 1983; Maynard and Jenkinson, 1984).

The output format of the CFAM was rather difficult to interpret. Nevertheless, it has been used to measure the effect of thiopentone (Frank *et al,* 1984), nitrous oxide (Williams *et al,* 1984), midazolam (Loughnan *et al,* 1986), halothane (Wark *et al,* 1986; Lloyd Thomas *et al,* 1990b), isoflurane (Lloyd Thomas *et al,* 1990b; Lloyd Thomas *et al,* 1990a) and propofol (Laycock *et al,* 1992).

3.6.2.3 Anaesthesia and Brain Monitor (ABM)

The Anaesthesia and Brain Monitor (ABM, Datex) allowed measurements of the cerebral function as well as neuromuscular transmission, frontalis EMG and respiratory CO_2. The signals were amplified, filtered, rectified and integrated with respect to time each second. The averages of successive 10 second intervals were displayed graphically on a semi-logarithmic scale.

It was found not to be sensitive enough to detect changes from atropine injection, although it could clearly indicate arousal time by electromyography after glycopyrrolate administration (Cozanitis *et al,* 1983). In another study, Chang and colleagues (1988) concluded that the ABM did not significantly improve administration of methohexitone anaesthesia in spontaneously breathing unpremedicated patients.

3.6.2.4 Klein's waveform analyser (period analysis)

Klein (1976) developed a waveform analyser which performed an analysis in the time domain and extracted wave shape information (amplitude and frequency) from the original wave and from its first and second derivatives using a zero-crossing technique. It has been used to compare the EEG effects of high dose fentanyl, sufentanil and morphine anaesthesia (Smith *et al,* 1984).

3.6.2.5 Augmented Delta Quotient (ADQ) monitor

The ADQ is an analogue device which measures the proportion of low frequencies (δ band) in the EEG. The "augmented-delta quotient" is a dimensionless quantity, equal to the ratio of the mean amplitude of "augmented" delta frequencies to the mean amplitude of the entire EEG signal (Volgyesi, 1978). The results obtained by the ADQ were found (Burrows *et al,* 1989) to be comparable to those obtained by compressed spectral array (*vide infra*).

3.6.2.6 Zero-crossing analysis

In this type of analysis, the instantaneous frequency of the EEG is measured by using a voltage comparator set to produce a trigger pulse each time the input signal crossed the threshold with positive or negative slope. The instantaneous frequency is the reciprocal of the time interval between two successive trigger pulses (Jaramillo, 1978).

3.6.2.7 Aperiodic analysis

Aperiodic waveform analysis (implemented in the Lifescan EEG monitor, Neurometrics Inc) is a method that estimates the number of EEG waves per second. Each waveform is mapped in relation to its frequency, amplitude and time of occurrence, instead of averaging waveforms over a given epoch. Proponents claim its main advantage over FFT calculation of the frequency spectrum is that it always produces meaningful results, even when the EEG becomes isoelectric.

It has been used to study the pharmacodynamics of thiopentone (Buhrer *et al,* 1992; Hung *et al,* 1992) and midazolam (Buhrer *et al,* 1990a; Buhrer *et al,* 1990b), and to investigate haemodynamic changes during rapid-sequence induction of anaesthesia with thiamylal (Kanaya *et al,* 1994). It has also been used to monitor the EEG effects of high dose opioid anaesthesia (Smith *et al,* 1984; Bazaral *et al,* 1985) and hypothermia during cardiopulmonary bypass (Stephan *et al,* 1989).

However, no relationship was found between haemodynamic changes during laryngoscopy and intubation and parameters derived from the EEG by aperiodic analysis (White and Boyle, 1989)

3.6.2.8 Spectral analysis

Spectral analysis is the most widely used method of processing the EEG. Any signal may be thought of as the summation of simple sine waves of different frequencies, to produce a single complex waveform. Spectral analysis mathematically decomposes the complex EEG into these simple frequency components. The most commonly employed algorithm is the Fast Fourier Transform (FFT). Various parameters of the FFT have been used to describe the effects of anaesthetic agents.

Spectral analysis has been used extensively to quantify the effects on the brain of various anaesthetic and other drugs (Findeiss *et al,* 1969; Bart *et al,* 1971; Myers *et al,* 1973; McEwen *et al,* 1975; Berezowskyj *et al,* 1976; Ingram *et al,* 1976; Bimar and Bellville, 1977; Smith and Baker, 1979; Smith *et al,* 1979a; Smith *et al,* 1979b; Sebel *et al,* 1981; Yamamura *et al,* 1981; Bovill *et al,* 1982; Sia *et al,* 1982; Bovill *et al,* 1983; Wauquier, 1983; James *et al,* 1986; Murray *et al,* 1986; Loper *et al,* 1987; Schwilden and Stoeckel, 1987; Bowdle and Ward, 1989; Long *et al,* 1989; Schwilden, 1989; Sugiyama *et al,* 1989; Yli Hankala *et al,* 1989; Avramov *et al,* 1990; Kangas Saarela *et al,* 1990; Yli Hankala, 1990; Avramov *et al,* 1991; Borgeat *et al,* 1991; Kochs *et al,* 1991; Algotsson *et al,* 1992; Veselis *et al,* 1992). It has, also, been used during cardiac arrest (Clute and Levy, 1990), laryngoscopy and intubation (Rampil and Matteo, 1987) and surgical incision (Kochs *et al,* 1994).

However, it failed to respond to increasing doses of sufentanil after the initial changes (Chi *et al,* 1991) and could not be precisely correlated with a standard clinical scoring system for sedation (Shearer *et al,* 1991). Others found it able to discriminate between adjacent sedation levels (Veselis *et al,* 1993).

Drummond and colleagues (1991) proved that none of various spectral EEG descriptors could serve as a completely reliable sole predictor of imminent arousal, even though a uniform anaesthetic technique had been used. Similarly, Levy (1984), found that traditional univariate descriptors of the EEG power spectrum, such as median frequency and spectral edge, are inadequate to describe the behaviour of the electroencephalogram during anaesthesia in a large percentage of cases.

Changes in the EEG power spectrum are agent-specific (Levy, 1986) and the effects of nitrous oxide are opposite to those produced by desflurane, isoflurane and other CNS-depressant anaesthetics (Rampil *et al,* 1991; Yli Hankala *et al,* 1993a).

In a recent study, Dwyer and colleagues (1994) demonstrated that no spectral EEG measure can predict depth of anaesthesia, as defined by the response to verbal command and surgery or the development of memory.

3.6.2.8.1 Spectral edge

Spectral edge is the frequency below which lies 95% of the EEG power. Spectral edge has been used in pharmacodynamic studies of thiopentone (Hudson *et al,* 1983; Homer and Stanski, 1985; Stanski and Maitre, 1990; Swerdlow *et al,* 1990), fentanyl and alfentanil through computer simulation (Ebling *et al,* 1990) and trefentanil (Lemmens *et al,* 1994). It has also been used to quantify the effects of morphine, fentanyl, sufentanil and alfentanil (Stone and DiFazio, 1988) and desflurane (Rampil *et al,* 1991).

3.6.2.8.2 Median frequency

Median frequency correlates better than spectral edge with drug concentrations in both the uptake and elimination phases. This was supported in a report which concluded that a median frequency of 5 Hz signifies an adequate level of anaesthesia (Schwilden and Stoeckel, 1987). Median frequency has been used to measure the effects of desflurane (Rampil *et al,* 1991) and propofol (Forrest *et al,* 1994).

3.6.2.8.3 Compressed Spectral Array (CSA)

The Compressed Spectral Array is a very popular method of presenting the frequency spectrum of the EEG signal. It provides a pseudo-3-dimensional display of frequency versus power distribution over time, where sequentially calculated spectra are drawn in a stack, one in front of the next. Usually, CSA is combined with spectral edge on the same graph.

3.6.2.8.4 Density Spectral Array (DSA)

The Density Spectral Array is a modification of the Compressed Spectral Array. Its main advantage over the CSA is that "valleys" of low power are not hidden behind peaks of higher power. Instead, relative power at various frequencies is plotted as dots of different density.

3.6.2.8.5 Bispectral analysis

Bispectral analysis is a technique that measures the nonlinear harmonic and phase relations between the various frequencies of the EEG. A bispectral index is derived from the bispectrum and plotted on the screen of a commercial device (A1000, Aspect Medical Systems Inc). This index has been used to predict haemodynamic responses to laryngoscopy and intubation (Kearse, Jr. *et al,* 1994b) and was correlated with patient movement to skin incision during propofol anaesthesia (Kearse, Jr. *et al,* 1994a).

Bispectral analysis is the most promising of the various EEG processing methods that have been described so far. Further prospective studies, involving the use of combinations of anaesthetic agents, are required to confirm the claim that the bispectral index "may be a sensitive and specific measure of anaesthetic adequacy" (Kearse, Jr. *et al,* 1994a).

3.7 EVOKED POTENTIALS

Evoked potentials (EPs) are the responses of the brain to auditory, visual, electrical and other stimuli. In general, anaesthetics increase the conduction

time between different neural generators. As a result, the amplitudes of those potentials are reduced and their latencies are increased. The effects of various agents on visual, somatosensory and pain evoked potentials have been examined (Clark *et al,* 1970; Clark *et al,* 1971; Clark and Rosner, 1973; Kano and Shimoji, 1974; Shimoji *et al,* 1974; Holder *et al,* 1975; Kriss *et al,* 1980a; Kriss *et al,* 1980b; Sebel *et al,* 1984; Hill *et al,* 1986; Sebel *et al,* 1986; Scheepstra *et al,* 1989; Sebel, 1989; Porkkala *et al,* 1994), but the most comprehensive investigation has been undertaken on auditory EPs. An introduction in evoked potential methodology, a description of the characteristics of various EP modalities and a detailed review of studies relating EPs to depth of anaesthesia are given in the next chapter of this thesis.

3.8 OESOPHAGEAL CONTRACTILITY

It has been known for many decades that there is a close relationship between stress and non-propulsive oesophageal contractions. However, it is only recently that the effects of general anaesthetics on the oesophagus have been recognised and studied (Evans *et al,* 1984; Evans *et al,* 1987).

In humans, the upper part of the oesophagus is composed of striated muscle and its lower part of smooth muscle, with a transitional area between these zones. There are three types of oesophageal activity:

- *Primary* (*peristalsis*). It is initiated by swallowing and its function is to move food along the oesophagus.
- *Secondary*. It arises in response to the presence of a foreign body in the lumen of the oesophagus and acts as a clearing mechanism.
- *Tertiary*. This non-peristaltic contraction is spontaneous and has no known physiological function.

Secondary provoked and tertiary spontaneous lower oesophageal contractions are termed *PLOC* and *SLOC*, respectively. Oesophageal motility is directly controlled by an oesophageal motility centre which is part

of the motor nucleus of the vagus nerve in the brainstem. It is, therefore, stress related and has been suggested as an indicator of anaesthetic depth, since it is not affected by muscle relaxants (Evans *et al,* 1984).

Evans and colleagues (Evans *et al,* 1984; Evans *et al,* 1987) were the first to use a purpose made oesophageal probe to demonstrate the presence of both PLOC and SLOC during light anaesthesia. The probe was equipped with three inflatable pressure sensing balloons and connected to the Lectron LOC monitor (Antec Systems Ltd). The amplitude of provoked contractions and the frequency of spontaneous contractions appeared to be most important (Isaac, 1989). As anaesthesia was deepened, lower oesophageal contractility was progressively suppressed.

Lower oesophageal contractility has been successfully related to depth of halothane (Evans *et al,* 1987) and Althesin anaesthesia (Evans *et al,* 1985) and level of surgical stimulation (Thomas and Aitkenhead, 1988). It has also been used during anaesthesia for cardiac surgery (Thomas and Evans, 1989).

However, Cox and White (1986) found that not all patients demonstrated lower oesophageal contractility, despite very light anaesthesia. Erickson and colleagues (1987) showed no correlation between LOC and movement of patients anaesthetised with isoflurane in response to skin incision. Sessler and colleagues (1989) found that lower oesophageal contractility was able to predict movement during skin incision in patients anaesthetised with halothane but not with nitrous oxide and alfentanil. Watcha and White (1989) had similar results when they attempted to use lower oesophageal contractility to predict patient movement in children anaesthetised with halothane and nitrous oxide. In another study, Thornton and colleagues (1989b) proved that lower oesophageal contractility was not related to blood concentrations of propofol. Finally, Isaac and Rosen (1988; 1990) concluded that lower oesophageal contractility was unable to detect awareness reliably.

Clearly, lower oesophageal contractility is a very limited indicator of anaesthetic depth, especially since it is affected by other drugs routinely used in everyday anaesthetic practice (Isaac, 1989).

3.9 OTHER INSTRUMENTAL METHODS

A number of other possible correlates with depth of anaesthesia have been described. Some of them are promising, while others never left the experimental stage.

3.9.1 Electroretinogram

The electroretinogram (ERG) is the electrical activity of the retina when flash stimuli are applied. Tashiro and his team (1982; 1983; 1986) suggested that the ERG could be used as a monitor of anaesthetic depth. Further evaluation with various anaesthetic agents is required before drawing final conclusions about the usefulness of this method.

3.9.2 Electromyography (EMG)

Fink (1961) was the first investigator to describe electromyography as a monitoring method of anaesthetised patients. Harmel and colleagues (1978) proposed the use of a combination of EEG and spontaneous frontalis muscle electromyographic monitoring and the technique was further investigated by Kay (1984) using the Anaesthesia and Brain Monitor (ABM, Datex Inc). The frontalis muscle is resistant to neuromuscular blockade and the suppression of its activity is associated with deepening levels of anaesthesia. The frontalis electromyogram (FEMG) was found to "markedly improve objective determination of anaesthetic adequacy" (Couture and Edmonds, 1989). It was also able to predict movement during emergence from anaesthesia (Yli Hankala *et al,* 1994).

The value of this approach requires further study with the use of different anaesthetic techniques. However, the variability in the mean level of activity during surgery, makes it difficult to differentiate between the awake and

anaesthetised state (Edmonds, Jr. and Paloheimo, 1985; Edmonds, Jr. *et al,* 1986).

3.9.3 Ocular microtremor

Ocular microtremor is the smallest movement made by the human eye. It is caused by high frequency (80-120 Hz) stimulation of the ocular muscles by the brainstem. In 1976, Coakley demonstrated that the frequency of ocular microtremor changed dramatically with deepening anaesthesia. However, ocular muscles are paralysed by muscle relaxants and this has reduced the value of the technique as a monitor of anaesthetic depth.

3.9.4 Processed electrocardiogram (ECG)

Respiratory Sinus Arrhythmia (RSA) is a cyclical variation in heart rate during breathing. The heart rate increases during inspiration and decreases during expiration. In a resting subject, heart rate is modulated by several other factors, including blood pressure and body temperature. Recently, instantaneous heart rate was found to correlate with EEG burst suppression patterns during deep enflurane (Yli Hankala *et al,* 1990) and isoflurane (Yli Hankala and Jantti, 1990) anaesthesia. In both studies, the heart rate increased at the onset of the EEG burst and decreased at the onset of suppression. Kato and colleagues (1992) used spectral analysis of heart rate variability during isoflurane anaesthesia. They found that both middle and high frequency components (of baroreceptor and respiratory origin, respectively) were decreased by isoflurane in a concentration-dependent manner and suggested that spectral analysis of Heart Rate Variability (HRV) may be used as an objective method for assessing adequacy of anaesthesia.

Annila and colleagues (1993) reported that the amplitude of the T-wave in the ECG is sensitive to both surgery and changes in the level of isoflurane anaesthesia.

Respiratory Sinus Arrhythmia correlated with indices derived from the EEG during propofol (Pomfrett *et al,* 1993) and isoflurane (Pomfrett *et al,* 1994) anaesthesia and did not decrease significantly with pharmacologically appropriate doses of atropine (Yli Hankala *et al,* 1993b; Pomfrett *et al,* 1994). However, inter-individual variation in the magnitude and phase relationship of RSA was found to be considerable. In addition, it was not found to be a reliable indicator of the level of anaesthesia, because it was significantly smaller under enflurane than under isoflurane anaesthesia (Yli Hankala *et al,* 1991). Further controlled studies with larger test populations are needed to resolve those conflicting results.

3.9.5 Galvanic skin responses

As seen earlier in this chapter, sweat production is an autonomic reaction to stress and is used as one of the clinical signs of light anaesthesia. Increases in sweating result in an increase in skin electrical conductivity (Eisele *et al,* 1976; Goddard, 1982).

Maryniak (1987) examined the production of sweat and compared it with changes in heart rate in patients undergoing cystoscopy. He found a close relationship between them and suggested that it might be used as an objective measure of the degree of sympathetic activity during surgery. This technique has not been studied sufficiently.

3.9.6 Peripheral vasoconstriction

Anaesthetic agents affect peripheral circulation. Digital plethysmography assesses the degree of vasoconstriction and can be used to monitor depth of anaesthesia. Johnstone (1974) suggested that digital vasodilatation may be regarded as a sign of unconsciousness in paralysed patients lightly anaesthetised with halothane. This response may indicate light anaesthesia, but is affected by volaemic status and body temperature.

3.9.7 "Pupillometer"

A device that measures the diameter of the pupil has been invented by Asbury and colleagues (1984). It is based on a fixed focal length microscope and allows the study of pupil diameter. It has been used to assess depth of anaesthesia, however, for the reasons examined earlier (par. 3.3.3), it is unlikely that it will ever be adopted as a monitor of anaesthetic depth.

3.10 SUMMARY

The only accurate and reliable clinical criterion of inadequate anaesthetic depth is movement in response to painful stimulation. When muscle relaxants are used, anaesthetists have to rely on other clinical signs indicative of sympathetic stimulation due to stress or pain. As Stanski (1990) wrote, "although anesthesiologists use these signs extensively to monitor depth of anesthesia clinically, they do so on a qualitative rather than quantitative basis".

Numerous attempts have been made to develop an objective monitor of anaesthetic depth. Clinical signs, electroencephalographic methods and pharmacokinetics have all been employed with limited success and, until now, no generally acceptable method has been found.

4. EVOKED POTENTIALS

4.1 DEFINITION

Evoked Potentials (EPs) are defined as electrical responses of the nervous system to sensory stimulation and are generally used to test conduction through sensory pathways. They consist of a series of voltage waveforms, each identified by latency and amplitude.

Different types of EPs can be classified by stimulus modality: Auditory EPs (AEPs), Visual EPs (VEPs) and Somatosensory EPs (SEPs). These are further divided into AEPs of short, middle, and long latency, VEPs to checkerboard pattern, flash, and other stimuli, and SEPs to stimulation of arm and leg nerves. EPs can also be distinguished by their source, as cortical and subcortical, by the recording site, as scalp, neck, clavicular and lumbosacral SEPs, by specific recording methods, as near-field or far-field EPs, and by other variations of stimulus and recording conditions.

In clinical practice, EPs are recorded from the surface of the body with electrodes on the scalp or on the skin over peripheral nerves or the spinal cord. Rarely, and mostly in research studies, EPs are recorded directly from the central nervous system. For that purpose, needle electrodes are inserted in the depth of or placed on the surface of the brain during surgical procedures and are used to record potentials evoked by electrically stimulating specific anatomic structures.

The generators differ depending on the EP type: cortical EPs are created by the addition in both space and time of post-synaptic potentials of cortical neurones, peripheral nerve and plexus EPs are produced by nerve impulses propagating in nerve fibres and subcortical potentials are generated by varying combinations of both types of elements.

The amplitude of a single response to a stimulus is usually very low and can be considered as a meaningful signal partly or completely buried in the ongoing spontaneous EEG (regarded as noise). Single responses are evoked repeatedly and their computer average is used to extract EPs from the EEG.

If f(t) is the continuous EEG, then a single stimulus presentation can be modelled (Aunon *et al,* 1981) by the following equation:

$$f_i(t) = \sum_{m=1}^{M} f_i(t_m)\,[u(t - t_m) - u(t - t_m - t_d)]$$

where $f_i(t)$ is the sampled waveform following the presentation of the i^{th} stimulus, u(t) is the unit step function, t_m is the sampling time, $f(t_m)$ is the value of the monitored waveform at the sampling time and M is the number of samples per stimulus presentation. The sampling duration t_d is usually very short and may be ignored.

The averaging is then represented by the summation of N waveforms as follows:

$$f(t) = \frac{1}{N} \sum_{i=1}^{N} \sum_{m=1}^{M} f_i(t_m)\,[u(t - t_m) - u(t - t_m - t_d)]$$

This method reduces the amplitude of the EEG and improves the quality of the response component (considered as signal) that is time-locked to the stimulus. Assuming that the noise is random, not time locked (not time correlated) to the stimulus and additive, one can formulate a model of the type:

$$f(t) = s(t) + n(t)$$

If the noise n(t) is independent (uncorrelated) of the signal s(t) and the signal repeats in exactly the same way with each stimulus presentation (i.e. it is deterministic, therefore $s(t_m)=s_i(t_m)$ for all i), then the signal-to-noise ratio (SNR) improves significantly by averaging. If, in addition, the expected value of the noise is zero, its average power is the same for each epoch and the noise in one epoch is not correlated with the noise in any other, then the addition of N single evoked potentials will cause the signal power to increase

by a factor of N^2, while the noise power will increase only by N. Hence, the improvement in the SNR will be proportional to the square root of the number of repetitions N ($SNR \propto \sqrt{N}$).

4.2 CLINICAL USE

Evoked potentials are used mainly to test conduction in the auditory, visual and somatosensory pathways. They are so sensitive that they can detect lesions not recognised by other clinical or laboratory techniques. Furthermore, EPs are often used to locate the exact position of lesions in a central sensory pathway. Consequently, they have become valuable diagnostic instruments in the hands of clinical neurologists.

Evoked potentials are very effective in the diagnosis of multiple sclerosis, some degenerative diseases, structural lesions and even a few metabolic encephalopathies. During some surgical operations, EPs are applied to determine the condition of the nervous system at the operative site. For example, somatosensory evoked potentials (SSEPs) determine the condition of spinal sensory pathways during operations on the spinal column. Brainstem AEPs (BAEPs) are utilised to monitor the brainstem and the acoustic nerve during the removal of acoustic neuromas. They are also used to monitor hearing and prevent its loss during surgical procedures in the posterior fossa because of excessive brainstem or cerebellar retraction.

Evoked potentials may be used in the diagnosis of amblyopia, conductive and sensori-neural hearing disorders, and damage to sensory nerves and nerve roots, especially in infants and other non-communicative subjects.

Sub-cortical middle latency responses have been the least used for diagnostic purposes. They are affected by multiple sclerosis and acoustic neurinomas. They are mostly used in patients with neurological and central processing disorders, especially to assess the status of the central sensory pathways in children with delayed speech development and patients with cortical lesions.

4.3 GENERAL CHARACTERISTICS OF EVOKED POTENTIALS

Evoked potentials are composed of a series of waves or peaks. Those peaks are classified by polarity, number of the deflection in the sequence, latency, amplitude, waveshape and distribution. In some EP types, peaks are named by polarity and latency and in others by number in sequence, or by combinations of polarity and number in sequence. Different nomenclatures exist for the various evoked potential entities.

Polarity applies to positivity and negativity between the two active electrodes which are connected to the amplifier. Upward and downward deflections depend not only on which electrode is connected to the non-inverting input and which to the inverting input of the amplifier, but also on which polarity convention is used in the recording system. Therefore, upward and downward deflections in an EP must be explained in both terms.

Latency is usually expressed either as peak latency or as interpeak latency. The peak latency is measured from stimulus onset to the point of maximum amplitude of a negative or positive peak. Interpeak latencies are measured between successive peaks and depict the conduction time between the various structures generating the peaks. Brainstem EPs are sometimes characterised with interpeak latencies.

Sporadically, various types of noise contaminate the EP signals. In that case, peak distinction and identification ("peak picking") may become a major problem. Several solutions exist:

- Reduction of artefacts like mains interference, muscle contractions and subject movements.
- Bandpass filters that eliminate frequency components outside the frequency spectrum of the EP signals.
- By averaging a large number of responses.

However, in many cases, the problem remains, despite these measures.

Automated methods using computer programs to identify peaks and measure latencies and amplitudes have been proposed (Wicke *et al,* 1978; Gabriel *et al,* 1980; Billings, 1981; Fridman *et al,* 1982; Callaway *et al,* 1983; Wilkison, 1983; Ciganek *et al,* 1984). However, all these methods have serious limitations. They cannot be used if the deflections depict separate peaks and are not due to residual noise. Therefore, they should be applied only to small deflections that are closely spaced and superimposed on a clearly defined single EP peak.

Another method of detecting peaks in noisy recordings uses the noise present in the average response and compares it with the EP in question. An estimate of this noise may be obtained by an average made without stimulation or by including a period before the onset of the stimulus (Kobayashi and Yaguchi, 1981) or by plus-minus average, i.e. successively adding and subtracting the responses while obtaining the averaged curve and, thus, eliminating stimulus-related components from the signals (Schimmel, 1967; Schimmel *et al,* 1975; Wong and Bickford, 1980).

EPs obtained from the same subject at different instances may differ from each other, although there is no change in stimulus or recording parameters. EPs recorded from different subjects with exactly the same equipment and methods may differ even more. The ability to detect abnormalities is inversely proportional to this intra-individual and inter-individual variability: the narrower the range of normal EPs, the higher the *sensitivity* and *specificity* of the method.

Several parameters may modify the ongoing electroencephalogram, the responses to sensory stimuli, or both. Most of the intra-individual EP variability was attributed to variations of background activity and noise. However, it was found that the response may also fluctuate during the averaging of an EP (Coppola *et al,* 1978; Spreng, 1981). This is extremely important, since the averaging process itself is based on the assumption that the evoked potential is purely deterministic (par. 4.1). Middle or long latency

peaks show greater variability than the short latency components (Ozdamar and Kraus, 1983).

Factors that affect the intra-individual variability are changes of attention and alertness, background EEG activity, heart rate and blood pressure (Callaway and Buchsbaum, 1965; Walker and Sandman, 1982), time between averages, age, abnormal cerebral function, and differences between laboratories (electrode positioning, amplifier and filter characteristics, recording and averaging techniques, and general electronic noise and interference of the equipment and the surrounding environment).

Differences in EPs between subjects are much greater than intra-individual variability, because they are affected by all the above factors and many others. These factors include body size, sex, age and the particular anatomy of the peripheral and central nervous system. Differences of mass and spatial orientation of the structures generating the evoked potentials and variations in the thickness, electrical resistance, capacitance and impedance of the structures between the EP generators and the recording sites are also significant.

4.4 AUDITORY EVOKED POTENTIALS (AEPS)

Responses to clicks and other types of auditory stimulation are usually recorded between electrodes on the vertex or forehead and the earlobe or mastoid process and produce auditory evoked potentials of various latency and amplitude ranges.

Auditory evoked potentials are categorised by their latency into the short latency Brainstem AEP (BAEP), the Middle Latency AEP (MLAEP) and the Long Latency AEP (LLAEP). Other categories include the slow brainstem AEP, the Frequency Following Potential (FFP), the 40 Hz AEP, the Electrocochleogram (ECochG) and the Sonomotor AEP (Figure 4.1).

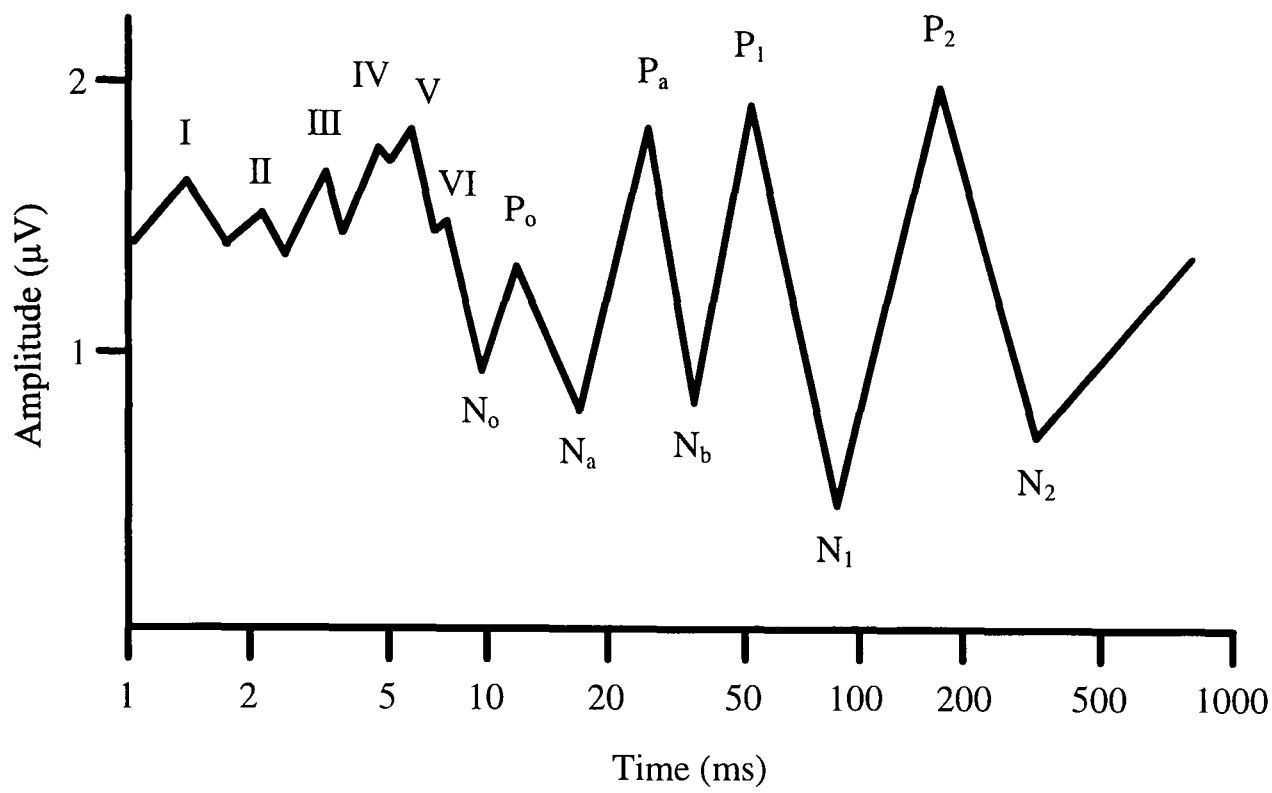

Figure 4.1 Schematic representation of the various AEP peaks (time axis has logarithmic scale).

BAEPs are used for the vast majority of neurological and audiological studies. They include peaks of up to 10 ms and of about 0.2 μV. They are generated by highly synchronised action potentials in the brainstem (Ozdamar and Kraus, 1983; Thornton and Newton, 1989; Thornton, 1991). MLAEPs consist of several peaks with latencies of 10-50 ms and amplitudes of 1-3 μV. They are thought to originate from the medial geniculate and primary auditory cortex (Thornton and Newton, 1989; Thornton, 1991). LLAEPs begin after 50 ms and have peaks of 1-10 μV. They depict later cortical excitation. Those three auditory evoked potentials are sometimes called early, middle and late AEPs. The sonomotor AEPs are recorded with electrodes placed near the neck or scalp muscles and the ECochG with electrodes near the cochlea.

During AEP acquisition, the subject either reclines in a special chair or lies on a bed. The muscles of the face and neck must be relaxed. Sound stimuli are delivered through earphones, or, less frequently, loudspeakers. Bone vibrators are not used routinely, because it is not easy to control the intensity

and frequency of the stimulus that reaches the cochlea (Arlinger *et al,* 1978; Harder *et al,* 1983). The recording room must be quiet.

Earphones are usually electrodynamic. This type has low impedance and can produce very loud stimuli. However, it generates electromagnetic fields, which induce stimulus artefacts. If this artefact is not wanted, then special shielding is required, especially at high stimulus intensities. In some laboratories, a piece of tubing that separates the sound source from the ear is used. It reduces the stimulus artefact but introduces a delay between the electric production of the sound and the AEP. Electrostatic and piezoelectric earphones are also used (Hughes and Fino, 1980; Stakenburg and Wit, 1983), but they have high impedance and may not be able to generate stimuli as loud as those produced by electrodynamic earphones.

Stimuli used to elicit AEPs are of various types (Arlinger, 1981; Davis, 1976). Most AEPs are produced by clicks or tone pips. Clicks produce a sudden stimulus which gives rise to a large and well defined EP. For that reason, they are very suitable for neurological studies, where the presence or absence of a response is all that matters. However, they contain a wide frequency spectrum and act mainly by virtue of their higher frequency components. Because of that, they do not test the lower frequencies which are important for speech and, therefore, are unsuitable for audiological studies.

Clicks are usually generated by driving the earphones with rectangular pulses of 0.1-1 ms duration. The pressure waves produced by the earphone membrane contain a wide frequency spectrum, which is further modified by the acoustical coupling between the earphone and the head (Coats and Kidder, 1980) and by the various anatomical ear structures, before the sound reaches the cochlea (Laukli, 1983; Burkard, 1984). This sound stimulus still consists of a wide range of frequencies with peak power at 2-4 kHz and is known as a *broadband*, or *unfiltered*, click. If a narrower frequency range is required, it can be obtained either by filtering the pulses that generate the

clicks (*filtered* clicks) or by using a continuous *masking* noise as a background while eliciting the AEP with broadband clicks. This masking noise contains the appropriate frequencies and cancels their effect in the click.

The stimulus rate depends on the type of the auditory evoked potential. Short and medium latency AEPs are usually elicited at rates of 8-10 Hz. Longer latency AEPs, such as the LLAEP, require stimulation rates as low as 1 Hz or even less. An important thing to remember when choosing the stimulus rate is to avoid fractions of the power line frequency, since it could lead to a considerable increase of mains interference. This also applies to frequencies used in computer equipment (especially CRT monitors).

The power of the sound stimulus that reaches the tympanic membrane, depends on the acoustic coupling between the earphone and the ear (Barnet *et al,* 1975; Coats and Kidder, 1980). In order to express audiometric intensities, power levels are standardised with sound level meters and a device that roughly corresponds to the human ear (*artificial ear*). Separate calibrations are required for different coupling materials.

The intensity of the stimulus is measured as a ratio between the stimulus level and a reference level. For neurological studies it is usually set to 70 dB above the hearing level. The *hearing level* is defined as the average hearing threshold of audiologically normal young adults. The *normal hearing level* for pure tones, that last 0.5 s or more, is the same as the hearing level. However, the normal hearing level for the brief and sudden sounds commonly used to elicit AEPs, is different from that for pure tones of the same amplitude. Therefore, the normal hearing level must be defined specifically for each stimulus type by measuring the average threshold intensity in a random sample of normally hearing young adults. The complicated process that is required to calibrate the equipment and give a valid intensity reference, is usually carried out by the manufacturer of the stimulating device.

There are two different types of clicks depending on the polarity of the electric pulse that produces them:

- *Condensation* or *compression* clicks, when the pulse produces an initial deflection of the earphone membrane toward the eardrum.
- *Rarefaction* clicks, when the initial deflection of the membrane is away from the ear, rarefying the air in the ear canal.

Stimulus polarity is important only for short latency AEPs, since condensation and rarefaction clicks produce slightly different responses. Longer latency AEPs are not affected by stimulus polarity.

4.4.1 The Middle Latency AEP (MLAEP)

The Middle Latency Auditory Evoked Potential (MLAEP) has several peaks which occur between 10 and 50 ms after the stimulus onset and, probably, include the earliest response of the primary auditory cortex. The MLAEP is quite variable in normal subjects and is often contaminated by muscle artefact. However, most experts agree that the MLAEP at the vertex may show up to five peaks of positive (P) and negative (N) polarity: No at 8-10 ms, Po at 10-13 ms, Na at 16-30 ms, Pa (usually the largest) at 30-45 ms and Nb at 40-60 ms (Goldstein and Rodman, 1967; Lane *et al,* 1971; Madell and Goldstein, 1972; Picton *et al,* 1974; Ozdamar and Kraus, 1983). The first or second peak is identical to the slow brainstem AEP. Sometimes, recordings include the first 100 ms after the stimulus and contain a sixth peak, Pb, at 50-90 ms. It is equivalent to the early cortical peak P1 of the Long Latency AEP.

The MLAEP is widely distributed on the scalp with a maximum over the frontocentral areas (Picton *et al,* 1974; Goff *et al,* 1977; Streletz *et al,* 1977). It is thought to be generated in the medial geniculate and primary auditory cortex (Vaughan and Ritter, 1970; Cohen, 1982; Wood and Wolpaw, 1982) and is supported by direct recordings (Ruhm *et al,* 1967; Celesia, 1976; Lee *et al,* 1984). However, depth recordings have suggested that the early peaks

No, Po and Na may originate from the midbrain (Hashimoto, 1982). MLAEP latencies decrease only slightly with age (McRandle *et al,* 1974; Barnet *et al,* 1975; Mendel *et al,* 1977).

During recordings, the subject must be completely relaxed, since sonomotor responses, which tend to obscure the MLAEP, appear with even slight neck muscle tension. Lack of attention, mild sedation and light sleep do not influence MLAEP latencies or amplitudes (Kupperman and Mendel, 1974; Picton and Hillyard, 1974; Mendel *et al,* 1975; Skinner and Shimota, 1975; Ozdamar and Kraus, 1983).

The most commonly used stimuli are clicks and high frequency tone bursts. Tone pips and filtered clicks are also used, due to the ability of the MLAEP to provide frequency-specific information. Stimulation rates are up to 15 Hz without any change of the response (Goldstein *et al,* 1972; McFarland *et al,* 1975). At higher rates, amplitudes decrease progressively (Picton *et al,* 1974).

For data acquisition, cup EEG electrodes are usually placed on the vertex or forehead and the earlobe or mastoid. MLAEPs to monaural stimuli recorded from the two sides of the head do not differ from each other (Peters and Mendel, 1974), therefore only one channel is required. Amplification needs high gains (x20000-x50000), since the MLAEP has amplitudes of 1-3 μV.

Several types of filters are used to remove unwanted frequencies from the signals either before or after averaging. These unwanted frequencies can arise from electronic noise of various origins such as internal electronic noise from the electrodes and the amplifiers, mains interference, and artefacts caused by the use of diathermy, ground loops and other theatre equipment, from biological signals generated in the patient (ECG, EEG, EMG) and from slow potentials arising from movement of the patient or the electrodes. Both a high electrode impedance and an imbalance between the impedance of the recording and reference electrodes may increase the amount of interference in the signals.

Optimal filtering of the MLAEP requires careful examination of the frequency spectra of evoked potentials taken from a large number of normal subjects and can be a complicated and time-consuming process (Bacon *et al,* 1990). The high-pass filter (-3 dB cut-off point) is usually set at 10 Hz or less (Scherg, 1982). A 25 Hz filter may accelerate collection of MLAEPs (McFarland *et al,* 1975). Low-pass filter settings (-3 dB cut-off point) of less than 150 Hz should be avoided (Lane *et al,* 1974) because they may distort slower components of the MLAEP. This is especially true for analogue filters which not only change the amplitude of certain peaks, but they also cause a frequency-dependent phase-lag, that changes the latency of the peaks.

For MLAEPs, the sweep length is usually about 100 ms and the sampling rate of the analogue-to-digital converter is 1-10 kHz. Typically, the averaged signal contains 1000-2000 responses, although 512 responses (Goldstein *et al,* 1972) or less (McFarland *et al,* 1975; Thornton and Newton, 1989; Davies *et al,* 1996) may be sufficient. Digital signal processing techniques are often used to enhance the quality of the signals and, thus, reduce the number of repetitions required to obtain an acceptable curve. Analogue and digital band-pass filter solutions are described later in this thesis.

4.5 EFFECTS OF GENERAL ANAESTHETICS ON THE AEP

With the exception of nitrous oxide, the effects of early anaesthetic drugs on the AEP have not been studied. Ether, chloroform, cyclopropane and ethylene had almost disappeared by the time computer averaging of the EEG was introduced.

The first study of the effects of anaesthetics on the AEP, that appeared in the literature, was by Lader and Norris (1968). They studied the effect of sub-anaesthetic concentrations of nitrous oxide (12.5% and 25% in oxygen) in twelve volunteers. Although it is not clear precisely which waves they were referring to, they found that the latencies were not altered, but the amplitudes of what were probably Pb, Nc (or N1) and P2 were significantly reduced. Pa

and Nb were not affected. They concluded that evoked potentials can provide a sensitive index of the action of nitrous oxide and suggested that the technique could be used for the assessment of sedative and even other psychotropic drugs.

4.5.1 Northwick Park studies

The most comprehensive study of the effects of various anaesthetics on the AEP was carried out by the Northwick Park group. In a series of papers (James *et al,* 1982; Navaratnarajah *et al,* 1983; Thornton *et al,* 1983; Heneghan *et al,* 1984; Thornton *et al,* 1984; Thornton *et al,* 1985; Thornton *et al,* 1986; Heneghan *et al,* 1987; Newton *et al,* 1989; Thornton *et al,* 1989b; Thornton *et al,* 1992) they examined the effects of increasing concentrations of halothane, enflurane, etomidate, althesin, isoflurane and propofol on the AEP.

A common methodology was used in all studies: clicks were presented binaurally at a rate of 6 Hz. The EEG was amplified, filtered and recorded on FM tape. Auditory evoked potentials were obtained from 2048 sweeps of 80-130 ms duration averaged off-line. Values for latencies and amplitudes of BAEP and MLAEP waves were measured manually from printouts before anaesthesia, following induction and throughout the anaesthetic. Regressions of those values on end-tidal or blood concentration of the anaesthetic were calculated and the slopes of those regressions were examined. Regressions did not include data before anaesthesia or immediately after induction and the start of nitrous oxide administration.

The results showed that the BAEP latencies increased in a dose-dependent way with volatile agents, but showed no change with the intravenously administered agents etomidate (Navaratnarajah *et al,* 1983; Thornton *et al,* 1985), Althesin (Heneghan *et al,* 1984; Thornton *et al,* 1986) and propofol (Thornton *et al,* 1989b). The authors concluded that BAEPs cannot measure depth of anaesthesia.

MLAEP parameters changed linearly with increasing anaesthetic concentrations and showed similar changes with different anaesthetics. The amplitudes of all peaks were reduced and the latencies were increased markedly as the concentrations of anaesthetic agents were increased. However, the numerical data published were only for Pa and Nb. At the highest concentrations, Pa and Nb were almost abolished and the AEP curves were virtually flat. In a number of patients, delays in the commencement of surgery allowed the administration of the anaesthetic to be discontinued. There was a partial recovery of Pa and Nb in all those subjects.

Awake latencies for Pa and Nb (Thornton *et al,* 1983; Thornton *et al,* 1984; Thornton *et al,* 1985) were similar to those found in the literature (Picton and Hillyard, 1974).

However, the regression slopes during anaesthesia were never similar for equipotent anaesthetic drug concentrations. This was particularly apparent for nitrous oxide (Newton *et al,* 1989). In that study, the authors found that equivalent MAC fractions of N_2O and isoflurane had quite different effects on the AEP. The anomalous properties of N_2O were attributed to its good analgesic but weak hypnotic properties.

In a later study (Thornton *et al,* 1992), where both auditory and somatosensory evoked potentials were recorded, there was no significant difference between N_2O and isoflurane on Pa and Nb amplitude. Also, changes in AEPs were not affected by the time elapsed from induction and intubation. In the previous study (Newton *et al,* 1989) amplitudes were greater and latencies were shorter immediately after intubation.

A possible explanation for those contradictory results might be that the simultaneous electrical stimulation required to obtain the SEPs had lightened the level of isoflurane anaesthesia and hence decreased the difference in effect between the two agents. Another explanation might be the small number (eight) of subjects in both studies.

The most interesting result from the comparison of the effects of N_2O and isoflurane on AEPs and SEPs (Thornton *et al,* 1992) was that isoflurane had a more potent effect than nitrous oxide on the AEP, whereas N_2O had a more potent effect on the SEP. It is widely known (Newton *et al,* 1990) that at 0.6 MAC of isoflurane, unstimulated patients tend to be inert, while at 0.6 MAC of nitrous oxide they tend to be aware. Perhaps the two modalities are measuring complementary aspects of anaesthetic action, i.e. AEPs reflect mainly the hypnotic component and SEPs the analgesic component.

The effects of propofol on middle latency AEPs (Thornton *et al,* 1989b) were compared with those of the other anaesthetic agents investigated in previous studies. End-tidal and blood concentrations were converted to ED_{50} units and regressions against ED_{50} were calculated. There appeared to be large differences between the slopes of the inhalation and intravenous agents. The authors speculated that this expressed the low analgesic properties of etomidate, Althesin and propofol. The MAC value reflects analgesia as much as hypnosis, but, in contrast, the AEP reflects mainly the hypnotic component.

In the same study, AEPs were compared with lower oesophageal contractility (LOC). The authors found that LOC was not related to propofol concentration in any obvious way and concluded that this technique would have limited value for the determination of depth of anaesthesia.

4.5.1.1 MLAEPs and surgery

An important requirement for any method measuring anaesthetic depth is that it reflects the effect of surgical stimulation on the level of consciousness. If the AEP remained unchanged when the anaesthetised patient was subjected to a painful stimulus, then it would be interpreted as a sophisticated bio-assay of anaesthetic concentration, but not a measure of CNS activity.

Thornton and colleagues (1988) recorded MLAEPs before and after incision in 11 patients anaesthetised with 0.3% end-tidal concentration of halothane

and 67% N_2O. They found that the amplitude of Pa increased in six patients, the amplitude of Nb in eight and the amplitude of what was probably Pb (they called it Pb/Pc because they were not sure whether it was Pb, Pc or a combination of those two peaks) increased in nine patients.

The signals observed resembled what would be expected from a lower end-tidal concentration of anaesthetic (i.e. amplitudes were reduced and latencies were increased). There was some variability in the effects on the MLAEPs and this was attributed to variability of sensitivity to the anaesthetic agent.

The trend before surgery was compared with the trend after incision and this proved that there were no progressive time-related changes. An important finding was that there was no correlation between autonomic signs and changes in the AEP. This was probably due to the long time required to obtain an averaged AEP curve. Two thousand and forty-eight sweeps at a rate of 6 s^{-1} required 5.6 minutes (or more, if diathermy and other artefacts were present), which was too long to detect transient changes in the AEP.

The authors concluded that the amplitudes of the early cortical response, but not the latencies, show promise as measures of depth of anaesthesia and that Nb and Pb are worthy of further investigation.

4.5.1.2 MLAEPs and awareness

Another important requirement for any method measuring anaesthetic depth is that it can indicate awareness or very light anaesthesia. One of the critical questions to be answered was whether AEPs could be used to identify such conditions.

Thornton and colleagues (1989a) analysed data from previous studies and found that Nb latency was the best feature distinguishing the "three wave" AEP pattern (which they found from experience that correlated to light anaesthesia) from the "two wave" pattern, which corresponded to deeper levels. Then, in a specially designed study, they compared AEPs obtained

from paralysed patients with their responses to verbal commands, using the isolated forearm technique.

They found that Nb latencies less than 44.5 ms were associated with a high incidence of responses and with very light anaesthesia. They concluded that the MLAEPs reflect the change between wakefulness and unconsciousness. However, they stated that further studies were needed to develop pattern recognition techniques of the AEP and to allow on-line analysis if it were to provide a clinical indicator of awareness.

In a related study, Newton and colleagues (1992) investigated the relationship between the AEP and simple tests of consciousness in volunteers breathing sub-MAC concentrations of isoflurane.

The general effect of increasing isoflurane concentrations was a sudden change in the subject's state. The AEP patterns obtained from aware subjects, were very different from those seen when there was no response and during surgical anaesthesia. Several parameters of the AEP were measured (latencies of Na, Pa, Nb, Pb and Nc and amplitudes of Pa, Nb and Pc) and all exhibited progressive changes with increasing anaesthetic doses. Correlations of AEP parameters with changes in end-tidal isoflurane concentration tended to be better than with the actual response. However, there was a failure to demonstrate that Nb latencies less than 44.5 ms were associated with consciousness. In fact, the mean baseline Nb latency was 44.9 ms and it was reduced to 46.3, 46.7 and 53.9 ms at 0.1, 0.2 and 0.4% isoflurane, respectively. The authors attributed this discrepancy to differences in the methods. Different type of headphones, quieter clicks and transmission of commands through the same headphones could account for the longer Nb latencies in both the awake and anaesthetised states, although earlier waves were not affected.

There was no difficulty in communication with either patients or volunteers when eliciting the AEP. Digital filters improved the signals significantly and reduced the degree of EMG contamination seen in awake patients.

A drawback in the use of the AEP to observe subjects whose CNS state was not stable, was the time taken to obtain an averaged response. The authors experienced difficulty in the interpretation of some of the AEP signals while the subjects were changing back and forth from consciousness to unconsciousness. This might be because the averages were probably combinations of more than one type of response. Therefore, shorter averaging time would be a great improvement on the method.

4.5.2 Studies by other groups

The above results published by the Northwick Park group were confirmed by several other independent studies.

4.5.2.1 BAEPs and anaesthetics

Volatile anaesthetics that were studied are: enflurane (Dubois *et al,* 1982), isoflurane (Manninen *et al,* 1985; Schmidt and Chraemmer Jorgensen, 1986; Sebel *et al,* 1986; Madler *et al,* 1991; Schwender *et al,* 1994a; Schwender *et al,* 1994b) and nitrous oxide (Sebel *et al,* 1984).

Intravenous agents that were studied are: propofol (Savoia *et al,* 1988; Chassard *et al,* 1989; Purdie and Cullen, 1993; Schwender *et al,* 1994a; Schwender *et al,* 1994b), diazepam and fentanyl (Loughnan *et al,* 1987), alfentanil, fentanyl and morphine (Schwender *et al,* 1993b), ketamine (Schwender *et al,* 1993a) and a combination of flunitrazepam and fentanyl (Schwender *et al,* 1994a; Schwender *et al,* 1994b).

All these studies concluded that BAEPs were linearly affected by increasing concentrations of volatile agents. However, nitrous oxide and intravenous anaesthetics had minimal or no effect on BAEPs. It is clear that BAEPs cannot be measuring depth of anaesthesia.

4.5.2.2 MLAEPs and anaesthetics

The effects of anaesthetic drugs on the middle latency auditory evoked potentials were studied by several authors.

Savoia and colleagues (1988) examined the effects of propofol. Their results are qualitatively similar to those published by other authors, but there were large discrepancies in the latencies measured. This was probably due to a high-pass analogue filter setting of 100 Hz, which introduced considerable phase shifts in the AEP signals.

Chassard and colleagues (1989) also studied the effect of propofol on AEPs, however, they published latency and amplitude data of Pa and Nb only for the awake state, because "early cortical waves were affected by the propofol infusion"! Nevertheless, MLAEP changes, as illustrated in an accompanying figure, appeared to be similar to those described by the Northwick Park group.

Madler and colleagues (1991) examined AEPs under isoflurane anaesthesia. Latencies of Na and Pa and peak-to-peak amplitude Na/Pa (as measured from accompanying figure) are again comparable to the ones found in the literature. The authors found that amplitudes exhibited greater inter-individual variability than latencies and concluded that the only way to use them as an indicator of anaesthetic depth would be to compare pre- and intra-operative amplitudes individually.

Schwender and colleagues examined the effects of opioids (1993b) and ketamine (1993a) on the MLAEP. They found that even after the largest doses of alfentanil, fentanyl and morphine, Na, Pa and Nb showed a similar pattern as in awake patients. Only increases in latencies of Nb and P1 (or Pb) were statistically significant, but they were seen after the first or second bolus dose of opioid and remained stable with increasing doses. Relative amplitudes showed greater inter-individual variability than latencies.

After induction of general anaesthesia with ketamine, there was no change in latency and no apparent reduction in amplitude of any of the MLAEP peaks examined.

It seems that those two studies confirm the general perception that opioids are not "true" anaesthetics and that ketamine does not induce a general

suppression of the perception and processing of sensory stimuli which supports the concept of dissociative anaesthesia under ketamine.

In another paper by Schwender and colleagues (1994a), the effects of propofol, isoflurane and flunitrazepam/fentanyl on MLAEPs were examined. Once again, MLAEPs were found to be suppressed by propofol and isoflurane in a manner similar to that described in the literature. However, during general anaesthesia with flunitrazepam/fentanyl, MLAEPs continued to show a wave pattern similar to the awake state. An important finding of that study was that motor signs of wakefulness (patients were ventilated throughout the operation but paralysed only for intubation) occurred significantly more often in the patients in the flunitrazepam/fentanyl group. However, there was no further investigation of possible awareness of intraoperative events. The authors did not find any correlation between the incidence of motor reactions and cardiovascular parameters and this was attributed to the extensive epidural block in all patients.

4.5.2.3 MLAEPs and surgical stimulation

The effects of stimulation were presented in two papers. In the first one, Sneyd and colleagues (1992) examined the effect of physiotherapy on the MLAEPs of sedated critically ill patients.

The latency of Nb before physiotherapy was 44.8 ms, it was reduced to 41.0 ms during physiotherapy and increased again to 45.6 ms after physiotherapy. Nb amplitude was not affected consistently, as it increased in some patients and decreased in others. They also observed that patients who died showed a smaller response from those who survived. However, the number of the patients was too small to allow evaluation of the AEP as an outcome predictor. Another reason for that difference could be the deeper sedation that the non-survivors received. The authors speculated that the changes observed, were caused by cortical arousal provoked by physiotherapy.

In the second paper, Schwender and colleagues (1994b) investigated the effect of surgical stimulation on MLAEPs in cardiac patients anaesthetised with propofol, isoflurane or flunitrazepam. All patients received also high doses of fentanyl (1.2-1.8 mg/h).

The awake MLAEPs had a characteristic waveform with latencies and amplitudes similar to the ones described previously. The power spectrum had its maximal energy in the 30-40 Hz frequency range.

During general anaesthesia, in the propofol and isoflurane groups, MLAEPs showed either markedly increased latencies and decreased amplitudes or they were completely suppressed. In the flunitrazepam group, there were only slight increases in latencies and decreases in amplitudes. Na, Pa and Nb showed a pattern similar to the awake state.

After skin incision as well as after sternotomy, no significant changes in MLAEP amplitudes or latencies could be observed in any of the three groups. Also, no significant changes in haemodynamic parameters occurred as a result of surgical stimulation.

These findings were probably the consequence of the use of high doses of opioids in all patients, which blocked the nociceptive pathway, thus leading to a functional dissociation of the different sense modalities.

The authors were of the opinion that with pure inhalation anaesthesia they would have seen an effect of surgery on MLAEPs, similar to that described by Thornton and colleagues (1988). They concluded that surgical analgesia may be achieved independently from other anaesthetic effects using very potent opioid analgesic agents, and tolerance even to very painful stimuli does not automatically imply that other sense modalities are blocked completely and to the same extent.

4.5.2.4 LLAEPs and anaesthetics

Long Latency Auditory Evoked Potentials (LLAEPs) are affected by midazolam (Milligan *et al,* 1987; Milligan *et al,* 1989) and sedative concentrations of nitrous oxide (Jessop *et al,* 1991a; Jessop *et al,* 1991b), as

well as by lack of attention (Picton *et al,* 1974), premedication and light sleep. Long latency peaks N1 (or N100) and P3 (or P300) disappear with light levels of anaesthesia (Plourde and Picton, 1991; Plourde *et al,* 1993). As a monitor of consciousness, the P3 wave has high specificity but low sensitivity (Plourde, 1991). It is obvious that LLAEPs cannot be used as an index of anaesthetic depth.

4.5.2.5 Other AEPs and anaesthetics

The Auditory Steady State Response (ASSR) is a composite sinusoidal wave produced by auditory stimuli presented at rates near 40 Hz. It was first described by Galambos and colleagues (1981). The effects of anaesthetic drugs on the ASSR were examined by Hogan (1987), Plourde and Picton (1990) and Plourde and Boylan (1991). It was found that the changes of the ASSR paralleled those of the level of consciousness: it was reduced significantly during induction, completely abolished during surgical anaesthesia and increased again during emergence and recovery. More studies are needed to determine the effects of other commonly used agents.

The great advantage of this method, compared to the transient MLAEP, is the ease of interpretation of the results. However, its high sensitivity to stimulus frequency and intensity (Galambos *et al,* 1981) may limit its use in determining the depth of anaesthesia.

Munglani and colleagues (1993a; 1993b) found that the ASSR was too sensitive a variable to measure information processing and proposed another method, related to the ASSR. According to that technique, the auditory stimuli were presented to the subject at frequencies from 5 Hz to 47 Hz. Fast Fourier transformation (FFT) was applied to the averaged curves and the resulting power spectra were examined. At certain stimulation frequencies (or, more precisely, clicking rates), called "the coherent frequency" (CF), the power of the first (or fundamental, according to the authors) harmonic was very large, with little or no power in higher harmonics.

The coherent frequency was correlated with psychological tests which examined cognitive function of seven volunteers, who breathed sub-MAC concentrations of isoflurane. Conscious awareness with explicit memory was associated with a CF (25th-75th centile) of 32.8 (28.4-36.7) Hz. Conscious awareness without explicit memory was associated with a CF of 24.8 (21.5-30.6) Hz. No responsiveness with no implicit memory corresponded to a CF of 14.8 (14.2-17.3) Hz. Further studies are required to examine the effects of surgical levels of anaesthesia on the coherent frequency.

A different approach was introduced by Madler and Poppel (1987). Conventionally produced MLAEPs were subjected to fast Fourier transformation (FFT) and the power spectra were examined. The dominant frequency of 40 Hz, seen in the awake state, was no longer present in the anaesthetised patients. Instead, it was replaced by lower frequencies at the range of 10 to 15 Hz. Similar findings were presented in a series of papers (Madler *et al,* 1991; Schwender *et al,* 1993a; Schwender *et al,* 1993b; Schwender *et al,* 1994a; Schwender *et al,* 1994b), however no formal investigation of the usefulness of the FFT and its equivalence to conventional parameters of the AEP has appeared in the literature.

4.6 Comparison Of MLAEP Results

A comparison of the AEP parameters published by the various researchers (a table with all results can be found in Appendix A) shows similar qualitative changes of the MLAEP, but a closer examination reveals several quantitative differences in amplitudes and latencies of the various peaks. This might be due to dissimilar techniques and methods. However, even when one considers only the results published by the Northwick Park group, where a common methodology was followed in all studies, some inconsistencies are apparent (Table 4.1).

Study	Agent	Latency Slopes		Amplitude Slopes	
		Pa	Nb	Pa	Nb
(Thornton *et al,* 1983)	Enflurane (n=6)	11.2 ms/%vol (SE 2.70)	14.1 ms/%vol (SE 3.13)	-0.97 mV/%vol (SE 0.140)	-0.95 mV/%vol (SE 0.195)
(Thornton *et al,* 1984)	Halothane (n=6)	10.5 ms/%vol (SE 1.28)	12.4 ms/%vol (SE 2.40)	-0.53 mV/%vol (SE 0.09)	-0.31 mV/%vol (SE 0.102)
	Enflurane (n=6)	11.6 ms/%vol (SE 1.14)	10.7 ms/%vol (SE 1.56)	-0.27 mV/%vol (SE 0.065)	-0.23 mV/%vol (SE 0.051)
(Thornton *et al,* 1985)	Etomidate (n=7)	22.6 ms/mg/ml (SE 3.12)	28.3 ms/mg/ml (SE 4.72)	-0.50 mV/mg/ml (SE 0.124)	-0.49 mV/mg/ml (SE 0.124)
(Thornton *et al,* 1986)	Althesin (n=6)	5.5 ms/mg/ml (SE 0.98)	9.5 ms/mg/ml (SE 3.98)	-0.25 mV/mg/ml (SE 0.053)	-0.29 mV/mg/ml (SE 0.048)
(Heneghan *et al,* 1987)	Isoflurane (n=6)	18.7 ms/%vol (SE 2.4)	29.6 ms/%vol (SE 3.4)	-0.21 mV/%vol (SE 0.03)	-0.21 mV/%vol (SE 0.04)
	Isoflurane (n=6)	23.7 ms/MAC (SE 4.9)	37.1 ms/MAC (SE 9.6)	-0.28 mV/MAC (SE 0.14)	-0.27 mV/MAC (SE 0.11)
	Halothane (Thornton *et al,* 1984)	6.8 ms/MAC (SE 2.7)	8.9 ms/MAC (SE 5.8)	-0.51 mV/MAC (SE 0.15)	-0.23 mV/MAC (SE 0.18)
	Enflurane (Thornton *et al,* 1984)	20.1 ms/MAC (SE 6.2)	18.3 ms/MAC (SE 8.9)	-0.43 mV/MAC (SE 0.30)	-0.37 mV/MAC (SE 0.23)
(Thornton *et al,* 1989b)	Halothane (n=6) (Thornton *et al,* 1984)	24%change/ED_{50} (CI 16 to 33)	29%change/ED_{50} (CI 14 to 45)	-59%change/ED_{50} (CI -41 to -71)	-48%change/ED_{50} (CI -25 to -65)
	Enflurane (n=6) (Thornton *et al,* 1984)	62%change/ED_{50} (CI 32 to 100)	45%change/ED_{50} (CI 26 to 68)	-81%change/ED_{50} (CI -63 to -90)	-73%change/ED_{50} (CI -55 to -84)
	Isoflurane (n=6) (Heneghan *et al,* 1987)	58%change/ED_{50} (CI 35 to 85)	60%change/ED_{50} (CI 34 to 92)	-76%change/ED_{50} (CI -63 to -85)	-74%change/ED_{50} (CI -57 to -84)
	Etomidate (n=7) (Thornton *et al,* 1985)	387%change/ED_{50} (CI 110 to 1028)	402%change/ED_{50} (CI 64 to 1433)	-98%change/ED_{50} (CI -94 to -99)	-99%change/ED_{50} (CI -89 to -100)
	Althesin (n=6) (Thornton *et al,* 1986)	560%change/ED_{50} (CI 264 to 1096)	896%change/ED_{50} (CI -16 to 7469)	-100%change/ED_{50} (CI -100 to -100)	-100%change/ED_{50} (CI -99 to -100)
	Propofol (n=6)	80%change/ED_{50} (CI 39 to 133)	139%change/ED_{50} (CI 40 to 307)	-96%change/ED_{50} (CI -85 to -99)	-94%change/ED_{50} (CI -79 to -99)

Table 4.1 Summary of studies performed by the Northwick Park group describing the effects of various anaesthetic agents on latencies and amplitudes of AEPs (CI = Confidence Interval, SE = Standard Error).

The regression slopes of latency or amplitude against concentration changed from one study to the next, even for the same agent, such as enflurane (Thornton *et al,* 1983; Thornton *et al,* 1984). Even more important, they were never equivalent to the MAC or ED_{50} of the anaesthetic agent used. In fact,

the authors were not convinced about the validity of their results (Thornton *et al,* 1989b). Thornton and colleagues (1988) suggested that *amplitudes* but not latencies show promise as measures of depth of anaesthesia, nevertheless Nb *latency* less than 44.5 ms was associated with very light anaesthesia (Thornton *et al,* 1989a). This was not confirmed in a later study (Newton *et al,* 1992), where the mean Nb latencies were found to be significantly longer. Those differences were attributed to minor changes in the evoked potential technique, however, the authors were unable to explain the quantitative differences based on conventional measures of potency between the anaesthetic agents used (Thornton *et al,* 1989b).

4.7 SUMMARY

The MLAEP is a complex signal and the effects of anaesthetics are dramatic: peaks disappear, amplitudes diminish and the curve as a whole appears flattened. Differences between awake and asleep signals are very obvious. However, no automatic computerised method has appeared so far to provide a single measurement that would be fully adequate to determine the level of consciousness.

In addition to difficulties in pattern recognition, the large number of epochs required to obtain an averaged response renders present systems impractical. A measurement, indicating the condition of the patient three or four minutes earlier, cannot be used in every day clinical practice to predict the level of anaesthesia.

Some aspects of the problem were discussed in an editorial by Sebel and colleagues (1985) who suggested that the final index derived from evoked potentials would probably be a function of both latencies and amplitudes. A numerical index, based on the average "double differential" of the AEP waveform, was proposed by the Northwick Park group (Thornton and Newton, 1989; Thornton, 1991). However, no further investigation was undertaken to explore its usefulness. What is really needed is a single

number, extracted from the AEP, reflecting unequivocally the depth of anaesthesia and updated in short, clinically useful intervals.

5. DEVELOPMENT OF AN AEP SYSTEM

5.1 INTRODUCTION

Several commercial evoked potential monitoring systems are available (e.g. Nicolet, Neurotrac). They are very sophisticated, with state-of-the-art EEG amplifiers and comprehensive software. However, they have some disadvantages. They are bulky, very expensive and, most importantly, no software development kits are available for the end user. As a result, one has to rely on the software already supplied by the manufacturer, which is not always the most suitable, especially for research purposes. The solution is the development of a prototype auditory evoked potential (AEP) system using readily available electronic components and equipment. Until a decade ago, this was an almost impossible task. With recent advances in semiconductor technology, a wide range of low cost, high performance microprocessors became available as discrete components, on development boards or as complete microcomputer systems.

The main requirements for such a system are the following:

- The system should have a high quality medical grade EEG amplifier, complying to appropriate standards (BS 5724, IEC 601, ISO 8185).
- The microprocessor should have adequate computing power to allow on-line sampling, averaging of the EEG and further processing of the AEP.
- Appropriate interfaces to allow high speed analogue-to-digital conversion and digital communications with other systems.
- Robust and reliable construction.
- Small size and portability, if the system is to be used in more than one location.
- Readily available components.

- Easy programming interface.

5.2 HARDWARE DESCRIPTION

A system fulfilling all the above requirements has been developed (Figure 5.1).

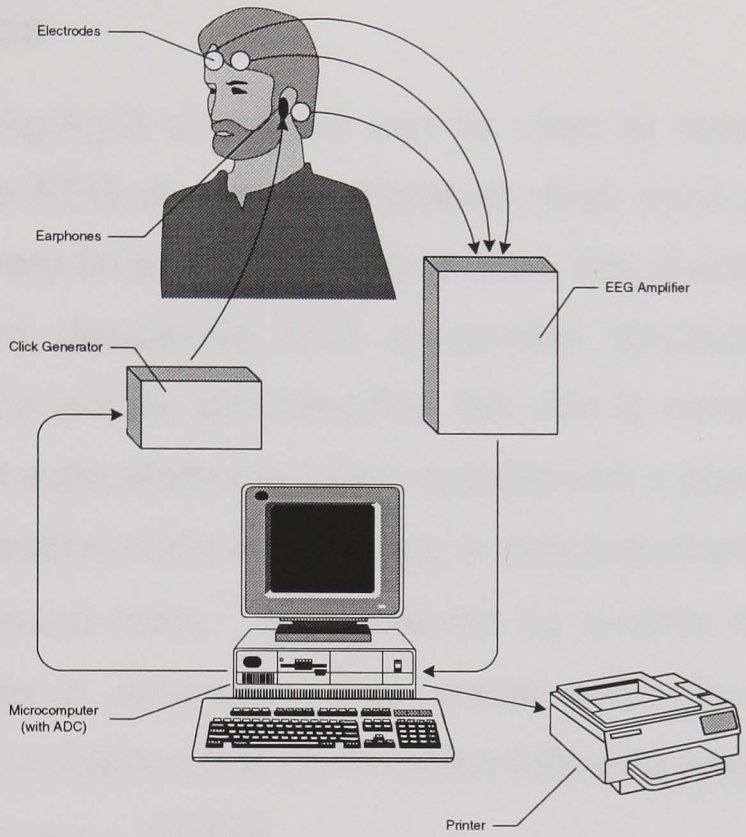

Figure 5.1 Block diagram of the AEP system.

Initially, it consisted of an IBM-compatible desktop personal computer (PC) and a commercial EEG amplifier (Neurotrac). A custom-built EEG amplifier soon replaced the Neurotrac and a smaller computer (either a commercial notebook PC with a PCMCIA card or a purpose-built system) replaced the desktop PC.

The patient usually lies on a bed. The muscles of the face and neck must be relaxed. After skin preparation with alcohol swabs, three electrodes are applied. A pair of standard moulded electrodynamic earphones are inserted into the ears. All connections to the AEP system are made and the

programme is started. All necessary information is entered into the system. The patient is instructed to close their eyes and relax and the acquisition of the auditory evoked potentials begins.

The AEP is produced by averaging 256 EEG sweeps. Each sweep consists of 256 data samples and has a duration of 144 ms. More details are given later in this chapter.

5.2.1 Electrodes

Several types of Ag/AgCl electrodes can be used to obtain the EEG. The best ones are cup EEG electrodes. However, their application on the skin with collodion is very time consuming and often not practical in the clinical situation. Standard disposable ECG electrodes (M-00-S by Medicotest) produce acceptable results, provided that the skin is carefully cleaned with alcohol swabs and extra electrode jelly is applied with a blunt needle.

Maintaining low electrode/skin impedances is very important for two reasons:

- Thermal or Johnson noise. This is caused by random fluctuations of the molecules within a conductor. The actual open-circuit noise voltage generated by a resistance R is given by the following equation:

  $$V_{noise}(rms) = \sqrt{4kTRB}$$

  where k is Boltzmann's constant, T is the absolute temperature in degrees Kelvin, and B is the bandwidth in Hz. For example, a 10 kΩ resistor at room temperature has an open-circuit rms voltage of 0.4 μV, measured with a bandwidth of 1 kHz.
- Common Mode Rejection Ratio (CMRR). CMRR is reduced significantly if the electrodes do not have balanced impedances. The best way to ensure that the impedances are balanced is to make them as low as possible.

A new type of electrodes (Zipprep by Aspect Medical Systems) became available recently. Those electrodes achieve very low impedances (1-3 kΩ) with minimal skin preparation. This is a major improvement and allows easy and reliable use of the system by the average anaesthetist.

The electrodes are placed on the right forehead (+), right mastoid (-) and middle forehead (reference). The position of one of the active electrodes on the forehead was dictated by the nature of the electrodes applied and has been used by other research groups (Sneyd *et al,* 1992; Munglani *et al,* 1993b). It produces MLAEP signals with slightly smaller amplitudes but similar latencies compared to the ones produced by electrodes placed on the vertex (Ozdamar and Kraus, 1983).

5.2.2 Amplifier

The main requirements for the amplifier are the following:

- Very high Common Mode Rejection Ratio (CMRR > 110 dB) even when electrode impedances differ considerably (more than 10 kΩ).
- Frequency response 1-300 Hz.
- System must be suitable for theatre use (shielded or guarded leads, proper patient isolation, electrical immunity to diathermy and other sources of interference).
- Portable with small physical dimensions.
- Battery life must be at least 30 minutes, if running on both battery and mains, or at least 72 hours, if running only on batteries.
- Computer controlled electrode impedance test.
- Computer controlled gain settings (at least between x20000 and x50000).
- Computer controlled test signal (about 100 μV peak-to-peak).
- Computer interfacing.

The first five points are crucial for the correct operation of the system.

The circuit consists of three separate boards: the main amplifier, the gain control board and the power supply (Figure 5.2).

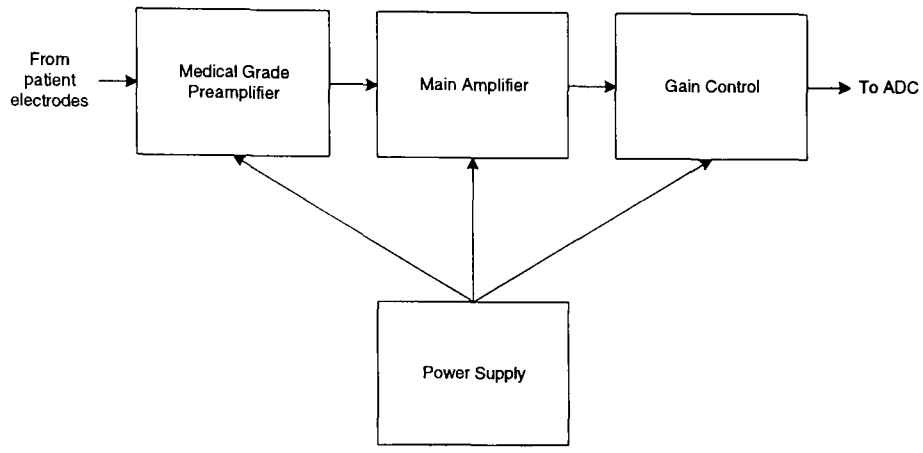

Figure 5.2 Block diagram of the EEG amplifier.

5.2.2.1 Amplifier

The schematic diagram of the amplifier is shown in Figure 5.3.

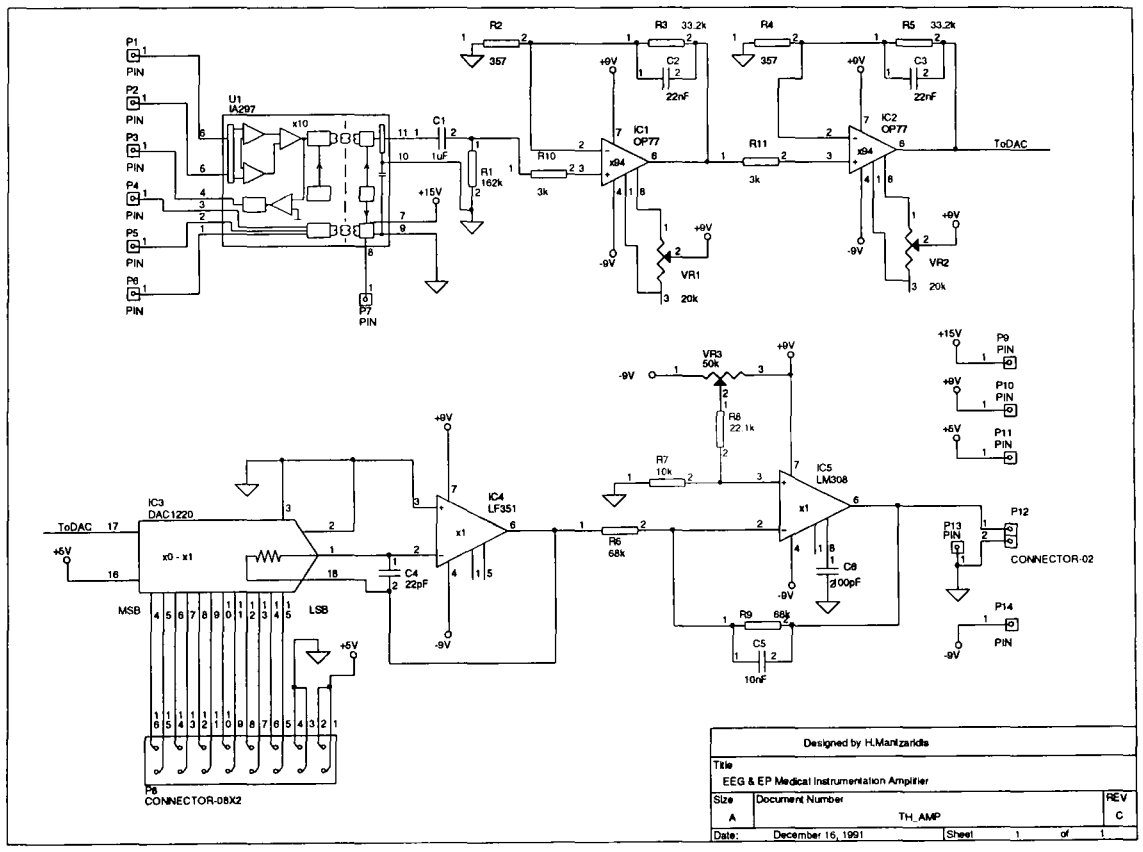

Figure 5.3 Schematic diagram of the EEG amplifier.

The front-end (preamplifier) of the amplifier is the IA 297 (or IA 294) medical isolation amplifier manufactured by Intronics, USA. It offers full patient protection from leakage currents and amplifier fault currents. This applies to both input protection and input/output isolation currents.

The IA 297 is an ultra low noise true medical isolation amplifier. It can operate at common mode input voltages up to 5000 V DC continuous. The Common Mode Rejection Ratio (CMRR) is 170 dB with balanced source impedance and 160 dB with 5 kΩ source imbalance. Input voltage noise is 0.3 μV (10 Hz - 1 kHz rms) and current noise is 4 pA (0.05 Hz - 1 kHz rms). Input bias current is 200 pA and, on the failure of any component, is limited to 10 μA. The frequency response is DC to 10 kHz and the overload recovery time is 20 ms.

The IA 294 is a lower cost low noise true medical isolation amplifier. It offers active guard and separate drives for either individual shielded inputs or a common outer shield. CMRR is 126 dB with balanced source impedance and 120 dB with 5 kΩ source imbalance. Input voltage noise is 5 μV (10 Hz - 1 kHz rms) and current noise is 10 pA (0.05 Hz - 1 kHz rms). Input bias current is 2 nA and, on the failure of any component, is limited to 10 μA. The frequency response is DC to 1 kHz and the overload recovery time is 20 ms. It also features 6500 V input to output and differential input protection for defibrillators.

Both IA 294 and IA 297 provide a gain of x10.

The output from U1 (IA 294 or IA 297) is high-pass filtered by the C1-R1 network (first order, -3 dB cut-off point at 0.9 Hz) and then amplified by two similar stages comprising IC1 and IC2 and related circuitry. The operational amplifiers used (OP 77) offer an exceptional gain linearity with an equivalent input noise of 10 $nV/\sqrt{Hz}$. The gain is x94 at each stage. The gain of the entire amplifier is x88360 (=10*94*94).

IC3 and IC4 form a digital attenuator. The gain varies between x0 and x1 in steps of 1/4096. IC3 is a 12-bit digital-to-analogue converter with a linearity error of 0.05% full-scale. This is essentially independent of the voltage

reference. IC4 is a wide bandwidth JFET operational amplifier, offering an input bias current of 50 pA and an equivalent input noise of 25 nV/$\sqrt{Hz}$.

The output stage consists of IC5 and allows a DC offset voltage to be introduced into the signal. This feature simplifies the connection with unipolar analogue-to-digital converters.

The signal is filtered by three low-pass first order filters (C2-R3, C3-R5 and C5-R9) with a -3 dB cut-off point at 219 Hz.

All resistors are precision metal film with 0.1% tolerance and temperature coefficient ±15 ppm/°C. Polarised capacitors are solid tantalum and non-polarised capacitors are metallised polycarbonate film with 5% tolerance and temperature coefficient ±50 ppm/°C. Ceramic capacitors (0.1 µF) are widely used for by-passing.

Later versions of the amplifier were built with surface mount components (SMD) and some of the operational amplifiers had to be replaced with equivalent ones. The characteristics of the system remained the same, but the physical dimensions were reduced dramatically. As a result, the whole amplifier could be positioned near the patient's head, thus reducing the sources of interference.

5.2.2.2 Gain control board

An additional circuit that allows remote gain control has been developed. It forms part of the amplifier and consists of a 12-bit digital-to-analogue converter (DAC) and an operational amplifier (see above for a detailed description).

A separate board provides the digital input signals required by the DAC. It offers the following facilities:

- Gain control of the main amplifier either manually or by a computer.
- Initial power-up gain can be pre-set by the use of DIP-switches.
- Reset button, which sets the gain to its pre-set value.

- Optical isolation between the computer and the board to avoid digital noise and ground loop problems.
- Indication of the gain by means of a LED bar or digital display.

The schematic diagram of the gain control board is shown in Figure 5.4.

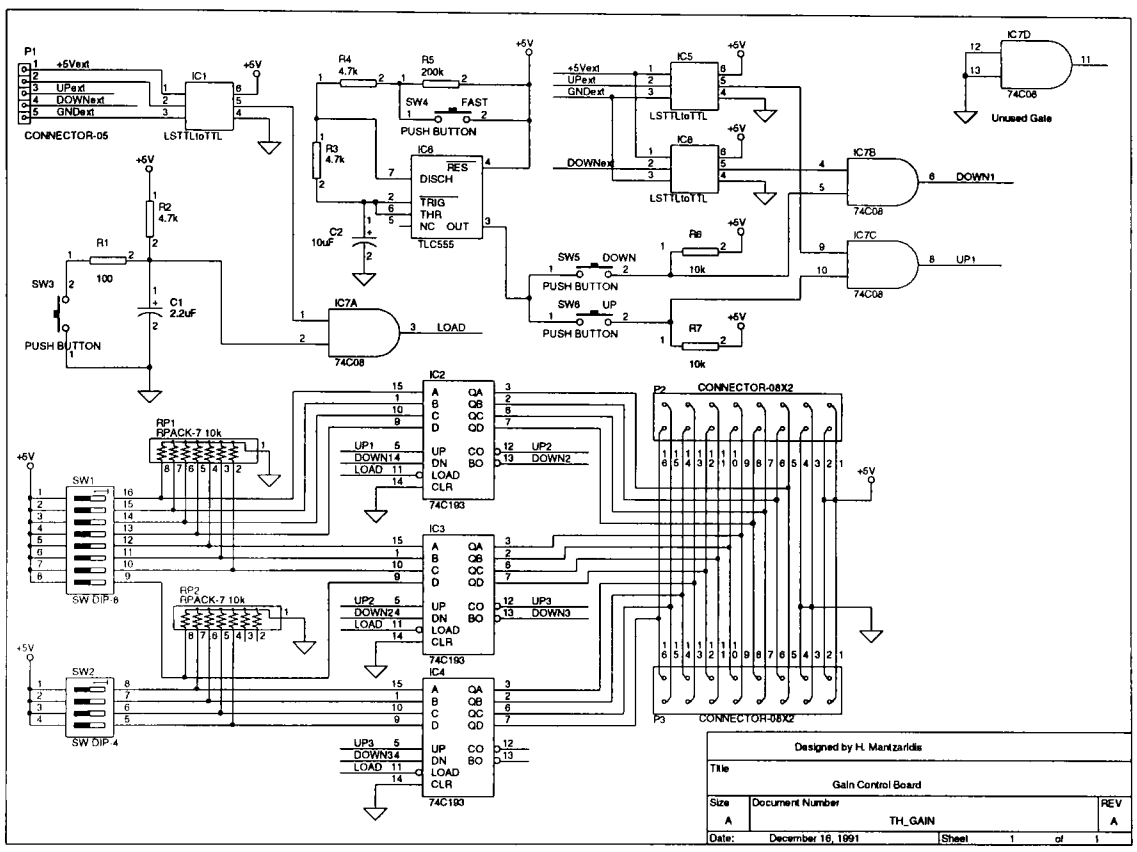

Figure 5.4 Schematic diagram of the gain control board.

IC2, IC3 and IC4 form a 12-bit up-down binary counter with 12 pre-set inputs and reset. The up and down pulses are provided either by the computer, through IC1, IC5 and IC8 (TTL-to-TTL optoisolators), or manually, with SW5 and SW6 push-buttons. IC6 provides the proper clock pulses for the manual operation. There is also a push-button (SW4) which increases the clock frequency from 0.5 Hz to 10 Hz for fast gain changes. C1 and R2 provide a power-up reset pulse and SW3 sets the gain to the value pre-set by SW1 and SW2. Three of the four AND gates of IC7 connect the input stage with the up-down counters.

All resistors are 5% tolerance and all capacitors are solid tantalum. Ceramic by-pass capacitors (0.1 μF) are used throughout.

This board was used initially to automatically set the gain of the main amplifier. However, it was soon found that the system would set the gain to a value that was similar for all patients. Thus, this facility was not necessary and was not included in later versions of the system.

5.2.2.3 Power supply unit (PSU)

The power supply is of a conventional linear AC/DC design. It provides high stability low noise outputs of +15 V, ±9 V and +5 V for the various stages of the amplifier and the gain control board. It also offers 5000 V isolation between the primary and secondary coils. Several different versions have been developed, including one with battery backup, therefore individual circuits will not be described.

Commercially available PSUs with similar characteristics can be purchased from most electronic component suppliers.

5.2.3 Click generator

The click generator is triggered by a digital microprocessor output and produces square monophasic electrical pulses of 1 ms duration. These pulses are fed to a pair of standard electrodynamic earphones and generate clicks with amplitude 70 dB above the normal hearing level. In its basic form (Figure 5.5), the click generator consists of a buffer transistor, which drives a high current power transistor. Current limiting resistors provide overload protection.

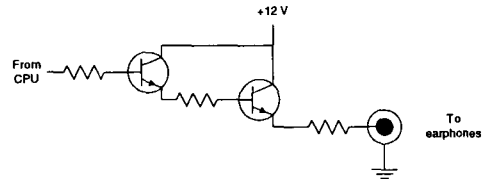

Figure 5.5 Schematic diagram of a basic click generator.

5.2.4 Microcomputer

The system was initially based on an Intel 80286 IBM-compatible personal computer (PC). It was later transferred to a faster 386-based system. At present, three different hardware configurations are used: a 486 IBM-compatible desktop PC with an AT expansion card (PC-27 by Amplicon), a 486 notebook with a PCMCIA card (PCM-DAS08 by Amplicon) and a purpose-built microprocessor system, which will be described below. All three systems use the same software, with only minor modifications to allow for some hardware differences.

5.2.4.1 Purpose-built microprocessor system

It consists of two main boards, the motherboard and the memory board. There is also an interfacing board, a commercially available LCD graphics display and a power supply. A keypad, LEDs, a reset button, RS-232 and amplifier connectors and a mains socket with switch, complete the system (Figure 5.6). Surface mount components (with only few exceptions due to unavailability) were used throughout. The system was designed on a PC running OrCAD/SDT v3.11 for the schematic diagrams and OrCAD/PCB v2.0 for the printed circuit boards.

5.2.4.1.1 Motherboard

The schematic diagram of the motherboard is shown in Figures 5.7 to 5.16.
The microprocessor used (U1) is the Intel 80C186EB running at 16 MHz. It contains an improved 8086 CPU (extra instructions and faster execution times, compared to the 8086), a clock generator, a programmable timer, a programmable interrupt controller, a chip select subsystem, power-down circuitry, a two-channel serial communications interface, a DRAM refresh control unit, a parallel input/output (I/O) interface and a direct interface to an 8087/80187 numeric coprocessor, all accommodated on a single chip. All these integrated on-chip peripheral devices have as a result the great reduction of the external chips required to build a fully functional system.

U2, U3 and U4 are used as address latches, since the 80C186EB address bus is multiplexed with the data bus.

U5A inverts the IRQ signal from the analogue-to-digital converter (U7) and U6 provides extra chip select lines.

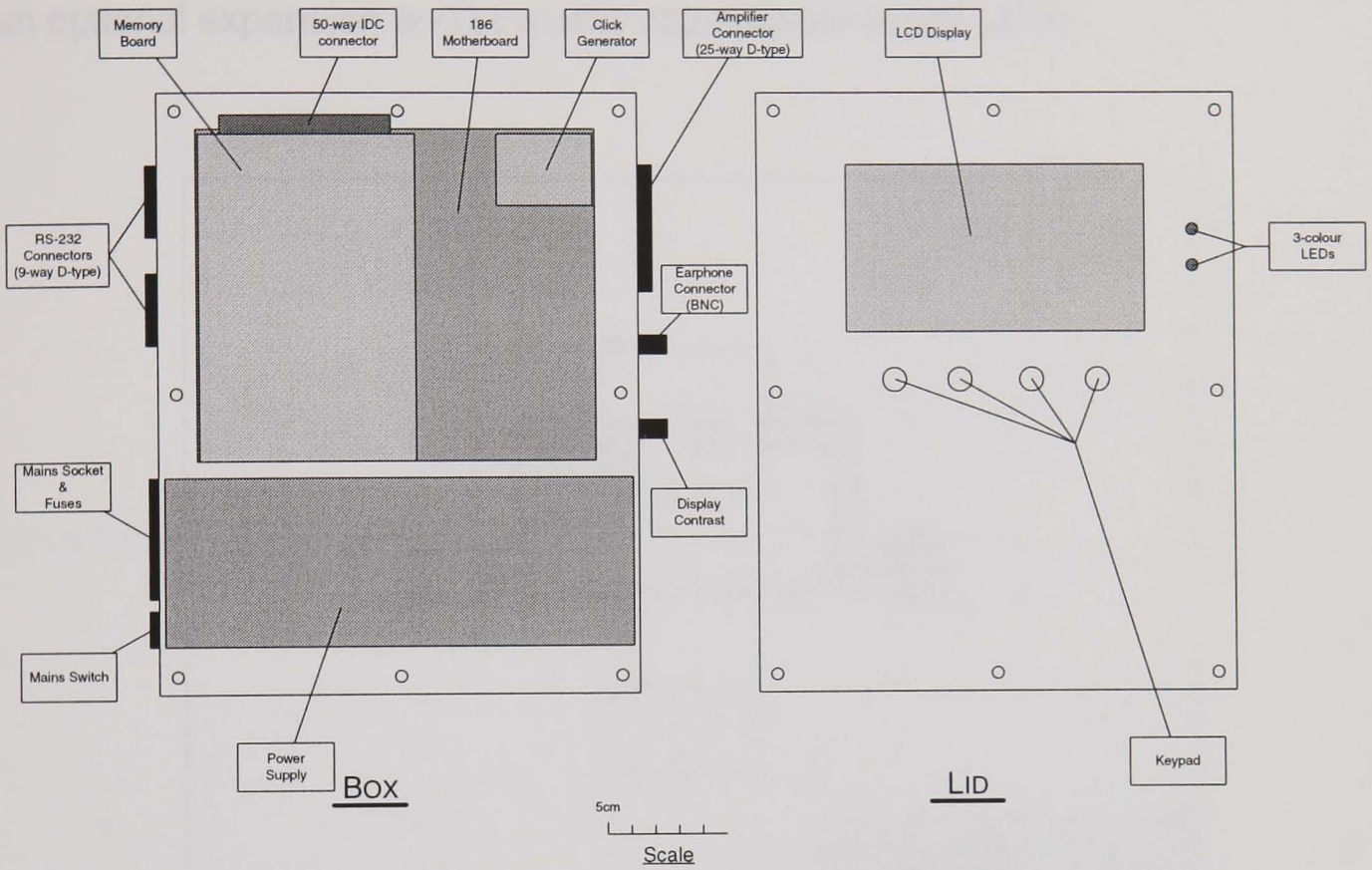

Figure 5.6 The complete 186 system.

U8 is an RS-232 driver, U9 and U10 are programmable I/O chips and U11 is a real time clock (RTC). U5E and U5F invert the INT4 and NMI signals respectively and U12 is a bi-directional buffer which isolates the LCD graphics display connected to JP7 from the system bus.

C1, D1, R1, R2 and an optional external switch connected to P1 and P2 form a hard reset circuit and X1, L1, C2, C3 and C4 are used by the on-chip clock circuit to generate the master system clock.

Q1, Q2 and the related resistors control the +12V power supply to the Flash EPROMs of the memory board.

By-pass capacitors are used throughout the board and tie-up or tie-down resistors hold the respective lines to the appropriate signal levels. Finally, a variety of headers allow connections with external boards and components, including the memory board (JP2), an I/O board (JP5), a keypad (JP6), LED indicators (P8, P11, P12, P13, P14), RS-232 serial communications (JP4) and an optional expansion and/or maths coprocessor board (JP3).

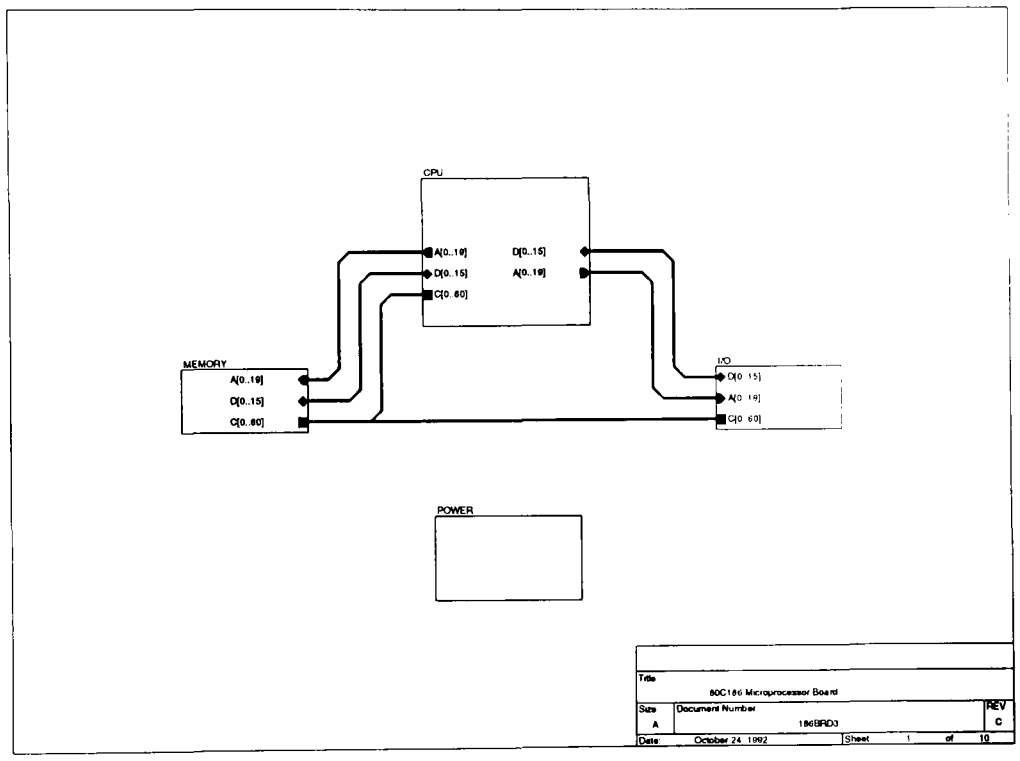

Figure 5.7 Schematic diagram of the 186 motherboard (general block diagram).

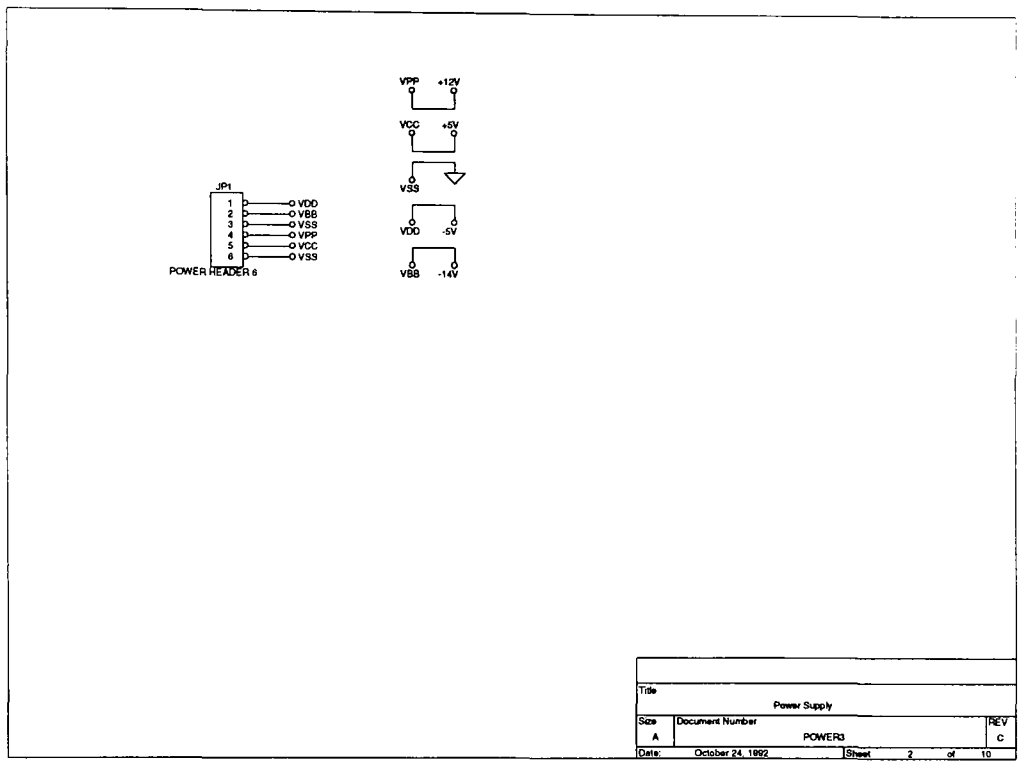

Figure 5.8 Schematic diagram of the 186 motherboard (power supply).

Figure 5.9 Schematic diagram of the 186 motherboard (CPU).

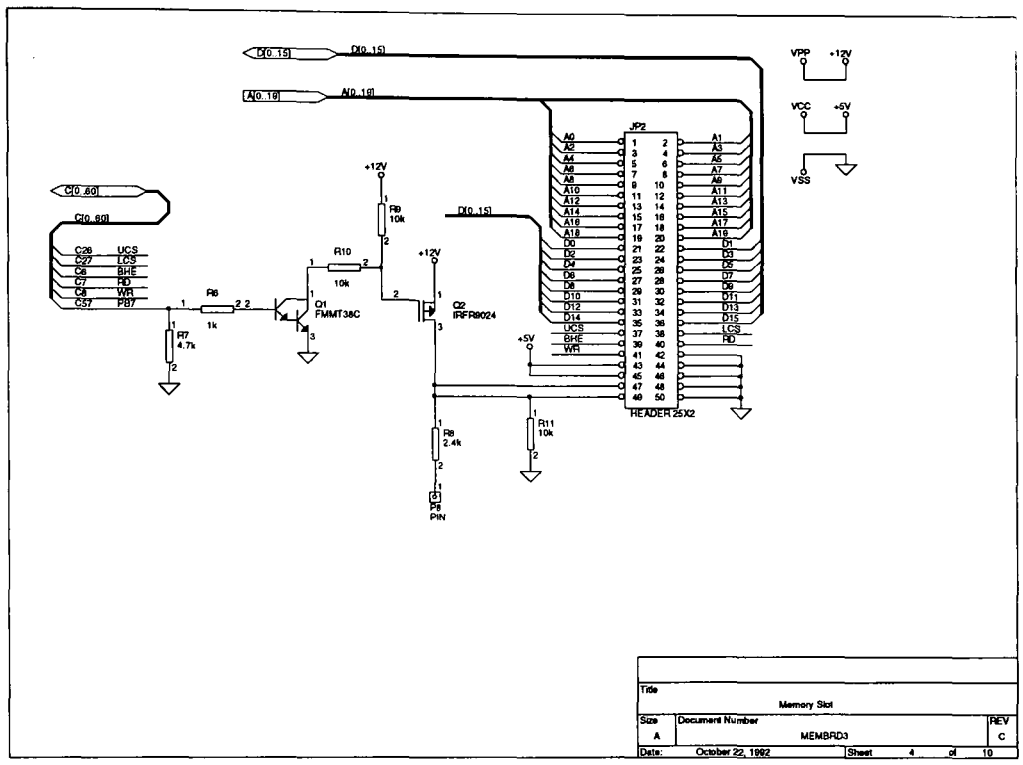

Figure 5.10 Schematic diagram of the 186 motherboard (memory slot).

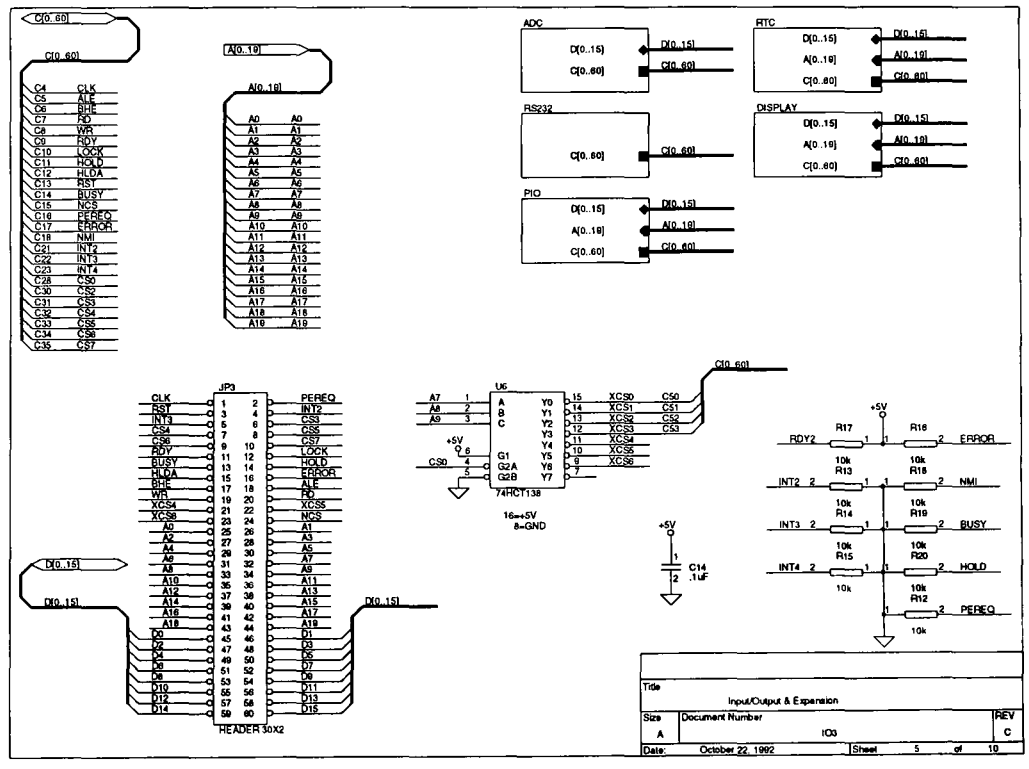

Figure 5.11 Schematic diagram of the 186 motherboard (input/output and expansion slot).

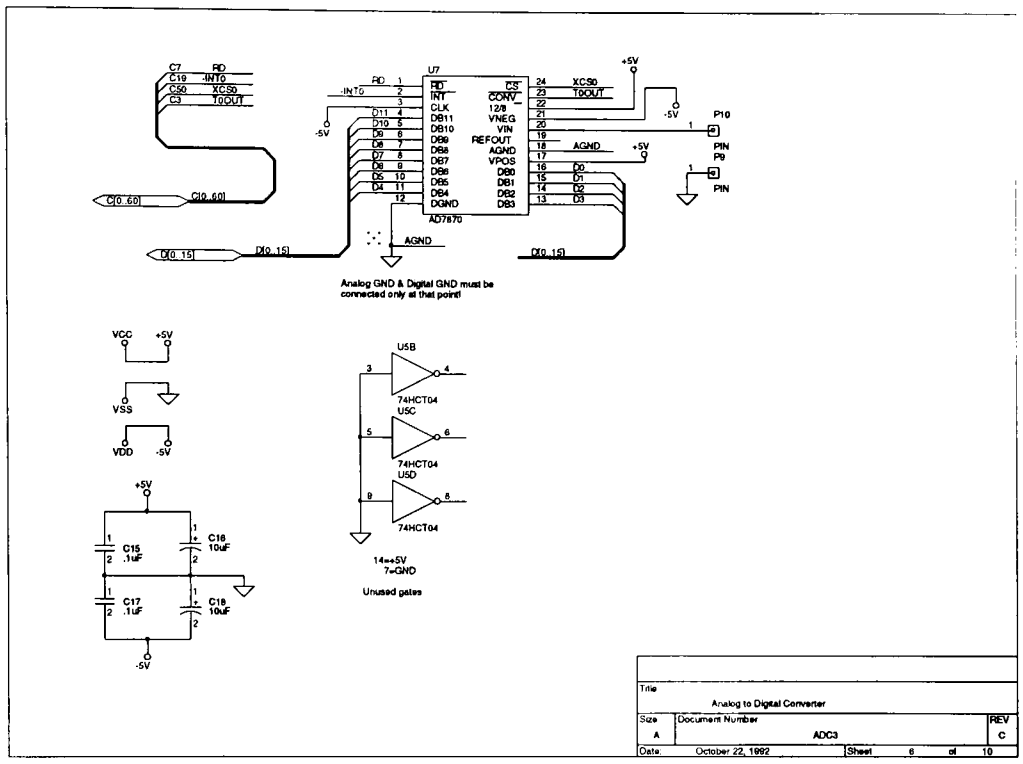

Figure 5.12 Schematic diagram of the 186 motherboard (ADC).

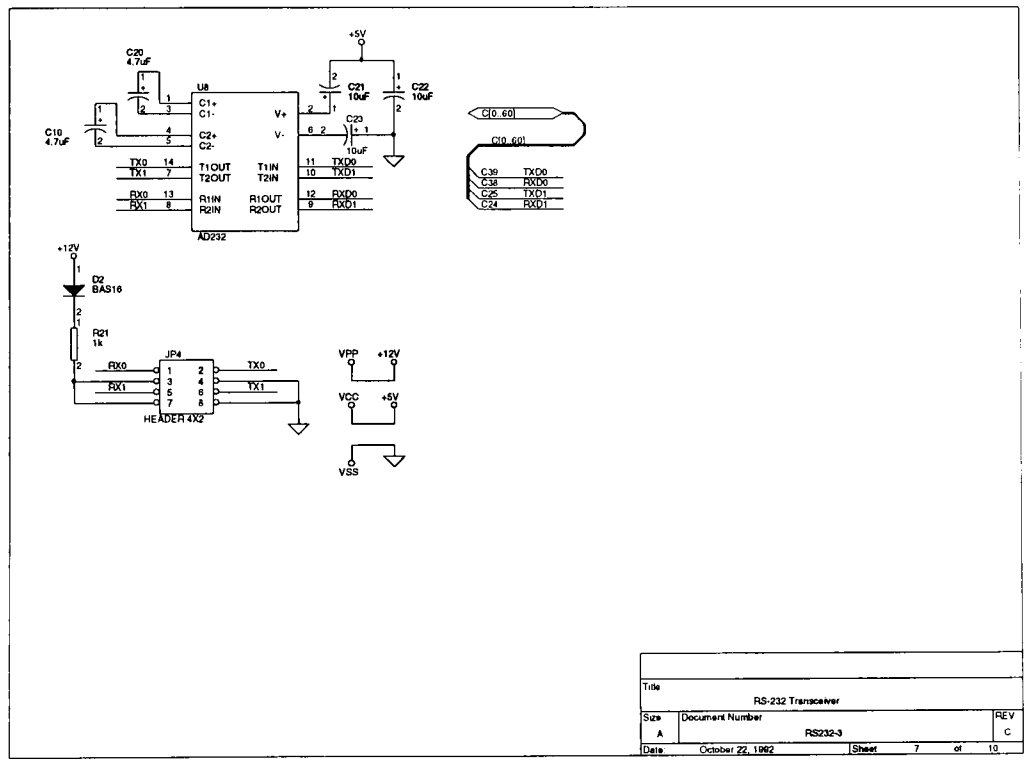

Figure 5.13 Schematic diagram of the 186 motherboard (RS-232).

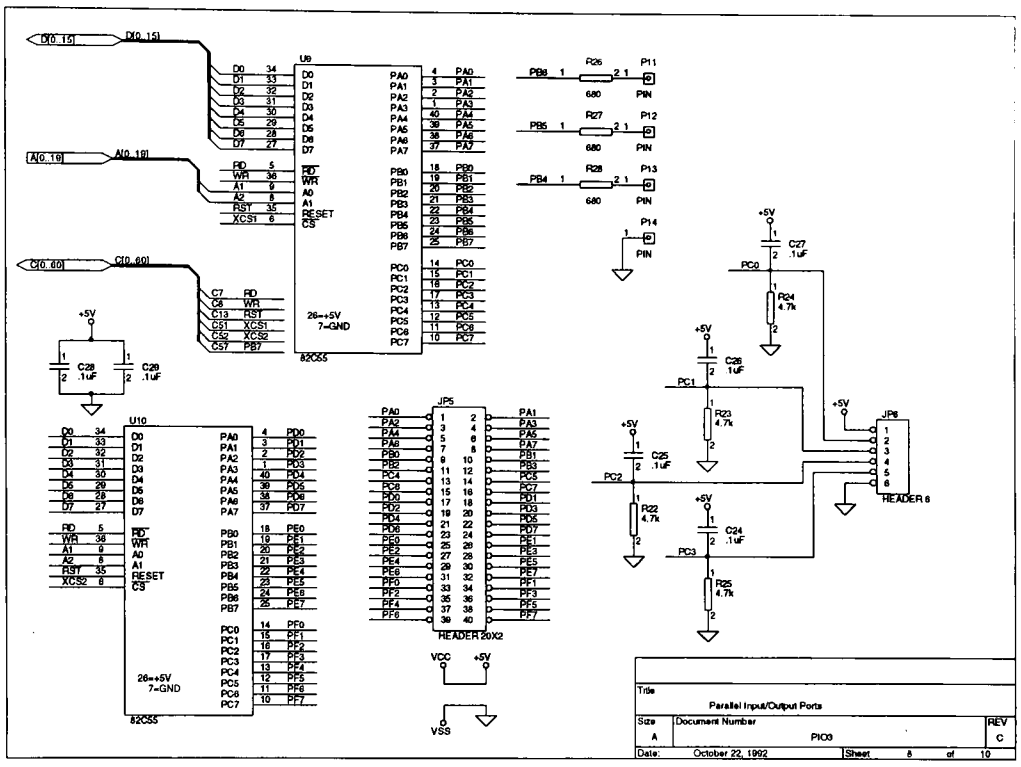

Figure 5.14 Schematic diagram of the 186 motherboard (parallel I/O).

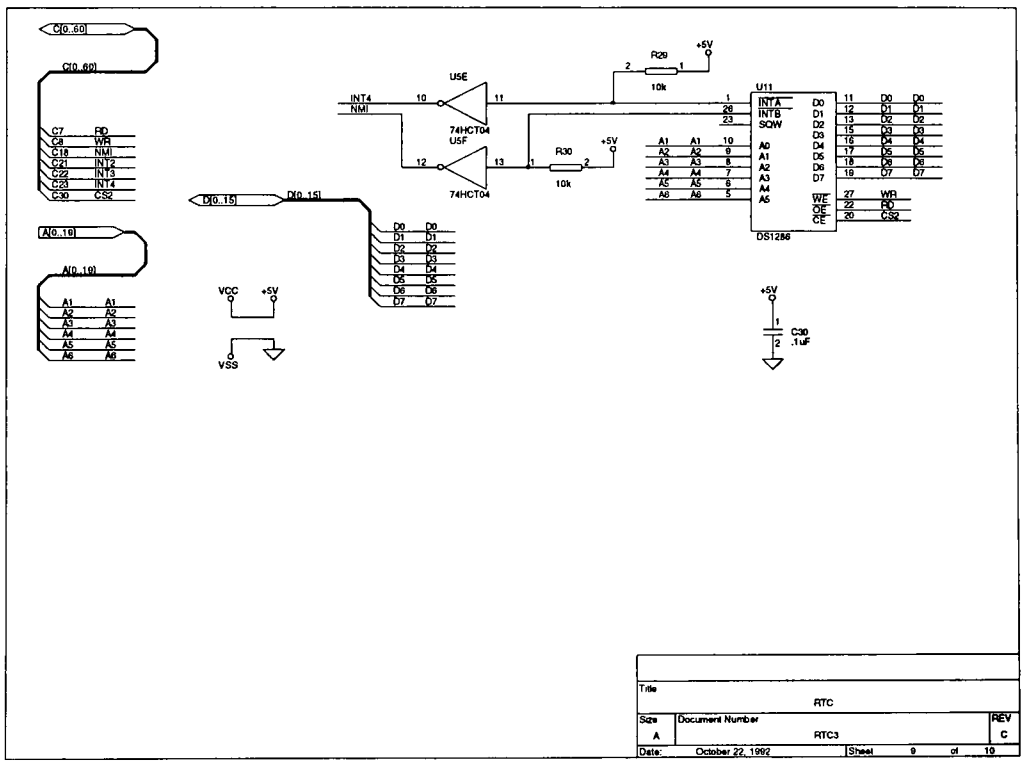

Figure 5.15 Schematic diagram of the 186 motherboard (real time clock).

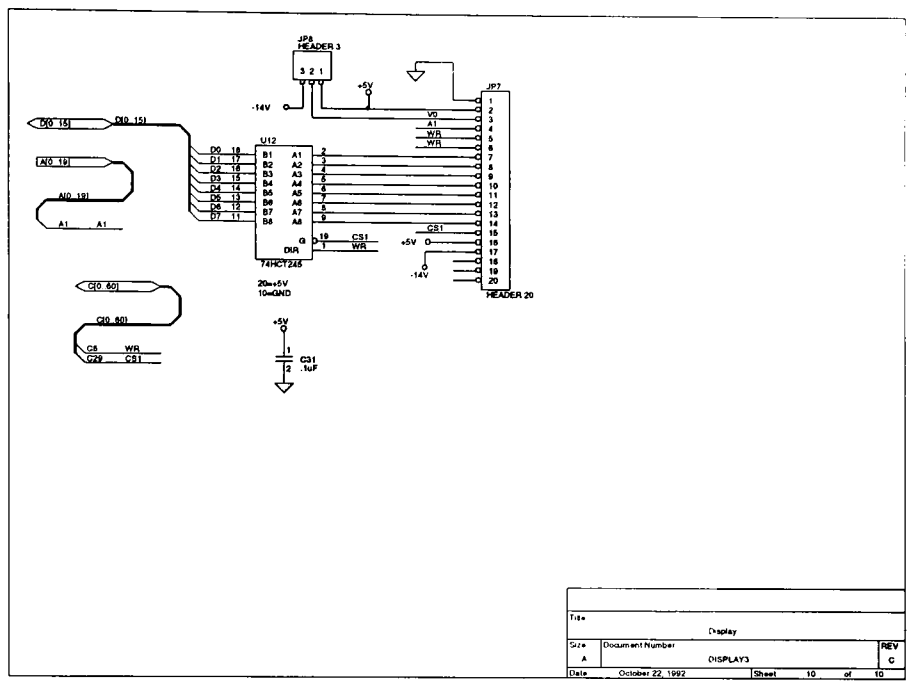

Figure 5.16 Schematic diagram of the 186 motherboard (display).

5.2.4.1.2 Memory board

The schematic diagram of the memory board is shown in Figures 5.17 to 5.19.

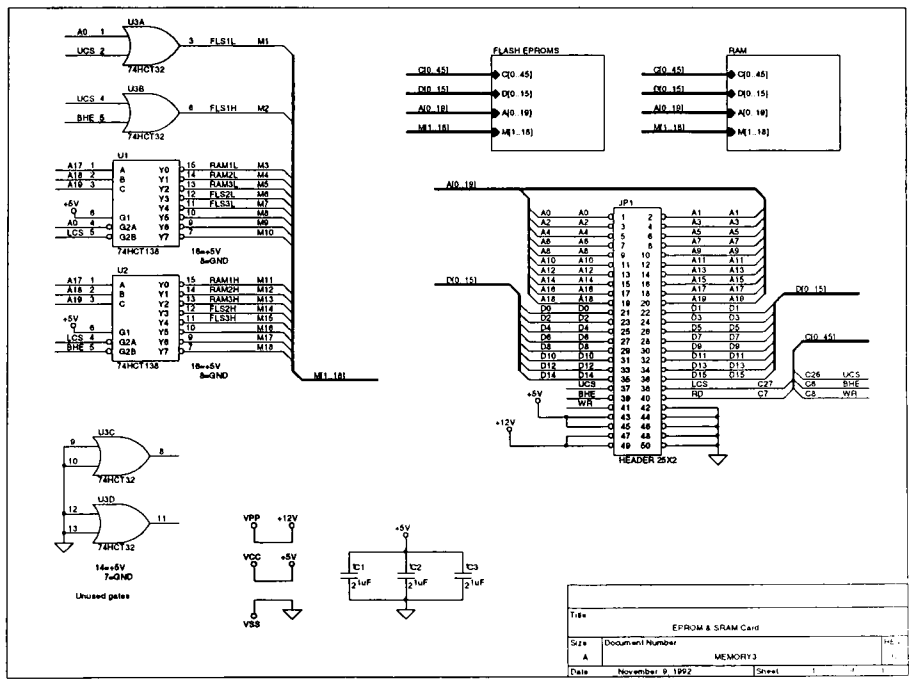

Figure 5.17 Schematic diagram of the 186 memory board (decoders).

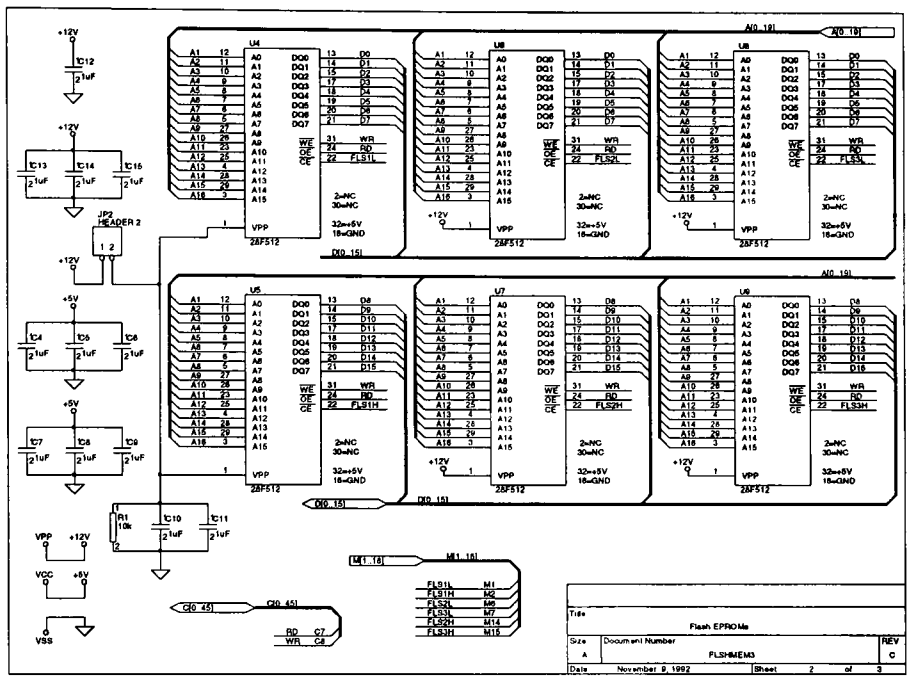

Figure 5.18 Schematic diagram of the 186 memory board (Flash EPROMs).

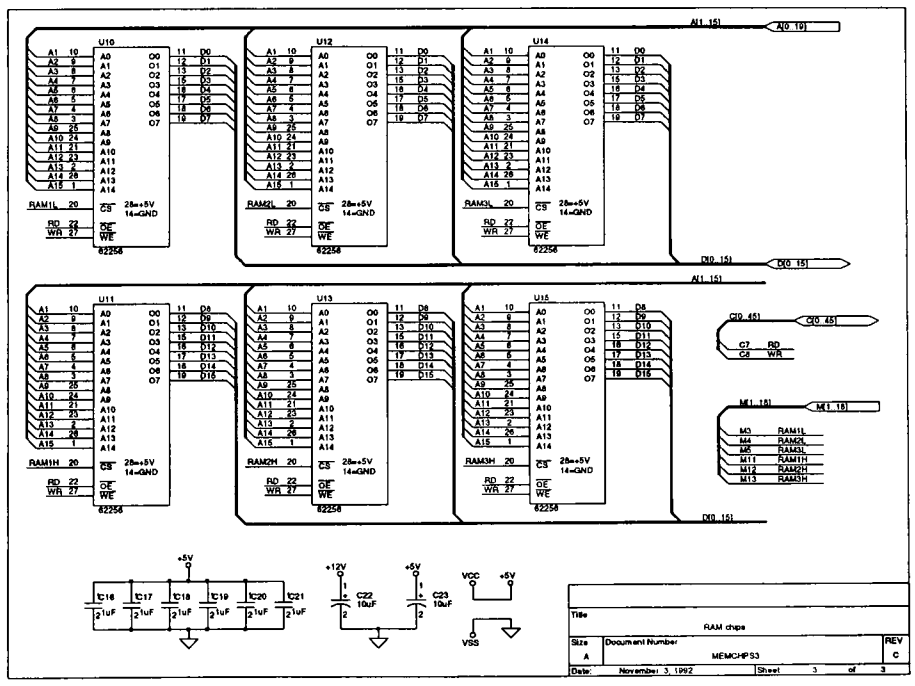

Figure 5.19 Schematic diagram of the 186 memory board (RAM).

The memory board consists of 6x64 Kbytes Flash EPROM chips (U4-U9) and 6x32 Kbytes SRAM chips (U10-U15) giving a total of 192 Kbytes RAM and 384 Kbytes of non-volatile media used both for programme and data storage. U1, U2, U3A and U3B perform all necessary address decoding and a series of capacitors are used for by-passing.

5.2.4.1.3 Interfacing board

This board contains the click generator. It was designed to allow future versions to contain an extended keyboard controller, a loudspeaker driving circuit (for audible alarms, etc.) and any other peripheral devices that might be needed.

5.2.4.1.4 LCD graphics display

The LCD graphics display is manufactured by Hitachi (model LMG6401PLGE with backlight and built-in controller and RAM). It has a resolution of 240 by 128 pixels and is controlled by a Hitachi HD61830B dot matrix liquid crystal graphic display controller.

5.2.4.1.5 Power supply

Several versions of this board have been built. The basic model provides power only to the 186 system. More advanced versions provide all necessary voltages for the 186 system and the EEG amplifier and are able to run for 20-30 minutes on battery power.

5.2.5 Other hardware

A separate hand-held *electrode impedance meter* has been designed (Figure 5.20).

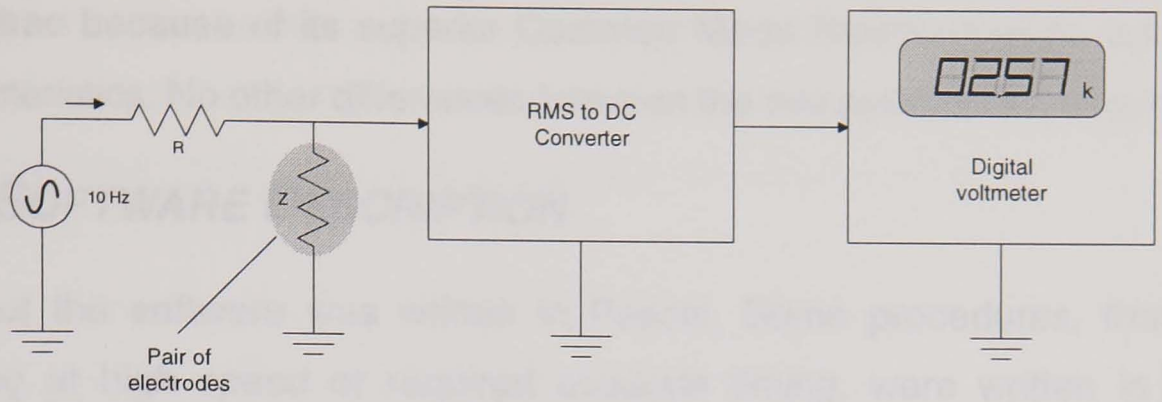

Figure 5.20 Block diagram of an electrode impedance meter.

It consists of a constant current AC voltage source, an RMS-to-DC converter and a digital voltmeter. The sinusoidal AC voltage generated by the constant current source is fed through R and Z. The RMS-to-DC converter (AD620AN by Analog Devices) converts the AC waveform into a constant DC voltage, which is measured and displayed by the digital voltmeter. If the amplitude of the AC voltage source and the value of R are known, then Z (which is the impedance of the pair of electrodes to be measured) can be calculated easily from the voltage drop across it (generalised Ohm's law).

5.2.6 System testing

The entire AEP system was tested by a qualified electronics technician using the appropriate testing equipment and was certified to comply to the standards governing the safety of electrical medical equipment (BS 5724, IEC 601, ISO 8185).

The various stages of the EEG amplifier were tested separately by the same technician and were found to conform to the specifications listed in paragraph 5.2.2.

Finally, the performance of the system was assessed by obtaining a large number of AEPs from volunteers (including the author of this thesis and his supervisors). These signals were similar to the ones described in the literature. They were also compared to AEPs recorded from the same volunteers with the commercially available Neurotrac system. The custom-built EEG amplifier generally produced better quality signals than the EEG amplifier of the

Neurotrac because of its superior Common Mode Rejection Ratio and noise characteristics. No other differences between the two systems were found.

5.3 SOFTWARE DESCRIPTION

Most of the software was written in Pascal. Some procedures, that were running at high speed or required accurate timing, were written in 80x86 Assembly. Additional Assembly software was developed for the 186 system, i.e. the start-up, self-test, graphics and other operating system or hardware-specific routines.

Microsoft Assembler v5.1 and Borland Turbo Pascal v6.0 were used for the PC software. For the 186 system, the software was developed with the Intel Development Tools (Macro Assembler ASM-86 v3.1, Pascal-86 v3.4, System Utilities and the ICE-186EB in-circuit hardware emulator).

5.3.1 Programme organisation

The programme is organised in two distinct entities: the *Foreground Task* and the *Background Task*. Both tasks run in parallel. They are completely independent from each other and communicate through *semaphores*. The user can control only the Foreground Task, which in turn, sets up, starts and stops the Background Task (Figure 5.21)

The Background Task (Figure 5.22) is basically an *interrupt service routine* (ISR). For a 144 ms sweep consisting of 256 samples, the ADC generates hardware interrupts at a rate of 1.78 kHz. Those interrupts are serviced by the Background Task, which is responsible for the click generation, data collection, artefact rejection, implementation of a Moving Time Average and calculation and presentation of an averaged response to the Foreground Task.

The Foreground Task is responsible for the digital filtering of the averaged response, the calculation of the Auditory Evoked Potential Index (AEPidx), the presentation of the data on the screen using high resolution graphics and the

storage of the curve-data on the hard disc (PC) or Flash EPROMs (186). It is also responsible for all other general "housekeeping" functions (time display, keyboard input, generation of sound signals and alarms, etc.).

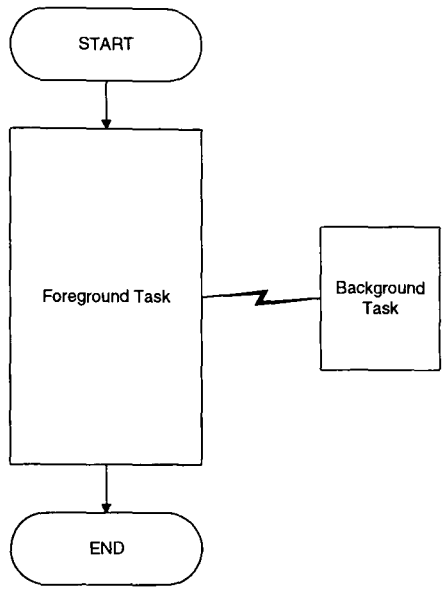

Figure 5.21 Block diagram of the Foreground and Background Tasks.

On the PC, the Background Task was implemented as a *Terminate-and-Stay-Resident* (TSR) routine and was written in 80x86 Assembly. Its TSR structure allows completely independent operation, thus making it totally transparent to the rest of the programs that might be running concurrently.

The Foreground Task (Figure 5.23) was written mainly in Pascal, but some procedures were written in Assembly.

During initialisation (Figure 5.24), the two tasks communicate via the *Intra-Application Communication Area* (a special DOS memory structure which is 16 bytes long from 0040:00F0H through 0040:00FFH), but thereafter, information flows between them via a set of pointers and buffers (*semaphores*).

A similar set-up was used on the 186 system, although there was no need for the implementation of the Background Task as a TSR. When power is first applied to the system, the CPU starts executing the instructions found in the boot Flash EPROMs (Figure 5.25).

The start-up routines perform several tasks:

- Run a quick reliability test to ensure that the hardware (including memory) is functioning properly.
- Initialise the peripheral units integrated in the 80C186EB and the external chips and devices connected to it.
- Set up the interrupt vector table.
- Pass control to the main programme.

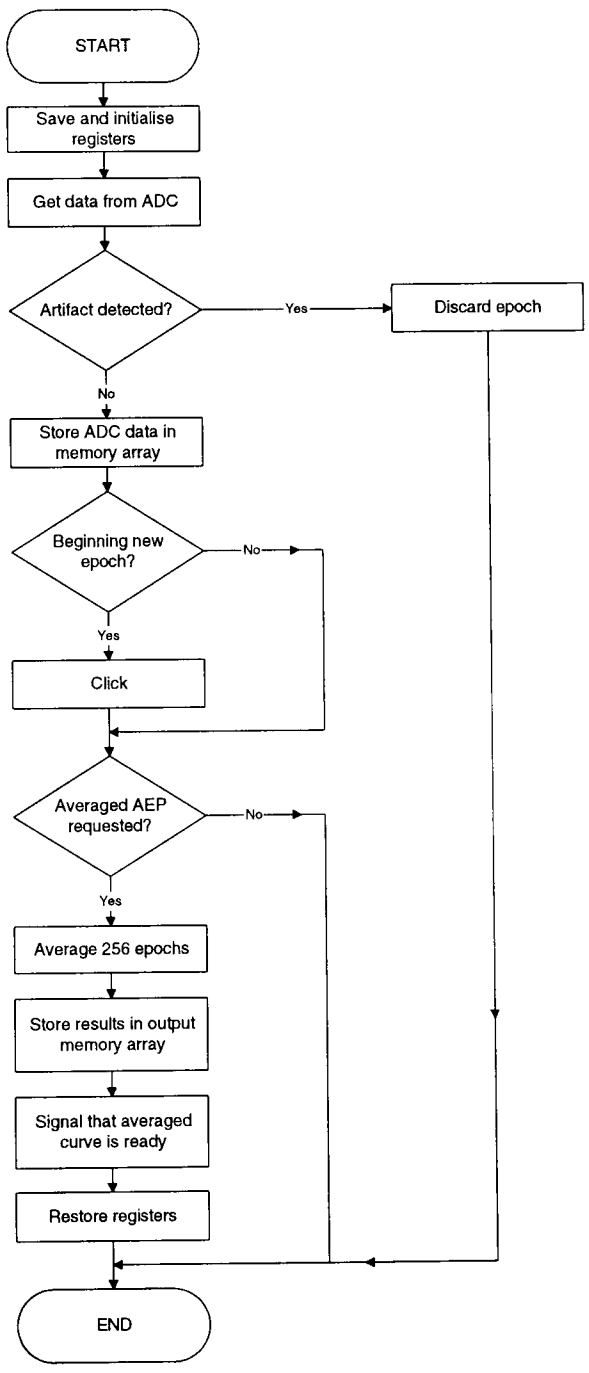

Figure 5.22 Flowchart of the Background Task.

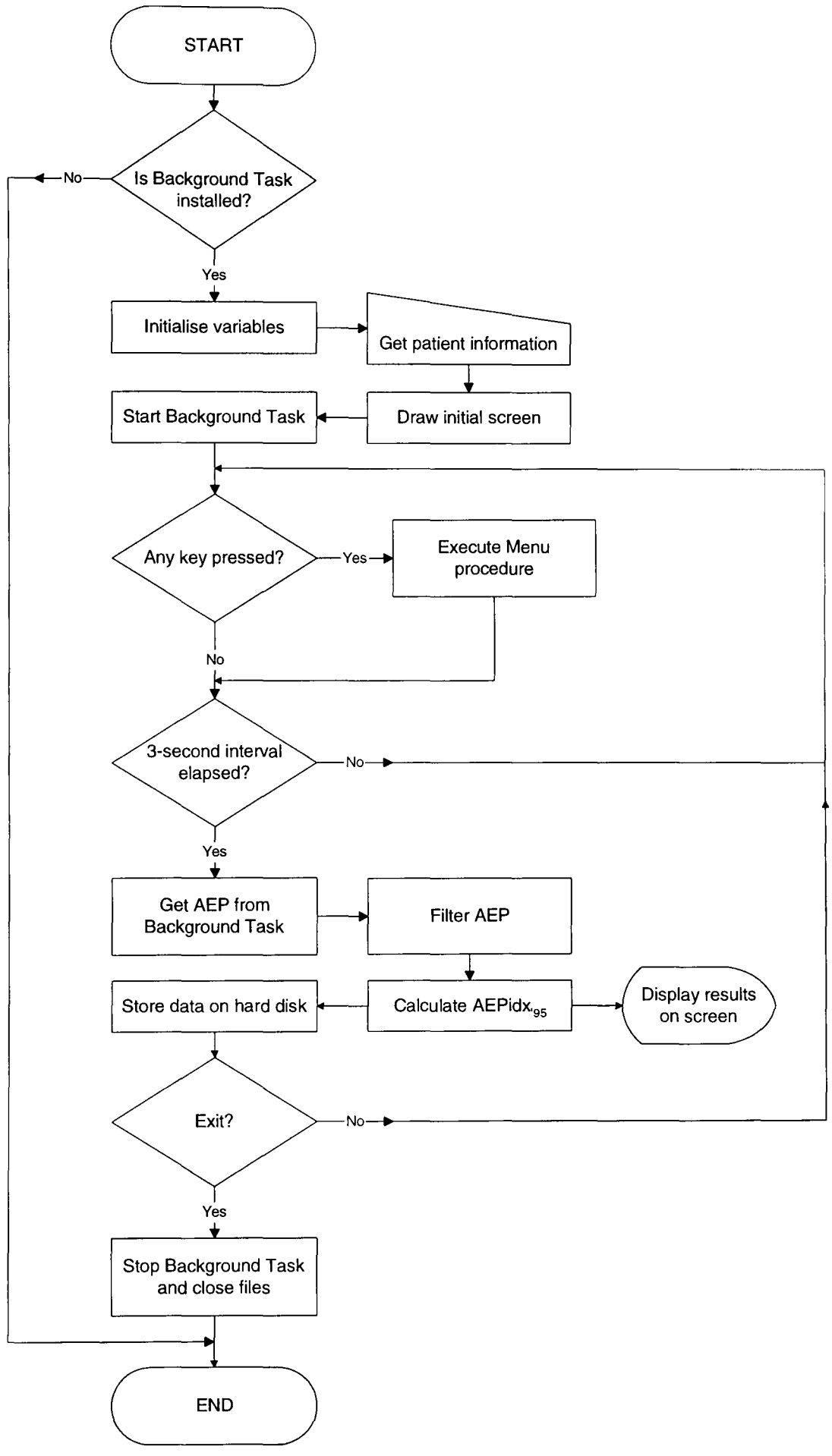

Figure 5.23 Flowchart of the Foreground Task (PC).

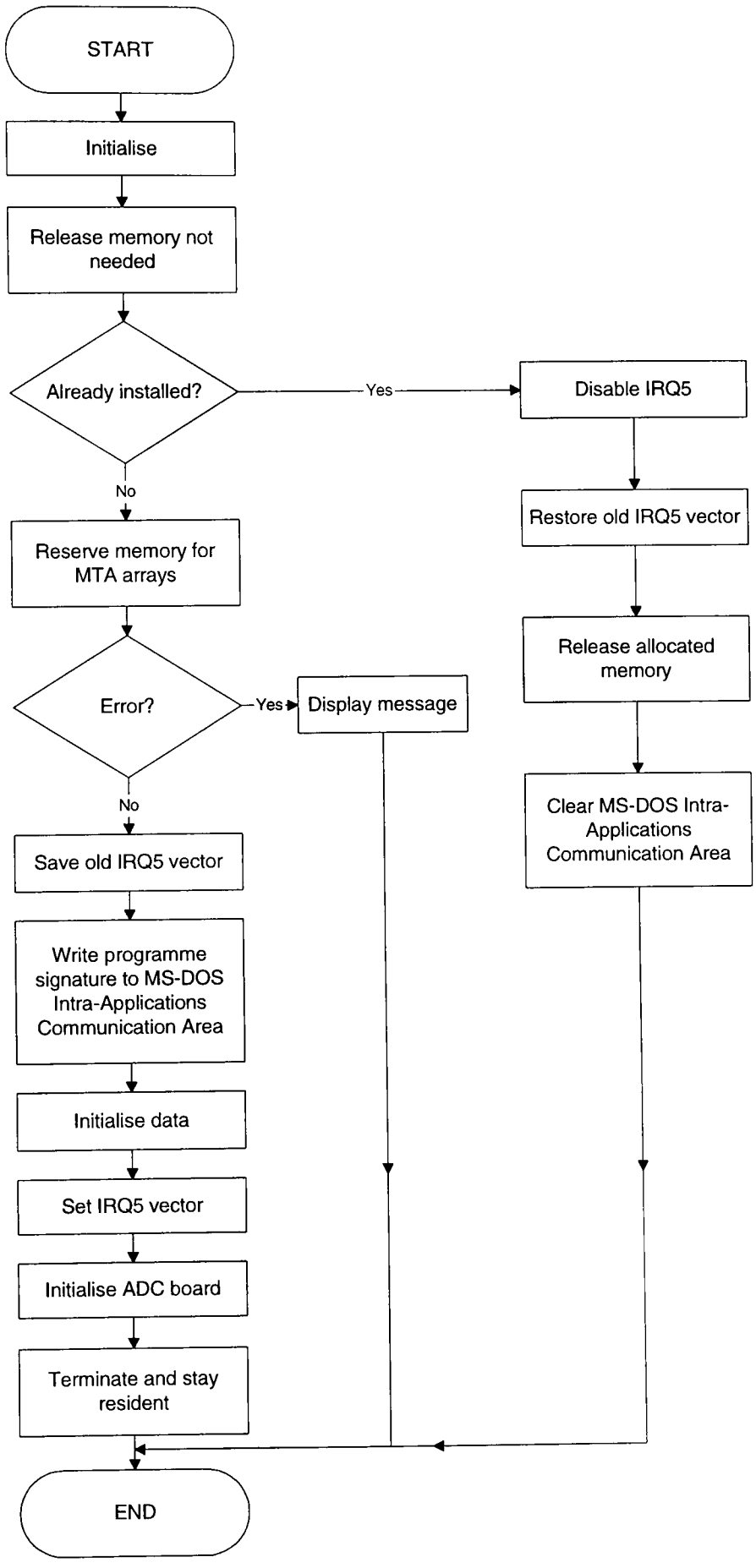

Figure 5.24 Flowchart of the initialisation of the Background Task (PC).

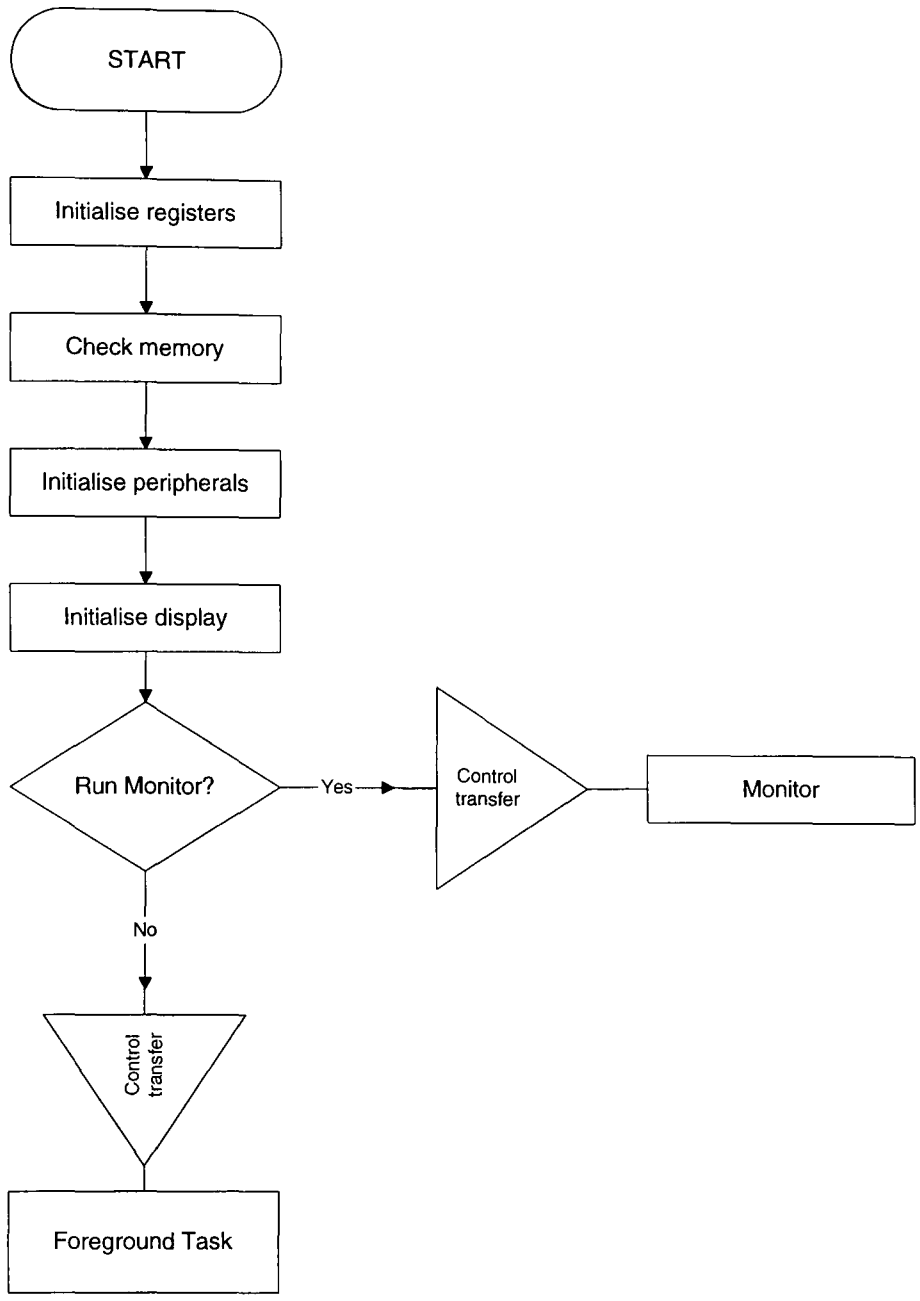

Figure 5.25 Flowchart of the bootstrap routines (186).

The main programme (Figure 5.26) initialises all necessary variables, draws the initial screen on the display and prompts the user to press a key to start clicking. Once clicking is started, the system is responsible for clicking, recording the raw EEG, extracting and processing the AEP and displaying all relevant information on the screen.

The *monitor* software module is a separate debugging tool. It was written in 80x86 Assembly and allows on-board reprogramming of the Flash EPROMs.

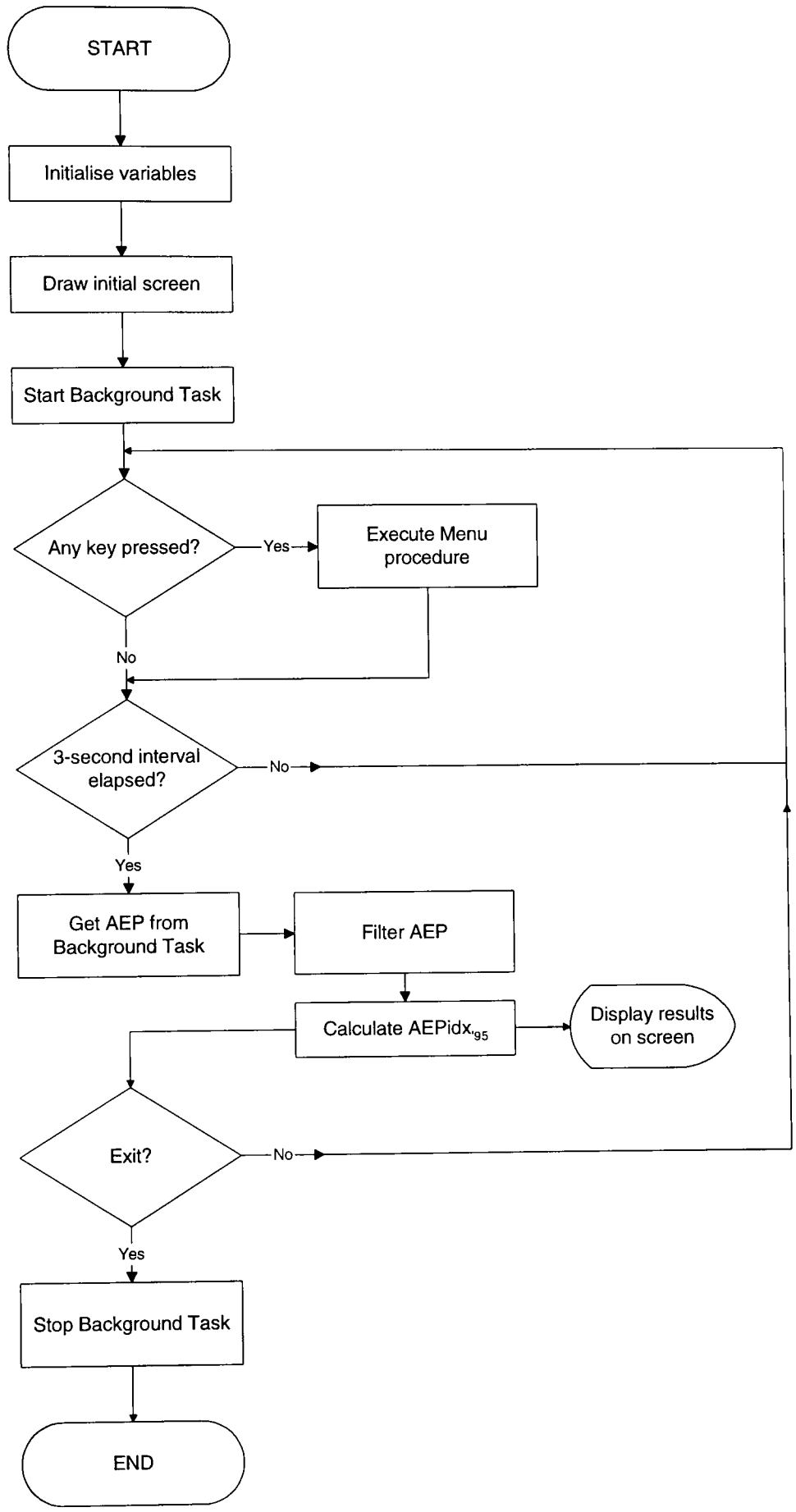

Figure 5.26 Flowchart of the Foreground Task (186).

The combination of the two tasks yielded a fast and reliable programme running in real time. There was even adequate CPU power to implement the

closed-loop control algorithm and communicate with a target-controlled propofol infusion system described later in this thesis.

5.3.2 Averaging

The Background Task stores the sampled raw EEG in a 256 by 256 memory array (Figure 5.27).

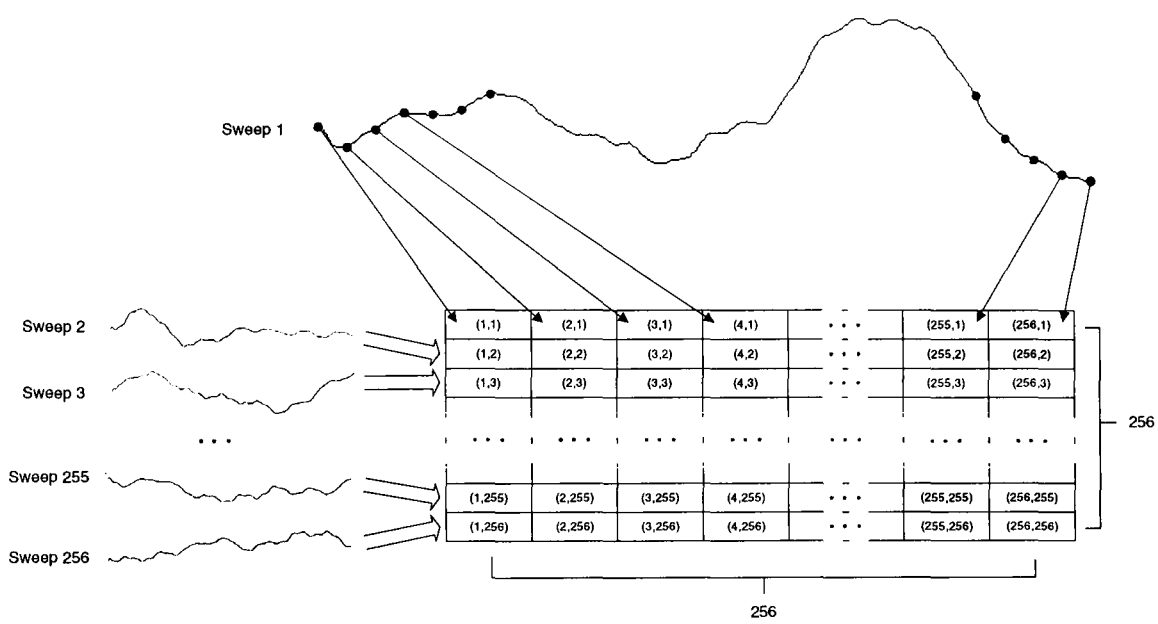

Figure 5.27 Sampling and storage of the EEG.

The first sample from the ADC is stored in cell (1,1), the second in cell (2,1) until the 256th sample, which is stored in cell (256,1). The first row of data thus constitutes sweep 1. Consecutive sweeps are stored in successive rows, until sweep 256, which is stored in row 256. The cycle is repeated continuously with sweep 257 being stored in row 1, sweep 258 in row 2, and so forth, until the end of the programme.

Every 3 seconds, the contents of each column of data are averaged to produce the final AEP curve (Figure 5.28).

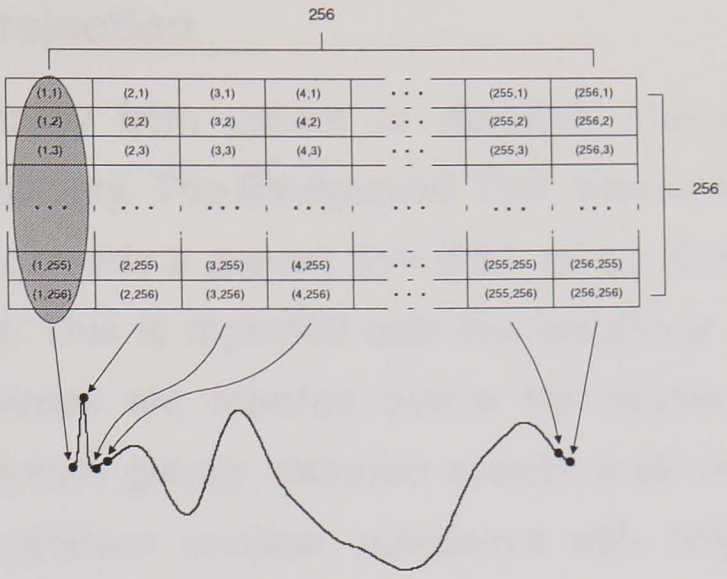

Figure 5.28 Averaging of the EEG.

5.3.3 Moving Time Average (MTA)

The *Moving Time Average* (MTA) technique allows a faster response of the system to changes in the AEP signals than traditional averaging methods (Figure 5.29). An array of the last 256 sweeps is kept in memory. New sweeps are stored in the array and the old ones are discarded. This process is performed continuously by the Background Task. As a result, the array always contains the most up-to-date EEG sweeps.

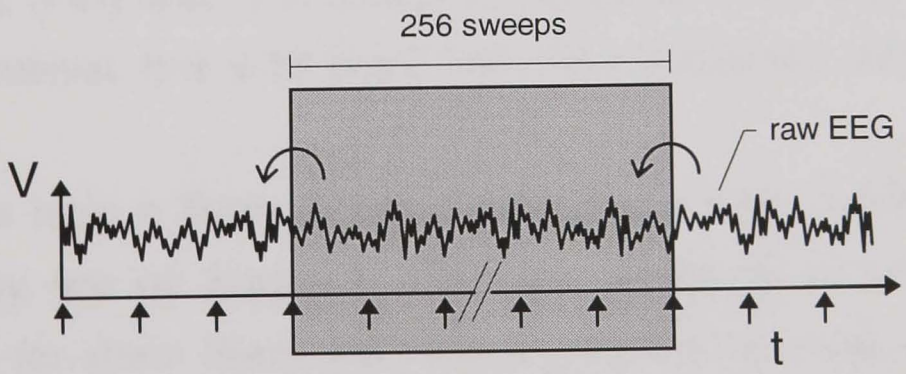

Figure 5.29 The Moving Time Average technique. The shaded area is the part of the EEG that is averaged to produce the AEP curve. Clicks are denoted by arrows.

5.3.4 Artefact rejection

Artefacts arise mainly from patient or electrode movement and use of diathermy during surgery. The Background Task examines the amplitude of each sweep. If it exceeds a pre-set limit (99% of the ADC range), then the sweep is rejected. This is repeated until the amplitude returns to normal. Several more sweeps are rejected before the system resumes normal operation. This feature greatly improves system performance, since some artefact sources produce unusual waveforms with only intermittent high amplitude peaks. Those waveforms would otherwise remain undetected and probably contaminate the AEP signals. Currently, seven extra sweeps are rejected, but this number depends on the characteristics of the diathermy and other equipment, and may change in the future.

In the 186 software version, the limit at which an artefact is detected can be set by the user. This option allows optimum artefact rejection in different operating theatre environments and will be available in future PC versions.

5.3.5 Digital filtering

In order to further enhance the signals, some smoothing of the curves is required. This task is performed by a digital low-pass Finite Impulse Response (FIR) filter. The frequency response of this filter is 0-0.049 of the Nyquist interval. It is a 35 point filter (18 coefficients), with a raised cosine window.

FIR filters have a linear phase response and their stability is guaranteed, since they use no feedback. They are simple to calculate and analyse, however, for sharp filters, the required number of coefficients is large and this can make the calculations very computationally intensive.

An FIR filter is described by the difference equation:

$$y(n) = b_0 x(n) + b_1 x(n-1) + \ldots + b_{M-1} x(n-M+1)$$

or:

$$y(n) = \sum_{k=0}^{M-1} b_k x(n-k)$$

where x(n) is the input, y(n) is the output, M is the length and $\{b_k\}$ is the set of coefficients.

Alternatively, the output sequence can be expressed as the convolution of the unit sample response h(n) of the system with the input signal:

$$y(n) = \sum_{k=0}^{M-1} h(k)x(n-k) .$$

The filter can also be characterised by its system transfer function:

$$H(z) = \sum_{k=0}^{M-1} h(k)z^{-k} .$$

The desired frequency response specification $H_d(\omega)$ is related to its corresponding unit sample response $h_d(n)$ by the relation:

$$H_d(\omega) = \sum_{n=0}^{\infty} h_d(n)e^{-j\omega n} .$$

In general, the unit sample response $h_d(n)$ obtained from the above equation is infinite in duration, therefore, it must be truncated at n=M-1. This truncation is equivalent to multiplying $h_d(n)$ by a *rectangular* window, defined as:

$$\begin{cases} 1, & n = 0,\ 1,\ldots,M-1 \\ 0, & \text{otherwise} \end{cases}$$

It can be shown that the problem of designing a FIR filter is simply to determine the M coefficients h(n), for n=0, 1,...,M-1 from a specification of the desired frequency response $H_d(\omega)$ of the FIR filter.

The rectangular window has some undesirable properties, which can be alleviated by the use of other windows that do not contain abrupt discontinuities in their time domain characteristics. Some of the most commonly used window functions are given in Table 5.2.

Name of window	Time domain sequence, h(n), 0 ≤ n ≤ M-1
Bartlett (triangular)	$1-\frac{2\left(n-\frac{M-1}{2}\right)}{M-1}$
Blackman	$0.42-0.5\cos\frac{2\pi n}{M-1}+0.08\cos\frac{4\pi n}{M-1}$
Hamming	$0.54-0.46\cos\frac{2\pi n}{M-1}$
Hanning	$\frac{1}{2}\left(1-\cos\frac{2\pi n}{M-1}\right)$
Kaiser	$\frac{I_0\left[\alpha\sqrt{\left(\frac{M-1}{2}\right)^2-\left(n-\frac{M-1}{2}\right)^2}\right]}{I_0\left[\alpha\left(\frac{M-1}{2}\right)\right]}$

Table 5.2 Some window functions for FIR filter design.

Historically, the use of *windows* to truncate the impulse response $h_d(n)$ and to obtain the desired spectral characteristics was the first method proposed for designing linear phase FIR filters.

Two other methods, the *frequency sampling* method and the *Chebyshev approximation* method, were developed in the 1970s and have since become very popular in the design of practical linear phase FIR filters. The Chebyshev approximation method provides total control of the filter specifications, and, as a consequence, it is usually preferable over the two other methods. The window design method can be used as a reasonable approximation, if efficiency of the design is not critical.

Further description of FIR and other digital filters is beyond the scope of this thesis. Several digital signal processing books describe not only FIR filters, but, also, present the fundamentals of discrete time signals, systems and modern digital signal processing algorithms and applications in great detail

(Cohen, 1986; Ludeman, 1986; Williams, 1986; Roberts and Mullis, 1987; Hamming, 1989; Proakis and Manolakis, 1992).

5.3.5.1 FIR demo

This programme demonstrates the implementation of an FIR filter in Turbo Pascal (Appendix B) . The user is asked to provide the number of coefficients and the frequency response of the filter. The programme then plots the frequency response and the coefficients. It also filters an array of 4000 random points and displays the results on the screen.

5.3.5.2 FIR in assembly

A FIR filter, suitable for AEP curve smoothing, has been developed in Assembly (Appendix C). It is a 35-point, raised cosine filter with frequency response 0-0.049 of the Nyquist interval. The coefficients had been previously calculated with *FIR demo*. A pointer to a 256-word array is the input. The results are stored in the same array which is the output of the procedure.

5.3.6 Calculation of an AEP index

At present, AEPs are analysed mostly in terms of amplitudes and latencies of the various peaks. Spectral analysis with the *fast Fourier transformation* (FFT) has also been used. However, as discussed in the previous chapter, a single number, reflecting the morphology of the AEP, is highly desirable but not yet available.

From a mathematical point of view, the problem can be defined as mapping a two-dimensional vector into a one-dimensional space. Obviously, this is not possible. A data reduction technique, that will take only the relevant features of the AEP into account, is required.

It was observed that when patients lost consciousness, the amplitudes of the AEP peaks were reduced and their latencies were increased. Those changes were occurring almost simultaneously and in the same direction in all

patients, therefore a measurement that would reflect those changes could be promising.

Figure 5.30 is a schematic representation of those changes. A sinusoidal signal is sampled at two successive points A and B. The sampling interval is t_s. V is the voltage difference between A and B at any given frequency and amplitude. When the frequency increases and the amplitude remains constant, V increases ($V_2>V_1$, curve b). Similarly, when the frequency remains constant and the amplitude increases, V also increases ($V_3>V_1$, curve c). Finally, when both the frequency and the amplitude increase, the voltage difference between A and B increases even more ($V_4>V_1$, curve d).

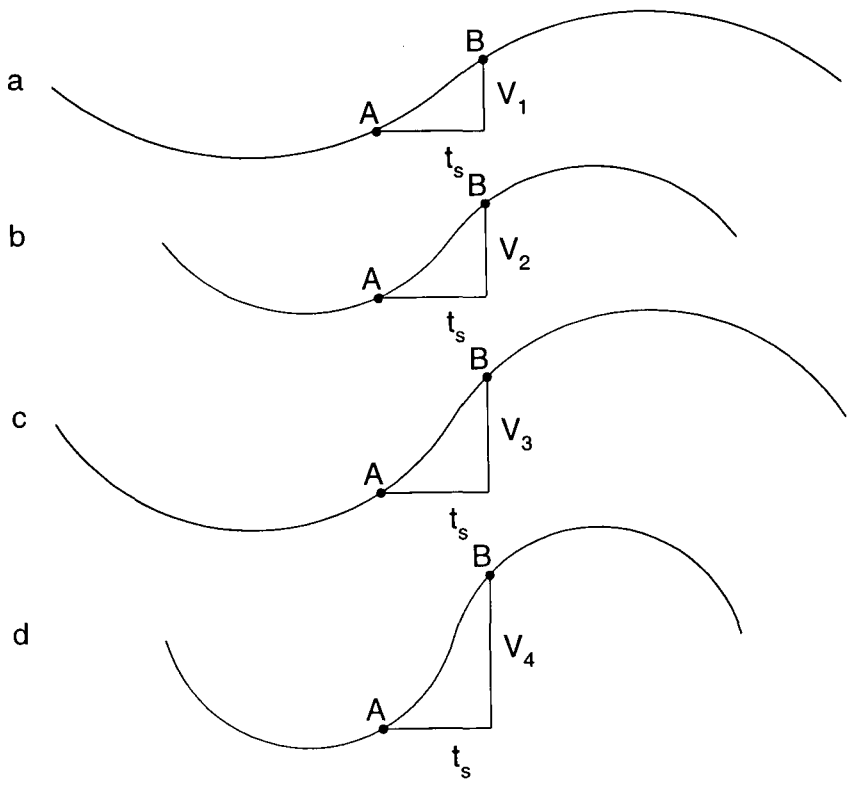

Figure 5.30 Principle of the AEPidx calculation (see text for details). The x-axis represents time and the y-axis voltage.

An empirical algorithm, based on those observations, was developed. It calculates the sum of the square roots of the difference between every two successive points in the curve and produces a single number which reflects the "curviness" of the AEP.

This number is called *Auditory Evoked Potential Index* (AEPidx) and is given by the following equation:

$$AEPidx = k\sum_{i=1}^{255}\sqrt{|V_i - V_{i+1}|}$$

where $V_1 ... V_{256}$ describes an averaged AEP curve as stored in the computer memory (par. 5.3.2) and k is a scaling constant, equal to 0.25. This scaling constant was determined empirically in order to provide an AEPidx approximately equal to 100 in fully alert volunteers. The units of this constant are $\sqrt{\text{Volt}}^{-1}$ since the AEPidx is dimensionless.

The square root of the absolute difference between two successive points (and not simply their absolute difference) was selected in order to enhance the resolution of the algorithm in lower frequencies and amplitudes.

Figure 5.31 shows the relationship between amplitude (in arbitrary units) and frequency (in Hz) of a sinusoidal signal and the corresponding AEPidx.

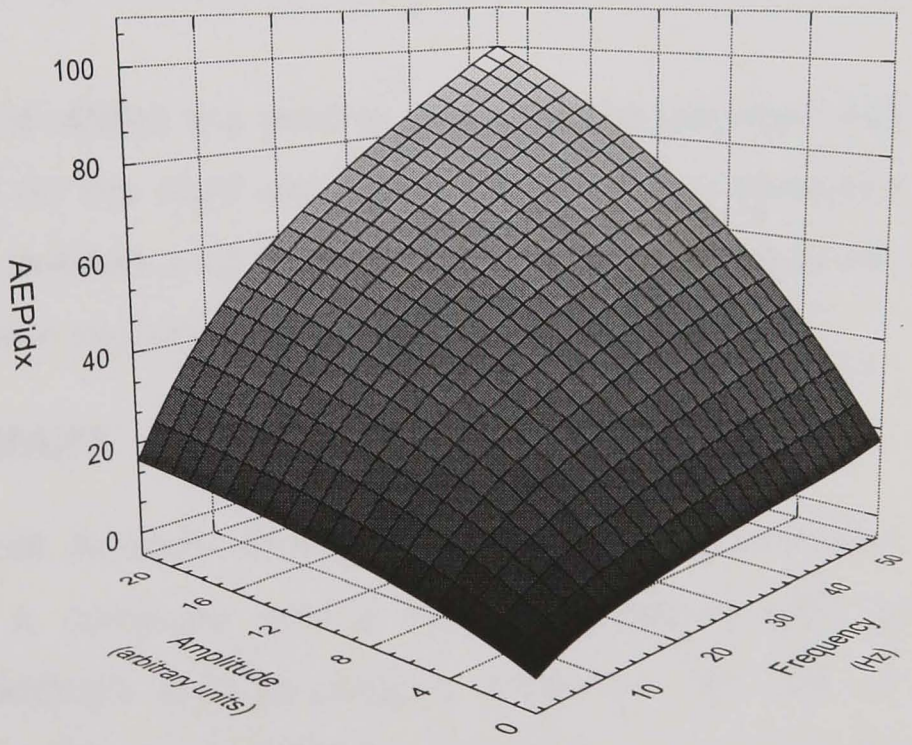

Figure 5.31 3-D plot of the AEPidx against amplitude and frequency.

The system calculates this index from every smoothed AEP curve and plots it on the screen. When the patient is awake, the AEPidx is approximately 80-90. During surgical anaesthesia, it is 35-40. On recovery, it returns to values slightly lower than the awake ones. Detailed results are given later in this thesis.

5.3.7 Other software utilities

Several other software utilities have been developed. The most important ones allow clicking and on-line sampling and storage of a large number of raw EEG sweeps, which can be processed off-line to produce averaged AEP curves. Either one or two channels can be recorded. The files created are stored temporarily on a RAM disc and later transferred on the hard disk. This allows *continuous* sampling of the EEG, without interruptions due to slow hard disk access times. This is very important for some advanced digital signal processing techniques. Several other researchers have been provided with such raw EEG data files and have explored different ways of producing AEPs.

Another set of utilities are used to play back the averaged AEP curves which were stored on the hard disk. This allows off-line recreation of the whole anaesthetic session and further study of the results, production of slides showing screen captures, etc.

5.4 SUMMARY

A custom-built Auditory Evoked Potential system has been developed. It consists of a computer and a high specification EEG amplifier. Three hardware platforms exist at present: a desktop PC with an AT expansion card, a laptop PC with a PCMCIA card and a purpose-built microprocessor system. Special software has been written. It is capable of supplying auditory stimuli, sampling the EEG and producing filtered AEPs in real time. It also calculates an Auditory Evoked Potential Index (AEPidx), which reflects the morphology of the AEP curves.

6. CLOSED-LOOP ANAESTHESIA (CLAN)

6.1 INTRODUCTION

People spend their lives trying to control things with varying degrees of success. The anaesthetist, too, is concerned with control. Most of the time, he (or she) finds himself to be part of a feedback system, manually "closing the loop" by changing a parameter (usually the concentration of a drug) in order to bring another parameter (blood pressure, heart rate, depth of anaesthesia, etc.) as close as possible to the desired value.

Basic concepts of dynamic systems and control theory can easily be applied in anaesthesia. *Systems* are the components of the process under study, while *signals* are the physical variables that "flow" in the interconnections between the systems. Each component has one or more signals called *inputs*, flowing into it from other components and one or more signals called *outputs*, flowing from it to other components.

Mathematical modelling of physical systems is the description of system behaviour by means of suitably chosen mathematical relations or equations. Since the mathematical description of real-world situations is an *approximation* and, therefore, to some extent, imperfect, there is never *one* model for a given system but rather a *spectrum* of models. When the analysis is in its early stages, a relatively simple model is chosen in order to allow some basic understanding of essential features without excessive analytical effort. As knowledge is accumulated, more complex properties are added to the model to improve its accuracy.

6.1.1 Open-loop control

An open-loop control system is one in which the signal controlling the output, is *independent* of the output. The principle is that, at some point in time, the operator controls its output as accurately as possible and, then, it is left to work on its own. Its accuracy depends on its calibration. Changes in the characteristics of the components of the system and external *disturbances* can substantially alter the output for a given input.

Feedforward control is a variance of open-loop control, in which measurements of the external disturbances are used to predict and correct the effect of those disturbances *before* they affect the controlled variable. Feedforward control has found widest application in the control of certain processes where elements downstream are subject to disturbances and long time constants or delays are present in the system. It is also used in situations where the controlled variable cannot be measured directly. Instead, accurate measurements of all the disturbances and a sufficiently detailed model of the system are required in order to predict the value of the controlled variable over time.

True open-loop control in anaesthesia could be disastrous. If, for example, an anaesthesia delivery system were allowed to run unattended, an external disturbance, such as a change in surgical stimulation, could cause the system to achieve either too deep or too light anaesthesia. In practice, somebody would (or should!) have to be present to "close the loop". The anaesthetist acts as a *controller*, comparing the actual depth of anaesthesia with the desired one and taking the appropriate corrective action. His brain acts as the *error detector* actuating his muscles to adjust the amount of anaesthetic. The *error signal* he sends to his muscles is a function of the difference between the *reference signal* and the *measured signal* fed back visually from the patient. His brain alone cannot adjust the anaesthetic. The error signal needs *power amplification*, which is provided by his muscles. This scheme is a manual-control, closed-loop system. For automatic control,

the human component must be replaced by a consistent and reliable mechanism.

6.1.2 Closed-loop control

For *true* closed-loop control, there must be:

- *No human intervention*, once the reference signal value has been set.
- *Negative feedback*, in which a feedback signal, which is a function of the output value to be controlled, is subtracted from the reference signal.
- *Error actuation*, in which the difference between the reference signal and the measured signal (the *error*) is used to adjust the output value to its required level.

Figure 6.1 depicts the fundamental components of a generic closed-loop control system. It consists of a *measuring system*, a *controller* and an *error-correcting device*. The measuring system measures the *controlled variable* and feeds the *measured value* to the *error detector* of the controller. The controller calculates the required *correcting signal* and sends it to the error-correcting device. The error-correcting device acts on the process under control and modifies its *output*, which, in turn, directly affects the controlled variable.

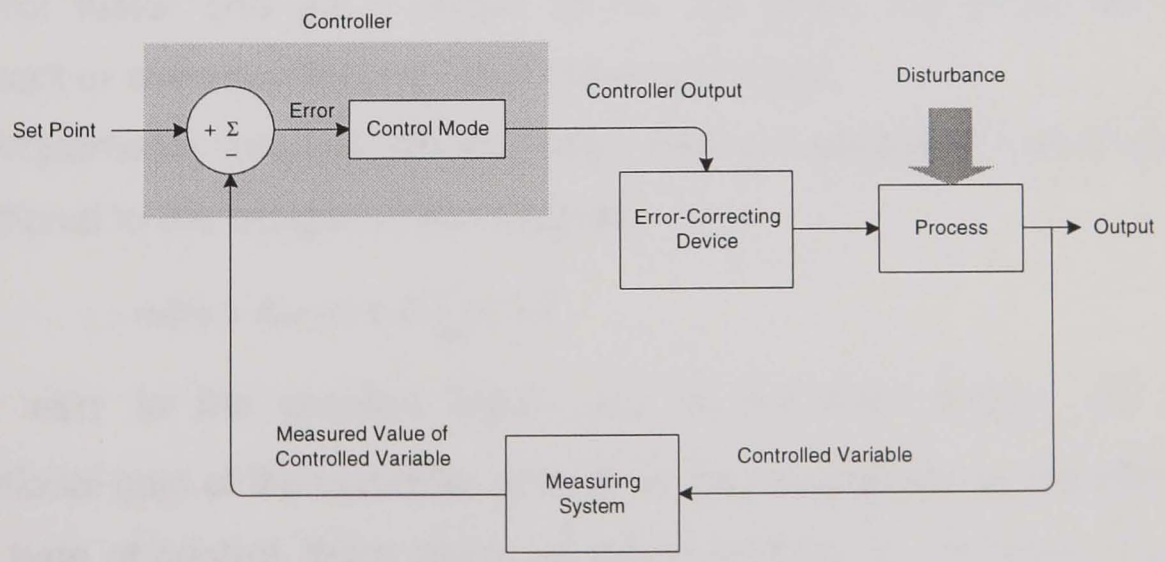

Figure 6.1 Block diagram of a closed-loop system.

6.1.2.1 Control strategies

A choice has to be made for the external control mechanism. There are two general categories of control strategies:

- *On-off control*, in which the anaesthetic is given to the patient at a constant rate, as long as depth of anaesthesia is above the desired value. Otherwise it is switched off.
- *Proportional control*, in which the amount of anaesthetic is proportional to the difference between the desired and the measured depth of anaesthesia. This difference is the *error signal*.

The *on-off* strategy is the simplest method of control, but it is known from experience that this type of systems can be unstable and will often oscillate.

The *Proportional* (P) controller can avoid such oscillations and can achieve better stability. It obeys the following equation:

$$m(t) = K_p e(t)$$

where $m(t)$ is the process input, $e(t)$ is the error signal and K_p is the gain of the controller.

However, because of interference from other control systems within the human body (*homeostasis*), the system response has a relatively long delay. As a result, the set point will never be reached. A higher K_p value will reduce the error faster and get it closer to the set point, but there will be an overshoot or even oscillations if this value is too high.

The *Proportional Integral* (PI) controller has an additional correction term proportional to the integrated error signal:

$$m(t) = K_p e(t) + K_i \int_0^t e(t)dt$$

where $m(t)$ is the process input, $e(t)$ is the error signal, K_p is the proportional gain of the controller and K_i is the integral gain of the controller.

In this type of control, there still is an upper limit for K_p, to avoid overshoot and oscillations. But, because of the integrating correction term, the amount of drug will increase until the target value has been reached.

A further improvement can be made by the addition of a third term, proportional to the derivative of the error signal. The *Proportional Integral Differential* (PID) controller finds wide application in process control systems. It can be modelled by the following equation:

$$m(t) = K_p(t) + K_i\int_0^t e(t)dt + K_d\frac{de(t)}{dt}$$

where $m(t)$ is the process input, $e(t)$ is the error signal, K_p is the proportional gain of the controller, K_i is the integral gain of the controller and K_d is the differential gain of the controller.

There are rules to be followed to determine the control method and find the best gain settings. The behaviour of the system must be known before the optimal controlling parameters can be decided. Often, many experiments have to be performed with the actual system. Moreover, because of the great inter-patient variability, the controlling parameters have to be adjusted for different groups of patients with common characteristics. Advanced strategies use *adaptive control* algorithms (e.g. Linear Quadratic Gauss, LQG) to adjust a certain model to the actual characteristics of the patient. Those systems are beyond the scope of this thesis and will not be discussed.

Another complicating factor is the *non-linearity* of most biological systems. The classical control theory rules are only appropriate to linear systems. Non-linear or chaotic behaviour can be described by advanced mathematical models of complex systems. However, conventional control methods may be applied if a *limited range* of responses is selected and conservative response times are specified.

One of the most fundamental prerequisites for a successful control method is the existence of a reliable input signal and the ability of the controlling device to adjust the output according to the error signal. By definition, if the input signal does not measure the controlled variable, there can be no closed-loop control of this variable.

Conversely, if there is adequate control of a variable, then, the signal that is used as input, actually measures that variable. The stronger the correlation between the controlled variable and the input signal, the simpler the control strategy will be.

6.1.2.2 Response to a step input

The *response time* can be determined by applying a *step input* (i.e. an instantaneous change of input) to the system. A *first-order system* has a response that can be modelled by a first-order differential equation. The response time is the time it takes for the output to get within some specified percentage of its final value. A *second-order system* can be modelled by a second-order differential equation. Its response will *overshoot* and the result is a *decaying oscillation*. The response time is the time it takes for the output to settle within some specified percentage of its final value (*settling time*). There is always a time delay between the step input and any visible change in the output. Any such delay must be included in the response time.

6.1.2.3 System stability

The stability of feedback systems is of great importance, since an unstable system will not be effective in maintaining the controlled variable at approximately the desired value. Large oscillations can have a destructive effect on the entire system. Relative stability is also important, because the performance of a system which exhibits excessive overshoot or an underdamped characteristic will be unsatisfactory.

A frequent cause of instability is the fact that, in a closed-loop system, the output of each component forms the input to the next one. When corrective action is required, the necessary changes take time to work their way through each component from input to output.

In engineering terms, every system has a gain and a phase lag dependent on the specific frequency applied to it. If at any frequency, the total phase lag in the loop is 180° while at the same time the loop gain is 1.0 or greater, then

the system will become unstable and oscillate. If the gain is just under 1.0, the system will still appear unstable. In practice, control systems are designed to have a gain much lower than 1.0 at the frequency at which the phase lag is 180°.

One could argue that if the system is not excited at the particular frequency at which it becomes unstable, then there will be no problem. In practice, this is impossible. Random noise or step inputs contain an infinite spectrum of frequencies.

The only way to avoid this problem is either to reduce the loop gain or modify the phase lag around the loop. Modification of the phase lag is not always possible, especially in biological systems. Consequently, the only way to achieve greater stability is by reducing the loop gain. Unfortunately, this will make the response of the system more sluggish.

Alternatively, some method of *compensation* may be employed to improve control system performance. For example, various forms of compensating elements may be placed in series with system elements or an inner feedback path around one or more system elements. The addition of feedforward control can substantially improve the performance of the system. Choice of compensation depends upon the nature of the system and involves a certain amount of trial-and-error effort and the use of judgement gained from experience.

6.1.2.4 Evaluation of system performance

Before it is concluded that an automated control system performs satisfactorily, an objective, quantitative evaluation of its performance must be carried out. Most systems are designed to minimise variations of the controlled variable about the target set point or to eliminate the need for human intervention. Therefore, the performance of the system must be evaluated with respect to the goals that it was designed to fulfil.

In biological systems, because of inter- and intra-individual variability, it is necessary for this assessment to be carried out in a large number of subjects

and to include the widest possible range of operating conditions. It is not sufficient to demonstrate the ability of the system to control one or two subjects under arbitrarily selected circumstances. Instead, it should be examined how well the system can control different individuals, and, also, how it performs when used for a single individual whose characteristics change over a period of time.

6.2 MEDICAL APPLICATIONS OF CLOSED-LOOP CONTROL

Several automatic control systems have been described in the medical literature. Most of them use chemical agents to provide control of physiological variables such as systolic blood pressure or arterial blood concentrations of various drugs. Physiological systems may also be controlled by mechanical or electrical means. The most commonly used devices of this type are cardiac pacemakers (Katona, 1982).

In anaesthesia, closed-loop systems have been applied mainly to control blood pressure (Reid and Kenny, 1987a; Reid and Kenny, 1987b; McMenemin *et al*, 1988; Colvin and Kenny, 1989a; Colvin and Kenny, 1989b; Colvin and Kenny, 1989c; Chaudhri and Kenny, 1992; Chaudhri *et al,* 1992a; Mackenzie *et al,* 1993) and degree of muscle relaxation (de Vries *et al,* 1986) with varying degrees of success.

An excellent review, published by Katona (1982), examined various clinical applications of automatic control, including automated insulin infusion, drug dosage planning by computer, control of anaesthetic depth and control of respiratory variables.

The first attempts to control depth of anaesthesia automatically date back to the early 1950s (Bickford, 1950; Bickford, 1951b; Bickford, 1951c; Bickford, 1951a; Soltero *et al*, 1951; Kiersey *et al,* 1954). Since then, a number of methods have been proposed and applied, but with limited success.

The majority of researchers used various measures of the EEG as the controlling variable. Those measures included the total power of the

unfiltered signal (Bickford, 1950; Soltero *et al,* 1951), the integral of the filtered signal (Kiersey *et al,* 1954) and the median frequency (Schwilden *et al,* 1987; Schwilden *et al,* 1989; Schwilden and Stoeckel, 1990; Schwilden and Stoeckel, 1993) or spectral edge (Schils *et al,* 1983) of the EEG.

Blood pressure has also been used to control anaesthetic depth automatically, either alone (Suppan, 1977; Robb *et al,* 1991; Robb *et al,* 1993) or combined with the spectral edge frequency of the EEG (Schils *et al,* 1983; Schils *et al,* 1987). Other measures used as the controlling variable in closed-loop control of anaesthesia included pulse rate (Suppan, 1972) and respiratory patterns (Suppan, 1974).

Although those systems could be made to provide anaesthesia automatically, none of them has gained acceptance as a clinical tool because of inherent limitations in their design. Some of them have only been tested on animals and others were used to control depth of anaesthesia in paralysed, ventilated patients. A closed-loop control system has been reported in volunteers breathing spontaneously. However, the anaesthetic depth achieved would have been inadequate for surgical procedures, since not all of the volunteers lost their corneal reflexes (Schwilden *et al,* 1987; Schwilden *et al,* 1989). No previous system has been described that is capable of inducing and maintaining general anaesthesia in non-paralysed patients undergoing surgery.

Other systems use a combination of automatic control of anaesthetic gas concentrations and mathematical models which describe the uptake and distribution of those gases and their effect on the brain (Chilcoat, 1973; Mapleson, 1979; Morris *et al,* 1983; Chilcoat *et al,* 1984; Ritchie *et al,* 1987; Vishnoi and Roy, 1991; Jee and Roy, 1992; Sharma *et al,* 1993). They are based on the fundamental assumption that there is a *single* blood concentration that achieves general anaesthesia in *all* patients. As seen in previous chapters of this thesis, this assumption does not hold for the entire population. Clearly, those systems do not control anaesthetic depth, but only

drug concentrations. In fact, they are not even closed-loop systems, since the controlled variable (blood gas concentration) is not used to drive the entire system. Instead, the alveolar gas concentration is measured and applied to a model in order to estimate the blood concentration. Therefore, they can only be characterised as *feedforward* control systems.

In a completely different approach, an expert system has been used to advise on the concentration of inhalational anaesthetics (Greenhow *et al,* 1993). Although its performance in producing adequate quality of anaesthesia was considered to be "acceptable", it has serious limitations which make it impractical for every day use by the average anaesthetist. For the same reason, it is most unlikely that it will ever be able to perform closed-loop control of anaesthesia.

The main requirement for any closed-loop system is that the input signal is reliable and correlates well with the controlled variable. As Katona (1982) wrote, "the measurement of the controlled variable is the most serious problem in the development of an on-line control system". He also noticed that "at present, there is no universally accepted automatic way to objectively measure depth of anaesthesia". It is only natural that most attempts to control depth of anaesthesia failed, since the parameter that was used did not correlate well with the clinical anaesthetic depth (Chilcoat, 1980).

6.3 SYSTEM DESCRIPTION

Any system used to control depth of anaesthesia automatically, must be able to produce satisfactory general anaesthesia during surgery. Unfortunately, there is no agreed definition of the term "satisfactory general anaesthesia".

The two most valuable signs of inadequate anaesthesia, movement and respiratory patterns, are lost when muscle relaxants are employed (Chapter 2). As Mapleson (1979) wrote, "a number of anaesthetists have said privately that, if they are honest with themselves, they have to admit that once they

have produced full neuromuscular block they cannot tell how deeply their patient is anaesthetised".

It appears, therefore, that the quality of control of anaesthetic depth can be assessed most accurately when the patient is breathing spontaneously while undergoing surgery. Excessively light anaesthesia leads to the patient moving, while excessively deep anaesthesia results in depression of respiration. Satisfactory anaesthesia requires:

- Adequate cardiovascular and respiratory stability.
- Ideally no, or at least only minimal, patient movement.
- No awareness or recall of events during the procedure.

Any closed-loop control system must be *reliable*, *robust* and sufficiently *rapid* in response. There is no point in having a system which is only capable of intermittent satisfactory performance. It must be able to induce the patient automatically, maintain satisfactory levels of anaesthesia throughout surgery and allow the patient to recover with minimal human intervention. Also, it must be able to withstand the rigours of the operating environment and be able to detect and deal with various artefacts like diathermy. In order to maintain satisfactory control, the system must have sufficient speed of response to changes in the input signal without overshoot.

A system capable of controlling depth of propofol anaesthesia has been developed. It consists of the input block, the controller and the output device (Figure 6.2).

It is based on the same system, described in the previous chapter, that was used to record and process the Auditory Evoked Potentials (Figure 6.3). It has been used to control depth of anaesthesia automatically in a large number of spontaneously breathing patients, as well as patients under neuromuscular blockade, including patients undergoing cardiopulmonary by-pass.

6.3.1 Input

The input to the system is the Auditory Evoked Potential Index (AEPidx). It is calculated by the Auditory Evoked Potential Monitor as described in the previous chapter.

6.3.2 Controller

The controller is an additional software module implemented as an integral part of the Auditory Evoked Potential Monitor. It was written in Pascal (Borland Turbo Pascal v6.0 for the PC system and Intel Pascal-86 v3.4 for the 186 system).

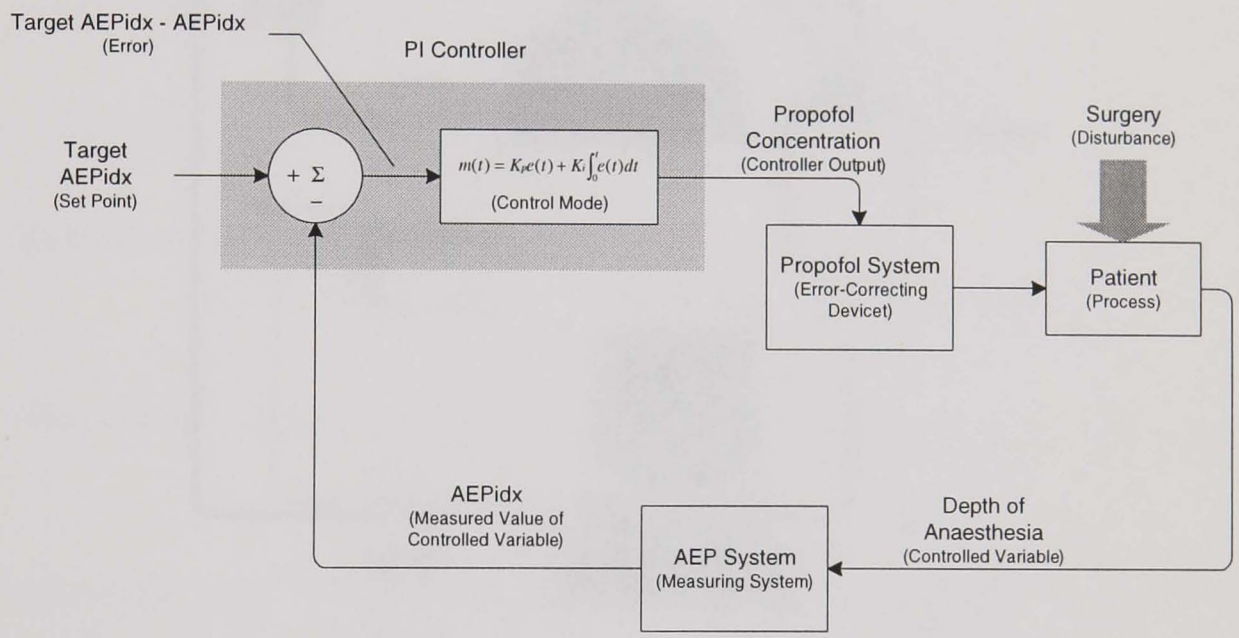

Figure 6.2 Block diagram of the CLAN system.

During initialisation, the user is prompted to enter the patient "category" (between 1 and 3), according to the patient's fitness. Category 1 is for unfit, elderly patients (e.g. cardiac). Category 3 is for young, fit, unpremedicated patients (usually day cases). Category 2 is for the majority of the population, who do not fall in any of the previous two categories. Different closed-loop parameters exist for each patient category. Patients in category 3 are induced very rapidly, with large increments, whereas patients in category 1

are controlled with much more conservative settings. Patient category also determines the gains of the controller used for maintenance.

There are no strict criteria about which patients are assigned to which category and the decision is based solely on the anaesthetist's clinical experience. By default, the system selects category 2, unless instructed differently. However, if this "guess" proves to be incorrect, settings can be changed easily at any time.

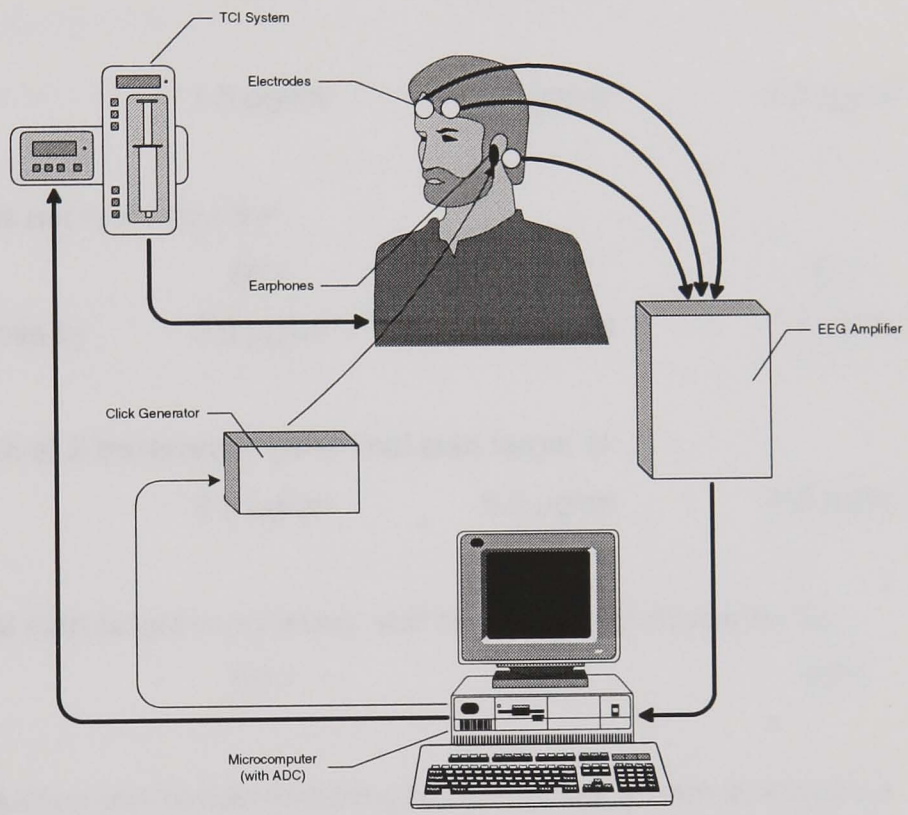

Figure 6.3 Detailed view of the CLAN system.

The closed loop controller consists of three different modes (or stages): induction, maintenance and recovery.

Induction is performed by an empirical (heuristic) algorithm, based on the actual steps taken by experienced clinicians using the Target-Controlled Infusion (TCI) system manually (Table 6.1).

The algorithm titrates the target blood propofol concentration against the patient's response. An initial target propofol concentration is selected. If the target AEPidx is not reached within a specified time, the target concentration

is increased by a pre-determined step value. This process is repeated for a maximum of three times. If after that, the measured AEPidx is still above the target AEPidx, a longer time interval is selected and the process is repeated until the target AEPidx is achieved. When this happens, the system reduces the target propofol concentration by 20% and switches automatically to the maintenance mode.

	UNFIT	MODERATE	FIT
Start at	1.0 µg/ml	2.0 µg/ml	4.0 µg/ml
If target is not reached after			
	60 s	50 s	40 s
increase by	0.5 µg/ml	1.0 µg/ml	1.5 µg/ml
Maximum of 3 increments gives final start target of			
	2.5 µg/ml	5.0 µg/ml	8.5 µg/ml
After final start target is achieved, wait before further increases for			
	60 s	60 s	60 s
After induction and before switching to maintenance, reduce target by			
	20%	20%	20%

Table 6.1 Induction algorithm.

The *maintenance* mode is a conservative proportional-integral (PI) controller. The target propofol concentration is calculated every three seconds but is averaged and transmitted to the TCI system only every thirty seconds. This was necessary in order to avoid too frequent adjustments of the target propofol concentration.

The time constant of the controller was selected to be much larger than the time delays of the entire system and the gain much lower than 1.0, thus ensuring stability of the system under all conditions (par. 6.1.2.3).

If, for some reason, the change in propofol concentration is above or below a certain level, then the system response is limited automatically (Table 6.2). This feature ensures that the patient will not be suddenly overdosed because, for example, of an artefact that caused the AEPidx to increase temporarily. There is also a minimum target propofol concentration, above which the system will maintain the concentration of propofol.

Another feature of the maintenance mode is its tendency to continuously decrease the amount of anaesthetic given to the patient. Every three minutes, the system decreases the target propofol concentration by a small amount, even if the measured AEPidx is exactly the same with the target AEPidx. As a result, the propofol concentration is reduced towards the end of the operation and the patient recovers more rapidly.

	UNFIT	MODERATE	FIT
If change in target propofol concentration is more than			
	1.0 µg/ml	2.0 µg/ml	3.0 µg/ml
change it by	1.0 µg/ml	2.0 µg/ml	3.0 µg/ml
If target propofol concentration is less than			
	1.0 µg/ml	1.0 µg/ml	1.0 µg/ml
set it to	1.0 µg/ml	1.0 µg/ml	1.0 µg/ml
Every 3 minutes reduce target propofol concentration by			
	0.1 µg/ml	0.2 µg/ml	0.3 µg/ml

Table 6.2 Algorithm limiting responses during maintenance.

In the *recovery* mode, the system simply sets the target propofol concentration to zero.

There are several safety features built in the system. The closed loop controller can be switched off at any time. In that case, the target propofol concentration can be set manually, either through the computer or directly with the use of the appropriate controls on the TCI system.

Several audible warnings and alarms draw the attention of the operator to unusual circumstances. For example, there are sound signals during induction to indicate that a new higher target concentration has been selected, or that the target AEPidx has been reached. The system will bleep when the target propofol concentration is below the pre-set minimum limit and when it attempts to cut back the amount of propofol (every three minutes). There is also a warning if at any stage the estimated propofol concentration is above 12 µg/ml.

If the TCI system does not receive any command from the computer for more than ten seconds, it will give a warning. The same will happen, if the computer does not receive any data from the TCI system or the data received are invalid. In this way, the operator is immediately alerted to any communications breakdown between the two systems.

6.3.3 Output

The output is provided by a computerised Target-Controlled Infusion (TCI) of propofol. This infusion system has been described previously in great detail (White and Kenny, 1990; Kenny and White, 1992) and has been used in a number of studies to deliver propofol (Church *et al,* 1991; Marsh *et al,* 1991; Akhtar *et al,* 1992; Chaudhri *et al,* 1992b; Davidson *et al,* 1993; Taylor *et al,* 1993) and alfentanil (Davies *et al,* 1992).

The particular system used, is a third-generation model with two microprocessors built-in as an integral part of the device. The operation of the main processor is supervised by the second processor, which receives

information on the actual performance of the pump and compares it with the expected one.

The device is programmed with the mathematical solution to a *three-compartment pharmacokinetic model* with *central elimination* of the drug. The model operates in real time to calculate the infusion rates which are necessary to achieve and maintain the theoretical target blood concentrations selected by the anaesthetist.

Induction is achieved by a rapid drug infusion until the desired predicted target has been achieved. Thereafter, the device automatically switches over to an infusion regimen, which continuously compensates for elimination and distribution of the drug and maintains the target value constant. A higher target concentration is achieved by the microprocessor automatically instructing the pump to deliver a rapid infusion rate until the new target concentration is obtained. New infusion rates are then delivered to maintain this new target. A lower target value is achieved by the microprocessor stopping drug delivery, until the pharmacokinetic model predicts that the new lower target has been achieved through elimination and distribution of the drug. Thereafter, the appropriate infusion rates are delivered to maintain the target blood concentration constant.

The device is controlled either manually, with a built-in keypad and a rotating wheel, or automatically by a remote computer through a serial RS-232 interface. Selection of the automatic control mode is done with the insertion of an electronic hardware “key”. When the “key” is removed, the system switches back to manual control.

6.4 SUMMARY

Several attempts in the past to achieve closed-loop control of anaesthesia had only limited success. The most serious problem was the fact that the controlling variable did not correlate well with the actual depth of anaesthesia.

A closed-loop control system of propofol anaesthesia has been developed. It is based on the Auditory Evoked Potential Monitor (described in the previous chapter of this thesis) and uses the Auditory Evoked Potential Index (AEPidx) as the controlling variable. The controller is a heuristic algorithm for induction and a conservative Proportional-Integral (PI) algorithm for maintenance. The output is a propofol Target-Controlled Infusion (TCI) system.

7. CLINICAL STUDIES

7.1 Study 1: Detection Of Awareness During Anaesthesia By Auditory Evoked Potentials

The objective measurement of anaesthetic depth and its implications for the production of a reliable monitor of awareness remain a desirable but elusive goal in anaesthesia (Brighouse and Norman, 1992). As discussed earlier in this thesis, analysis of AEP changes has previously been performed retrospectively, using FM tape to record the signals for subsequent off-line study. In order to be used as a monitor of awareness, analysis of the waveform should be simultaneous with the conduct of anaesthesia.

A computer-based system, which continually analyses the AEP, has been developed (Chapter 5). It uses a different method to that employed by other investigators who examined latencies and amplitudes of specific parts of the AEP. It calculates an Auditory Evoked Potential Index (AEPidx), which reflects changes in latencies and amplitudes of the AEP.

The relationship between the AEPidx and alternating periods of consciousness and unconsciousness produced by a target-controlled infusion of propofol combined with regional blockade has been investigated. The purpose of this study was to determine whether it was possible to use the AEPidx to discriminate between the *just* awake and the *just* anaesthetised state.

7.1.1 Patients and methods

The study was approved by the Hospital Ethics Committee. Twelve patients were studied and written informed consent obtained. All patients were

scheduled to have total knee replacement performed under spinal anaesthesia. All patients received a premedication of temazepam 10-20 mg approximately 1 hour before surgery. Spinal anaesthesia was established with the patient in the sitting position and 2.5 ml of 0.5% hyperbaric bupivacaine administered via a 26G needle.

The AEP system used has been described earlier in this thesis (Chapter 5) and also elsewhere (Kenny *et al,* 1992; McFadzean *et al,* 1992; Kenny *et al,* 1993a; Kenny *et al,* 1993b; Kenny *et al,* 1993c; Davies *et al,* 1996). Appendix D contains these papers in their original form.

The only difference from the methodology described in Chapter 5 is that the clicks were presented only to the right ear. This was done to allow easy communication between the patients and the anaesthetist.

The AEP was obtained following the onset of spinal anaesthesia. An initial baseline AEPidx value was calculated from the AEP. This initial AEPidx was taken, in all patients, to equal 100% and subsequent measured values were referred to that baseline.

Once the baseline AEPidx had been obtained, a target-controlled infusion (TCI) of propofol was commenced. The TCI system delivered a selected target blood propofol concentration employing a three-compartment pharmacokinetic model working in real time (White and Kenny, 1990; Kenny and White, 1992). Two investigators were present in addition to the anaesthetist responsible for conducting the spinal anaesthetic. The first investigator operated the AEPidx monitoring system. The second investigator recorded at 30 second intervals the patient's response to a verbal command to squeeze the investigator's hand and the presence or absence of an eyelash reflex. The presence of a response to verbal command and a positive eyelash reflex were taken as the indicator of awareness and their loss was taken as the indicator of unconsciousness. The second investigator administered the target-controlled propofol infusion to provide alternating periods of consciousness and unconsciousness, as defined above. The loss

of both the eyelash reflex and the response to command were taken to indicate the transition from consciousness to unconsciousness and the return of both responses as the transition from unconsciousness to consciousness. A point 2 minutes following this transition was taken to represent a steady state (Thornton *et al,* 1989a) and AEPidx data were obtained for analysis.

On the day after surgery, all patients were questioned about their recall of events during the procedure including any dreams or noises. They were also asked if the anaesthetic technique had been acceptable and if they would be happy to have the same technique again. Data were analysed using the Friedman Test and the Wilcoxon Rank Sum Test with Bonferroni correction.

7.1.2 Results

Five male and seven female patients participated in the study. Their mean weight was 74 kg (range 59-100) and their mean age 67 years (range 51-78). One patient became confused and uncooperative after starting the propofol infusion. This patient was withdrawn from the study.

The median number of periods of unconsciousness achieved during each procedure was 3 (range 1-6). The mean duration of surgery was 71 minutes (range 40-105). In a total of 38 transitions from the conscious to the unconscious state, the eyelash reflex was lost simultaneously with the response to command in 22%, the response to command was lost first in 39% and the eyelash reflex was lost first in 39%. AEPidx scores during the study are shown in Figure 7.1. The initial AEPidx was taken in all patients to equal 100% and subsequent values were referred to this baseline.

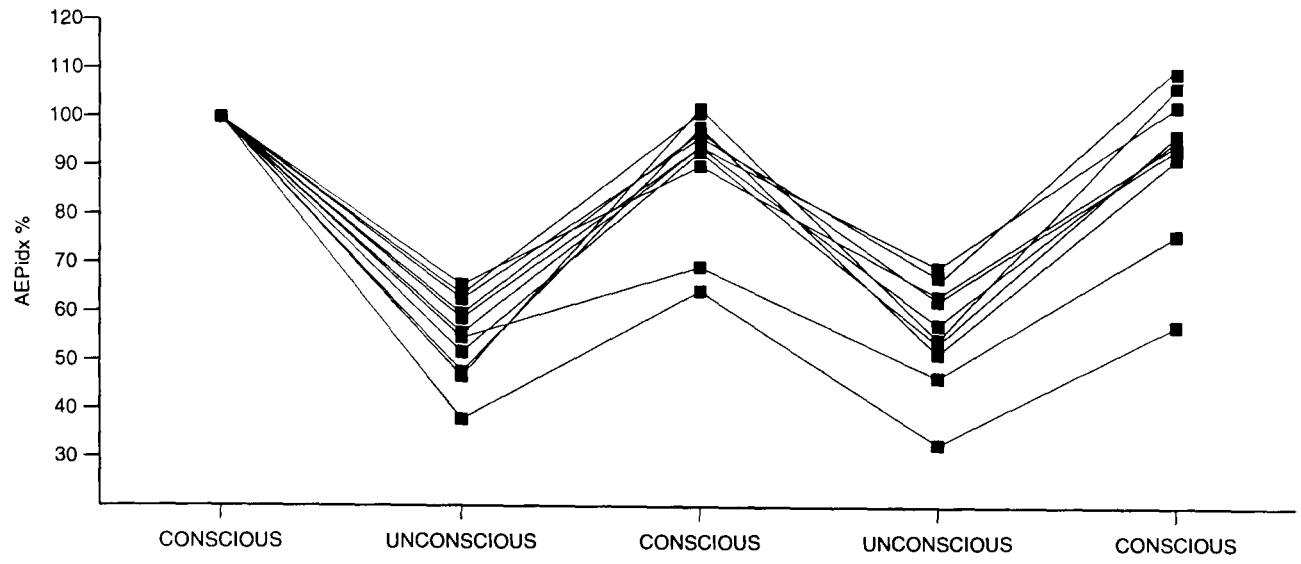

Figure 7.1 Changes in the AEPidx for each patient between consciousness and unconsciousness.

In Figure 7.2 data are represented as a mean with 95% confidence intervals.

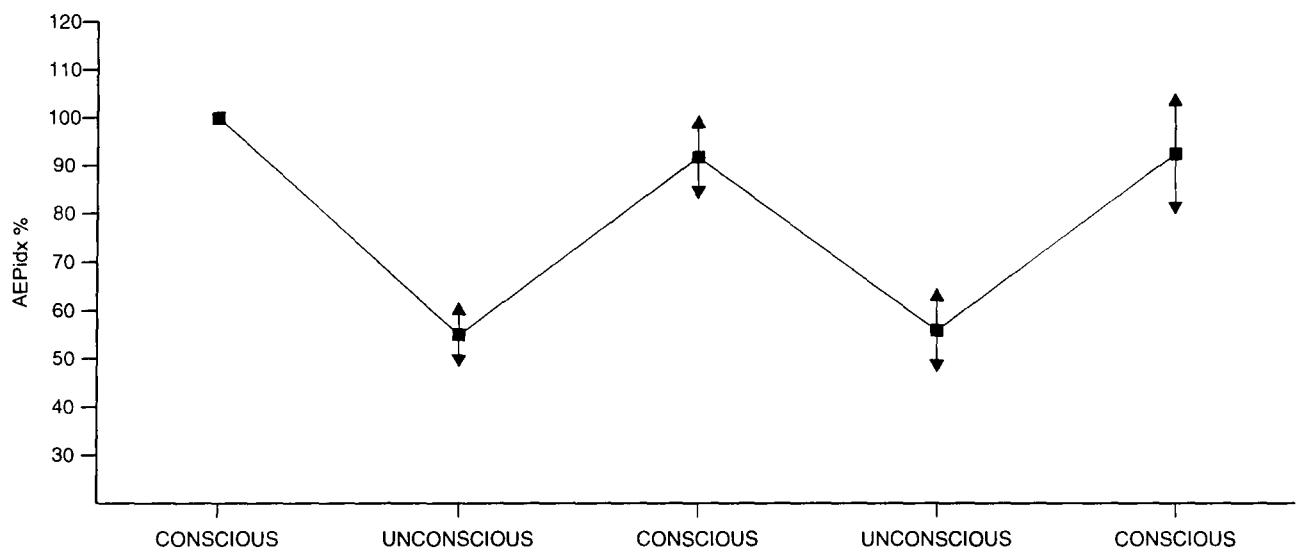

Figure 7.2 Changes in the AEPidx between consciousness and unconsciousness. (Mean and 95% C.I.)

All changes from consciousness to unconsciousness and *vice versa* were statistically significant (Wilcoxon Rank Sum Test - Table 7.1).

Conscious	Unconscious	Conscious	Unconscious	Conscious
n=11	n=11	n=11	n=10	n=9
100	55	92	56	93
	(50-60)	(85-99)	(49-63)	(82-104)
	p=0.013	p=0.013	p=0.020	p=0.031

Table 7.1 Changes in conscious level shown in Figure 7.1. (Mean and 95% C.I.)

Figure 7.3 shows an AEPidx tracing produced in a single patient during anaesthesia and surgery with the predicted blood propofol concentration below.

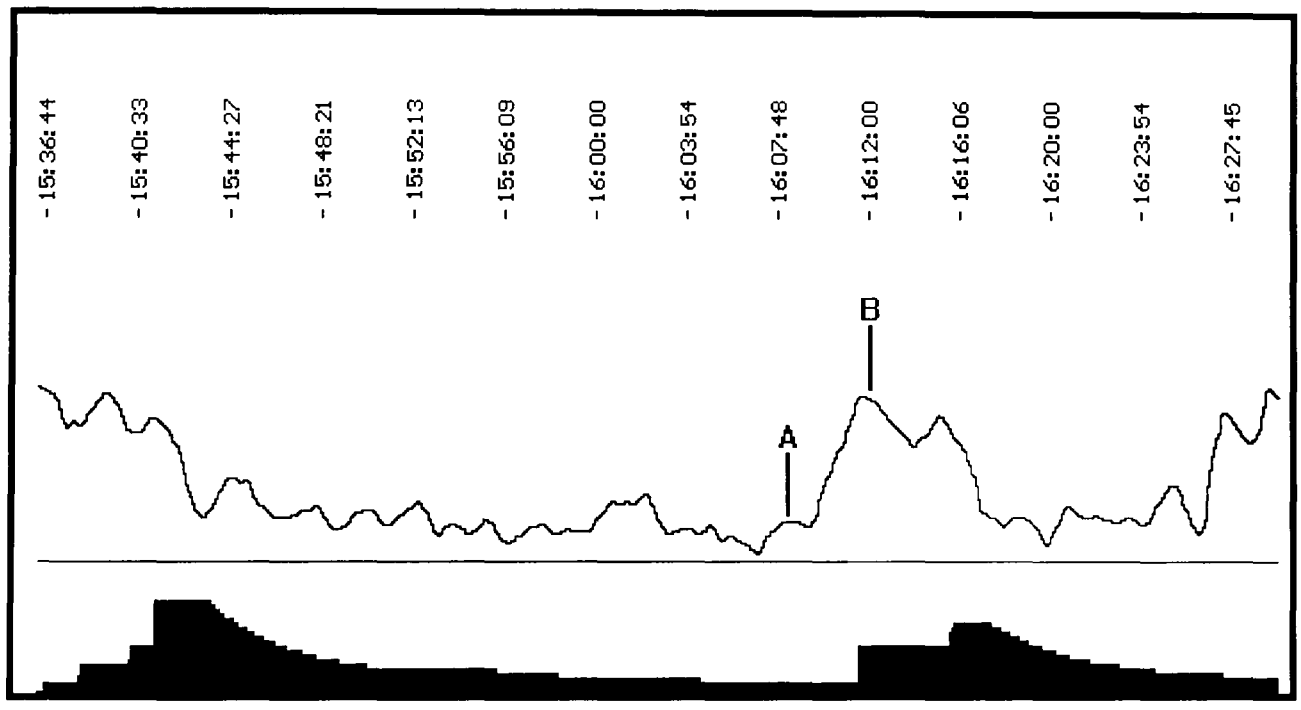

Figure 7.3 A typical trace of AEPidx as displayed on the computer screen during surgery (solid line). Predicted blood propofol concentration also shown (black area at the bottom of the screen). Horizontal axis represents time. Vertical axis represents the measured AEPidx and the estimated target propofol concentration.

Figure 7.4 shows the AEPs at points A and B from which the AEPidx was calculated.

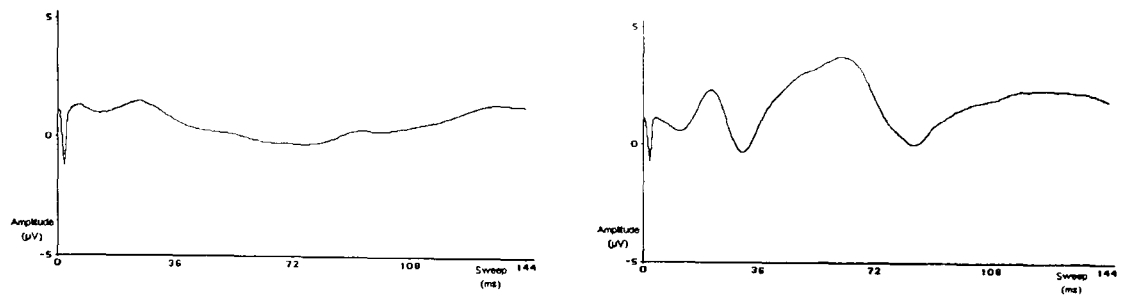

Figure 7.4 AEP curves at points A and B on Figure 7.3 as used to calculate the AEPidx. A: unconscious, B: conscious.

In all patients, the AEPidx decreased with the transition from consciousness to unconsciousness and increased from unconsciousness to consciousness. There were no significant differences in heart rate or systolic arterial pressure between the conscious and the unconscious state (Wilcoxon Rank Sum Test).

Eleven patients completed the study and were questioned on the day after surgery. All patients recalled clicks being played before propofol administration. Nine patients had no recollection of events after the onset of the propofol infusion and the remaining two patients remembered the instruction to squeeze the investigator's hand. All patients were satisfied with the anaesthetic technique and would have the same anaesthetic again.

7.1.3 Discussion

There is a fundamental problem encountered when attempting to assess the validity of a monitor of awareness, that is the lack of a universally accepted standard with which to compare the device. To solve this problem, the clinical end-points of consciousness and unconsciousness were related to simultaneously produced AEPidx. The assumption was made that patients defined as conscious were aware and that those defined as unconscious were not. This assumption has been made in previous studies in which a

response to command was considered as an indication of awareness (Thornton *et al,* 1989a; Newton *et al,* 1992).

It has been shown previously that awareness during surgery is possible without recall if anaesthesia is deepened subsequently (Rupreht, 1989). This is supported by the observation that only 18% of patients had any recall of events after the propofol infusion was started despite repeated prolonged periods of intra-operative wakefulness. The frequency of recall may have been greater had awareness been associated with fear or the pain of surgery although patients who experienced pain during anaesthesia produced by midazolam and alfentanil in a study by Russell did not have subsequent recall (Russell, 1993).

Consciousness was lost and regained a number of times in each patient. Figure 7.1 demonstrates a clear difference in AEPidx between patients considered to be conscious and aware and those considered unconscious. It was found, as did Newton and colleagues (1992), that a significant number of transitions (22%) between awareness and unconsciousness were rapid, without a graded change. However, retention of the eyelash reflex alone occurred in 39% of all patients and the response to command alone in 39%. It was therefore necessary to define a point for analysis where the state of awareness was similar within each patient and between patients. The point 2 minutes following transition represented a point at which both eyelash reflex and response to command had been unequivocally lost or regained and this was chosen as the measuring point for the AEPidx value (Isaac and Rosen, 1990).

Analysis of AEPidx values demonstrated a consistent reduction in score with transition from awareness to unconsciousness and a consistent increase in score from unconsciousness to awareness. This was true for all patients and for every transition. The Auditory Evoked Potential Index would, therefore, appear to represent a reliable indicator of potential awareness during anaesthesia.

The effects of premedication on the AEPidx and its relevance have yet to be determined. The initial AEPidx was taken following premedication and was normalised to 100%. Possible variations in level of sedation as a result of premedication may affect the use of the pre-induction value as the most accurate baseline. Previous authors have demonstrated that changes in the AEP with anaesthesia are related to anaesthetic depth and unrelated to anaesthetic agent (Thornton *et al,* 1984; Thornton *et al,* 1988; Thornton *et al,* 1989b). Analysis of the AEP by means of the AEPidx is unlikely to alter this finding, however the effect on the AEPidx of agents other than propofol and the effect of surgical stimulation have still to be investigated.

The AEPidx has already proved to be a sufficiently stable and reliable indicator of depth of anaesthesia to be used as the input signal for closed-loop anaesthesia in patients breathing spontaneously during body surface surgery (*vide infra*). The possibility of muscle artefact being responsible for changes in AEPidx in the present study is unlikely, because of the analogue and digital filtering used.

It is not yet possible from this study alone to predict an AEPidx below which absence of awareness is *guaranteed*. This may however be possible in the future given the consistent changes in the AEPidx noted in the present study. The view that the AEP can be used as a clinical monitor of potential awareness during anaesthesia (Newton *et al,* 1992) is supported by this study. Computer processing of the AEP in the form of the AEPidx would appear to offer a reliable indicator of change from light anaesthesia to awareness and *vice versa*. In addition the ability of the system to provide an updated AEPidx every 3 seconds makes continuous monitoring during anaesthesia possible.

7.2 STUDY 2: CLOSED-LOOP CONTROL OF ANAESTHESIA

In this study, the technique of closed-loop anaesthesia (CLAN) has been implemented. A single numerical parameter, the Auditory Evoked Potential Index (AEPidx), extracted from the Auditory Evoked Potential, has been used to control depth of anaesthesia in both spontaneously breathing and paralysed patients having surgery. This implies that the AEP may provide a true index of anaesthetic depth and may be used effectively to prevent intra-operative awareness and recall.

7.2.1 Patients and methods

The system used has been described earlier in this thesis (Chapters 5 and 6). In summary, Auditory Evoked Potentials were obtained by recording the EEG from electrodes attached to the forehead and mastoid for 144 ms after applying clicks at a rate of 6.9 per second to both ears. The EEG signal was amplified and connected to a microcomputer via a 12-bit analogue-to-digital converter. The AEPidx was derived from analysis of a 3-second moving time average of 256 EEG sweeps and was used as the input to a proportional-integral (PI) controller.

The controller altered the predicted blood concentration of propofol to minimise the difference between the measured and the target AEPidx. The new value for the predicted propofol concentration was transmitted to the infusion system which used a 3-compartment pharmacokinetic model to achieve and maintain the predicted value (Kenny and White, 1990; White and Kenny, 1990; Marsh *et al,* 1991).

The study was approved by the Hospital Ethics Committee. One hundred and thirty seven spontaneously breathing and 56 paralysed patients ASA 1-3 scheduled to undergo elective surgery were studied and written informed consent was obtained. All patients received temazepam premedication 20-30 mg approximately one hour before surgery.

Anaesthesia was induced automatically using a predetermined series of increasing predicted blood propofol concentrations until the required AEPidx was obtained. Thereafter, anaesthesia was maintained automatically by the PI regime.

During maintenance of anaesthesia, all patients breathed a mixture of 66% nitrous oxide in oxygen and received a target-controlled infusion (TCI) of alfentanil. The target concentration was 15 ng/ml for the non-paralysed patients and 25 ng/ml for the paralysed ones. Arterial oxygen saturation, respiratory rate and end-tidal carbon dioxide concentration were monitored continuously. Blood pressure, heart rate, degree of sweating and tear formation were used to calculate PRST anaesthetic scores (Evans *et al,* 1987) every five minutes.

7.2.2 Results - spontaneously breathing patients

Seventy seven male and 60 female patients participated in the study. Their mean age was 55.2 years (range 17-86 years) and their mean weight was 64.1 kg (range 40-108 kg).

The Auditory Evoked Potential Index was obtained throughout the procedure. The mean value before induction of anaesthesia was 81 (S.D. 21.5). The mean value required during surgery was 36 (S.D. 6.3). At recovery, the mean AEPidx was 88 with a standard deviation of 14.9.

The mean target AEPidx during maintenance was 35 (S.D. 6.8). The AEPidx remained within ±5 of the target for 64.9% of the time (S.D. 15.2%), within ±10 of the target for 89.0% of the time (S.D. 10.1%) and within ±15 of the target for 96.6% of the time (S.D. 4.6%).

Anaesthetic PRST scores during surgery did not exceed 2 in any patient (median value 0, range 0-2). The maximum decrease in systolic blood pressure was 23.5% of the pre-induction value (S.D. 14.3%) and the maximum increase was 10.9% (S.D. 12.4%). The maximum decrease in

heart rate was 15.3% (S.D. 12.6%) and the maximum increase was -4.4% (S.D. 15.7%).

One hundred and five patients maintained satisfactory spontaneous respiration during the entire procedure. Twenty one patients required assisted ventilation for less than 5 minutes (mean 3.0 minutes, S.D. 2.5) and 11 for more than 5 minutes (mean 11.2 minutes, S.D. 3.4).

Fifteen patients moved but the movements were slight and did not interfere with surgery. In two patients surgery had to be stopped for a while. The first of those two patients was not receiving any propofol for seven minutes because of a problem with the infusion line. The second one had his wound infiltrated with local anaesthetic at the beginning of the procedure. The closed-loop system reduced the propofol concentration to very low levels, since there was no pain and the patient needed very light anaesthesia. However, at two separate instances, the surgeons started operating outside the blocked area. As a result, the patient moved in response to pain and the system increased the target propofol concentration to bring the patient again under control. After that, the operator of the system reduced the target AEPidx slightly, anaesthesia was maintained at deeper levels and when the surgeons made another incision without local anaesthetic infiltration, the patient did not move (Figure 7.5).

At the end of anaesthesia, propofol, nitrous oxide and alfentanil were discontinued. No patient reported awareness during anaesthesia. One patient was concerned by the auditory stimuli, but all were prepared to have the same anaesthetic again in the future.

7.2.3 Results - paralysed patients

Fifty six patients (21 male and 35 female) underwent intra-abdominal surgery under muscle paralysis and IPPV. They had a mean age of 59.1 years (range 18-85 years) and a mean weight of 62.8 kg (range 41-96 kg).

Before induction, the mean AEPidx was 81 (S.D. 17.6), during maintenance it was 36 (S.D. 6.0) and at recovery it was 84 (S.D. 16.5).

The mean target AEPidx was 36 (S.D. 5.4). The AEPidx remained within ±5 of the target for 66.3% of the time (S.D. 9.4%), within ±10 of the target for 93.1% of the time (S.D. 5.1%) and within ±15 of the target for 98.7% of the time (S.D. 2.1%).

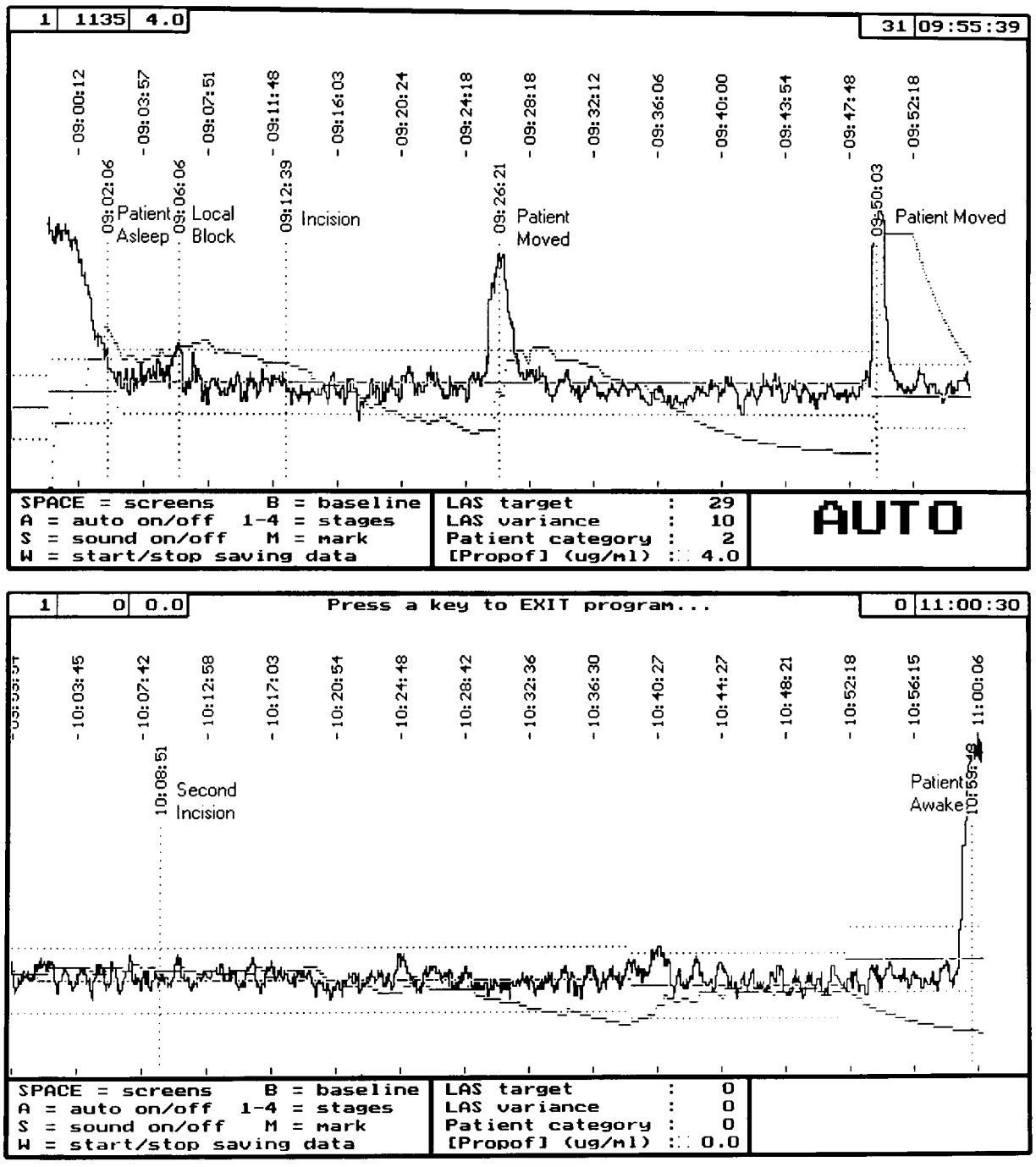

Figure 7.5 Effect of surgical stimulation on a patient who had a local anaesthetic block just before surgery commenced (see text for details).

The highest PRST score was 5 (median 1, range 0-5). The maximum systolic blood pressure decrease was 34.6% of the pre-induction value (S.D. 14.4%)

and the maximum increase was 5.4% (S.D. 16.1%). The maximum decrease in heart rate was 18.9% (S.D. 17.2%) and the maximum increase was 12.3% (S.D. 20.3%).

During a long procedure, one of the patients was given isoflurane at an end-tidal concentration of 1.9%. The closed-loop system reduced the propofol concentration to the lowest allowed target of 1 μg/ml. Shortly after isoflurane was stopped, the target propofol concentration returned to its previous levels (Figure 7.6).

No patient reported awareness during anaesthesia and all would have the same anaesthetic again in the future.

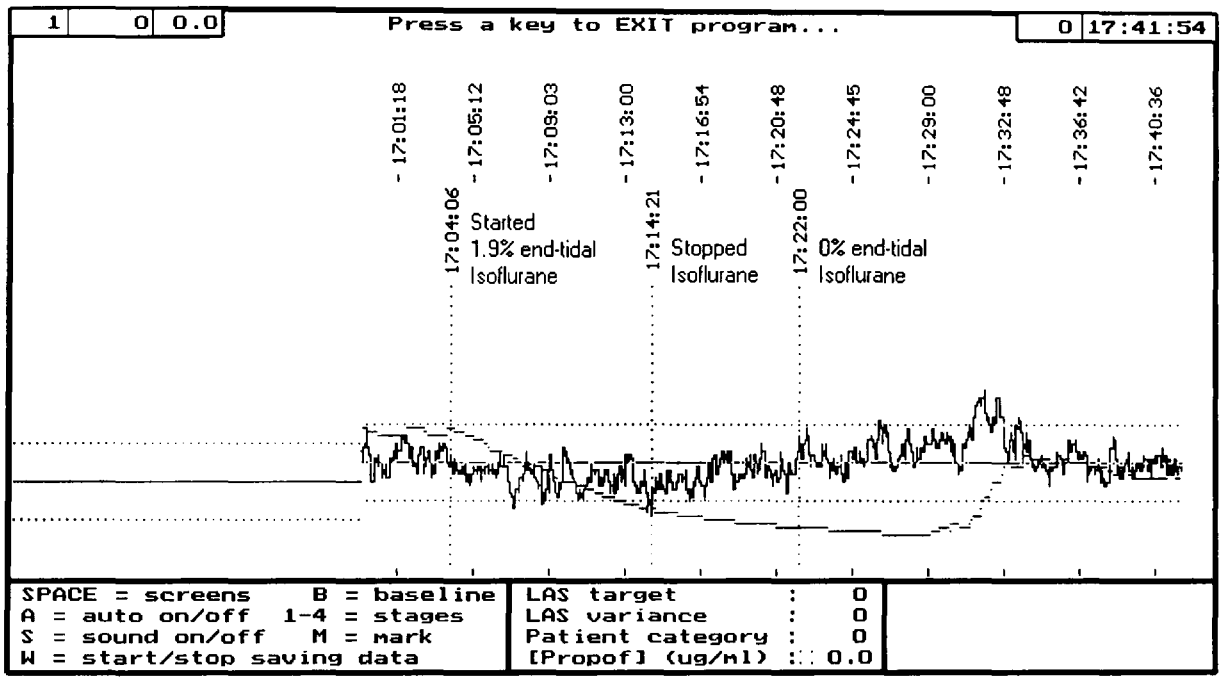

Figure 7.6 The effect of 1.9% end-tidal concentration of isoflurane during closed-loop anaesthesia with propofol.

7.2.4 Discussion

Closed-loop control of propofol anaesthesia in volunteers has been described previously using the median frequency of the EEG as the input signal (Schwilden *et al,* 1989). However, anaesthesia was not always adequate even to abolish the corneal reflex and would not be expected to produce adequate conditions for surgery. Median EEG frequency was used

by the same group to control maintenance of anaesthesia during surgery but not in patients breathing spontaneously (Schwilden *et al,* 1987). Systolic blood pressure has also been used to control anaesthesia by altering the administration of a volatile agent during surgery and to advise on the need for supplementary morphine (Robb *et al,* 1991). However in both studies, patients were anaesthetised to a satisfactory level before the controllers were employed and, further, were evaluated only in patients who had received paralysing drugs.

The system described in this thesis is the first enabling closed-loop control of anaesthesia from induction, during surgery to recovery in non-paralysed patients. The principal requirement of a closed-loop system is a reliable input signal. The use of the AEPidx as the input for closed-loop control of propofol anaesthesia validates it as a reliable index of anaesthetic depth with this technique.

An important observation was that no patient recovered consciousness at an AEPidx which was less than the value at which anaesthesia had been induced. Therefore, it would appear that if the AEPidx is maintained below the value at which consciousness is lost during propofol anaesthesia, awareness should not occur. Clearly, other anaesthetic agents and more patients must be assessed to determine whether this is a universal finding.

7.3 STUDY 3: PROPOFOL REQUIREMENTS DURING CLOSED-LOOP ANAESTHESIA[1]

It is well established that closed-loop control systems provide unbiased measurement of drug requirements (Colvin and Kenny, 1989c). A closed-loop anaesthesia (CLAN) system using the Auditory Evoked Potential Index (AEPidx) as its input signal has been described earlier in this thesis and has been used to control depth of anaesthesia automatically (par. 7.2 and Appendix D). In the present study, the same system was employed to assess propofol requirements in patients breathing spontaneously during surgery.

7.3.1 Patients and methods

Twelve patients scheduled to undergo body surface surgery were anaesthetised with the CLAN system. The study was approved by the Hospital Ethics Committee and informed consent was obtained. All patients received temazepam 20-30 mg as premedication approximately one hour before surgery. A target blood concentration of alfentanil 15 ng/ml was achieved before anaesthesia was induced. After induction of anaesthesia, patients breathed a mixture of nitrous oxide 66% in oxygen.

The CLAN system has been described earlier in this thesis (Chapters 5 and 6). Briefly, the AEP was calculated from 256 EEG sweeps of 144 ms duration using a click frequency of 6.9 Hz and a moving time average was obtained every 3 seconds. Auditory Evoked Potentials were processed on-line to provide the AEPidx. Anaesthesia was induced with a predetermined series of target blood propofol concentrations until the selected AEPidx value was achieved. Thereafter, anaesthesia was maintained by a proportional-integral (PI) controller which compared the measured with the selected AEPidx, calculated a new target propofol concentration and transmitted this

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[1] This study has been published as: Kenny GN, McFadzean WA, Mantzaridis H and Fisher AC, (1993) Propofol requirements during closed-loop anesthesia. *Anesthesiol.* **79**, A329.

new value via an RS-232 interface to the target-controlled propofol infusion system.

Blood samples were obtained from all patients and the concentration of propofol was measured by gas-liquid chromatography as described previously (White and Kenny, 1990). The predicted blood propofol concentration was also recorded to allow subsequent comparisons.

Arterial oxygen saturation (via pulse oximetry), respiratory rate and end-tidal CO_2 concentration were monitored continuously. Systolic blood pressure, heart rate, sweating and tear formation were used to calculate PRST scores (Evans *et al,* 1987) every five minutes.

7.3.2 Results

Quality of anaesthesia provided by the CLAN system was judged to be satisfactory in that slight movement occurred in one patient during insertion of the final sutures but did not disturb the operation. The highest PRST score recorded was 1 and the median maximum decrease in systolic arterial pressure was 25%. Respiration was assisted after induction in two patients for less than 5 minutes but otherwise all patients breathed spontaneously during surgery and no patient experienced dreams or recalled any event during the procedure.

A closed-loop anaesthetic of a patient requiring high propofol concentrations during surgery is shown in Figure 7.7. Induction of anaesthesia was achieved with moderate propofol concentrations. However, during maintenance, the system increased the concentration of propofol to much higher levels. In contrast, the patient in Figure 7.8 required slightly less propofol for induction and far less for maintenance of anaesthesia. Intra-patient variability can be seen clearly in both figures. It must be noted that both patients underwent similar procedures and both had satisfactory anaesthesia in terms of movement, respiration and PRST scores.

The relationship between predicted and measured blood values was: measured = 0.81 + 1.1 predicted (r=0.89) with a bias[2] of 29.1% and a precision of 34.5%. The median, maximum and minimum predicted and measured blood propofol concentrations required during surgery are shown in Table 7.2.

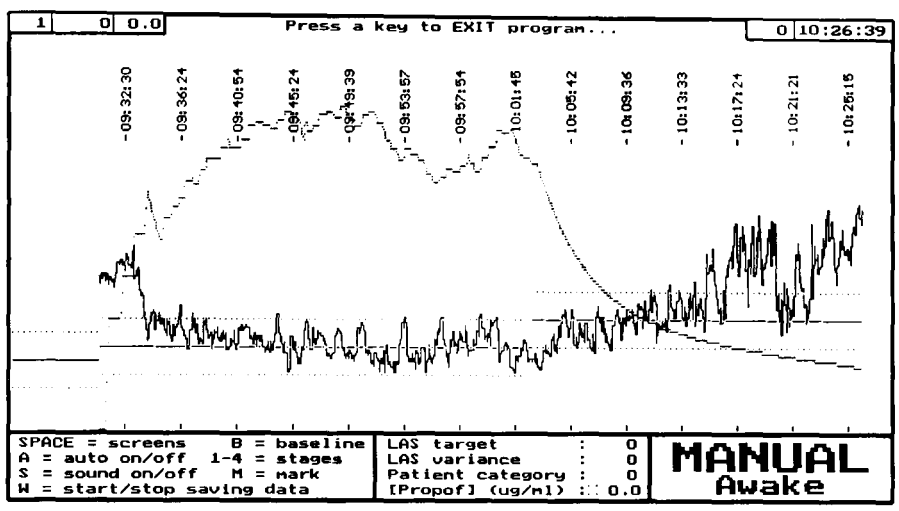

Figure 7.7 Screen capture of a closed-loop anaesthetic in a spontaneously breathing patient who required high propofol concentrations throughout surgery.

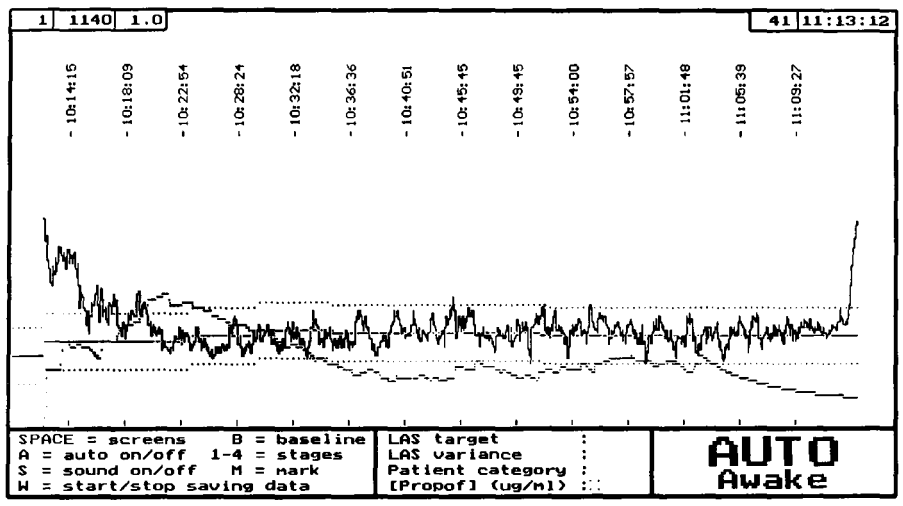

Figure 7.8 Screen capture of a closed-loop anaesthetic in a spontaneously breathing patient who had an operation similar to the one illustrated in Figure 7.7.

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[2] *Bias* is defined as the mean prediction error and is taken to represent the systematic tendency of the system to underestimate the measured blood concentration of propofol. If bias is positive, then the measured value is on average greater than the predicted one and *vice versa*. *Precision* is defined as the mean value of the sum of individual absolute values of prediction error and is a measure of the degree of scatter of the data about the line of perfect prediction.

The maximum blood concentration of propofol required to control anaesthesia for each patient was divided by the minimum value to calculate the percentage variation during surgery. Median variation in the predicted propofol concentrations was 225% (range 132%-422%). In the measured values median variation was 273% (range 122%-539%).

	Median	Maximum	Minimum
Predicted (µg/ml)	3.5 (0.9-10.9)	4.0 (2.9-10.9)	2.4 (0.9-6.1)
Measured (µg/ml)	4.2 (1.0-11.4)	6.2 (4.0-11.4)	3.1 (1.0-4.3)

Table 7.2 Predicted and measured blood propofol concentrations (medians and ranges).

7.3.3 Discussion

Measured and predicted blood concentrations of propofol showed the degree of variability which can occur with systems based on population pharmacokinetics. The precision of the propofol concentrations is a measure of the degree of scatter of the data about the line of perfect prediction and reflects the variability between patient pharmacokinetics. However, pharmacokinetic variability must be assessed in context with the variation in pharmacodynamics. This was clearly demonstrated using the CLAN system to provide an objective assessment of the variation in propofol requirements within patients. The median intra-patient variation in propofol requirements during surgery was 6-7 times greater than the median inter-patient pharmacokinetic variability.

This is the first time that a CLAN system has been employed as an objective and unbiased method of determining depth of anaesthesia. In the future, the same concept may be used to provide an unbiased comparison of relative potencies of different intravenous and inhalational anaesthetic agents and to

assess the cardio-respiratory effects of different analgesics with relation to their hypnotic effects.

8. CONCLUSIONS

8.1 ACHIEVEMENTS SO FAR

The achievements of this project can be divided into three areas. The first aim was to construct an Auditory Evoked Potential (AEP) monitoring system. A high quality, medical grade EEG amplifier was designed. Three different hardware platforms (desktop PC, laptop with PCMCIA card and purpose-built microprocessor system) were developed and special software was written. A combination of hardware enhancements and digital signal processing techniques allowed the extraction of AEPs by averaging only 256 sweeps, thus providing a full update of the signal in only 36.9 seconds. This reduction in acquisition time represents a dramatic improvement over existing systems and is arguably one of the most important achievements in this area.

The second aim of this work was to implement appropriate digital signal processing techniques in order to improve the signal quality of the derived AEPs and extract a single numerical parameter that reflects the changes occurring in the AEPs during general anaesthesia. This parameter was the Auditory Evoked Potential Index (AEPidx). It proved to be so reliable that has been used for the third aim of this study, to develop a closed-loop anaesthesia (CLAN) system.

The development of the CLAN system was the most ambitious task of this project. Despite several previous attempts, there has been no system capable of inducing and maintaining general anaesthesia in spontaneously breathing patients undergoing surgery. This is the first such system which has been used to automatically control depth of anaesthesia in more than 300 patients with excellent results. It has also provided an unbiased

measurement in several research projects including comparison of the pharmacokinetic and pharmacodynamic effects of propofol, the propofol-sparing effect of nitrous oxide during surgery (in progress) and the propofol-sparing action of local blocks.

8.1.1 Anaesthesia: a dynamic state

It is clear that the anaesthetised patient is in a dynamic state defined by the balance between stimulation (provided by surgical manipulations) and depression (provided by anaesthetic drugs) of the central nervous system (CNS). Loss of consciousness is an all-or-none phenomenon. However, the depression of the CNS is gradual. As a result, the higher the concentration of the anaesthetic, the more difficult it becomes for the patient to be aroused by a stimulus of given intensity. Conversely, a given drug concentration may render some patients unconscious under mild stimulation, but may prove inadequate when the same patients are subjected to much stronger stimuli.

The practical end result of this statement is that there is no "standard" anaesthetic drug dose that can keep all patients anaesthetised. Anaesthetic dose requirements depend on several factors, including patient characteristics and level of surgical stimulation. For example, spontaneously breathing patients having a closed-loop anaesthetic for hernia repair required trivial amounts of anaesthetic when a local block injection was administered before start of surgery. In similar patients with no local block, the concentrations of general anaesthetic delivered by the CLAN system were much higher. A paper describing the results of this study is under preparation.

The other practical conclusion is that it does not really matter whether low hypnotic and high opioid concentrations are used or *vice versa*. The choice of the appropriate combination of anaesthetic agents depends on the desired clinical outcome or is a matter of personal preference. For example, most UK patients undergoing body surface surgery breathe spontaneously. Some of

them are also day case patients, therefore a combination of relatively high doses of hypnotics and low doses of opioids is preferable, as it allows spontaneous respiration and fast recovery. In contrast, patients undergoing open heart surgery are ventilated for several hours after the operation. In these patients, haemodynamic stability is of paramount importance and high doses of opioids are often used.

8.2 Outstanding Problems And Future Developments

Several major areas of research remain to be explored. From the hardware point of view, a smaller, lighter and more compact system would be welcome. A dedicated microprocessor system with a Fast Digital Signal Processor (DSP) might be required, especially if computationally intensive digital signal processing techniques are applied. The present EEG amplifier performs very satisfactorily, however, it requires a built-in impedance test meter.

New software for a more intuitive front-end is required. Mouse support and on-line help are some of the areas that can be dealt with in the next major release. Ability of the system to log data from various monitors is another desirable feature.

A further area to be explored is artefact rejection and noise cancellation. Application of advanced digital signal processing techniques, including adaptive filtering, may lead to further improvements of the method.

Finally, spectral analysis and neural networks may provide a more robust and reliable Anaesthetic Depth Index (AEPidx).

A number of clinical studies are planned for the near future. They are divided into several categories:

- Further research on the effects of various anaesthetic agents (including premedication, muscle relaxation, ketamine, alfentanil and ketorolac and the use of regional blockade) on the AEP.

- MAC studies, where the closed-loop anaesthesia (CLAN) system is used to provide an unbiased comparison of the relative potencies of different anaesthetic agents. CLAN can also be used to compare volatile and intravenous agents and to assess various parameters of interest such as the cardio-respiratory effects of different intraoperative analgesics.
- Application of CLAN in various patient populations (paediatrics, cardiac surgery, obstetrics, in patients under sedation) and with different anaesthetic agents.
- Determination of patient awareness in a large number of patients (5000-10000) while monitoring the AEPs.

It is hoped that the application of advanced engineering and mathematical principles will result in further improvements and ultimately lead to a commercial monitor of anaesthetic depth, that will be of great value in clinical practice.

APPENDIX A: AEP AND ANAESTHETICS

Summary of the effects of various anaesthetics on the AEP.

Study	State	Latencies (ms)					Amplitudes (μV)			
		Na	Pa	Nb	Pb	Nc	Na	Pa	Nb	Pb
(Picton *et al*, 1974)	Awake		25	36						
(Thornton *et al*, 1983)	Awake (n=6)		28 (SD 2.9)	39 (SD 3.1)						
(Thornton *et al*, 1984)	Awake (n=12)		26 (SD 2.9)	39 (SD 6.6)						
(Thornton *et al*, 1985)	Awake (n=14)		26	32						
	Asleep		35	67						
(Thornton *et al*, 1992)	Asleep N_2O (n=8)		35.0	52.6				0.55	0.43	
	Asleep Isoflurane		40.7	62.5				0.37	0.41	
(Newton *et al*, 1992)	Awake (n=8)	18.2 (CI 17.3-19.1)	29.6 (CI 28.2-31.1)	44.9 (CI 42.9-46.9)	59.7 (CI 56.7-63.0)	73.8 (CI 69.4-78.5)		0.70 (CI 0.60-0.82)	0.51 (CI 0.42-0.61)	0.35 (CI 0.27-0.44)
	0.1 MAC isoflurane	18.9 (CI 18.0-19.8)	30.1 (CI 28.7-31.6)	46.3 (CI 44.3-48.5)	61.0 (CI 57.9-64.3)	75.1 (CI 70.6-79.9)		0.63 (CI 0.54-0.74)	0.43 (CI 0.36-0.52)	0.30 (CI 0.24-0.38)
	0.2 MAC isoflurane	18.3 (CI 17.4-19.2)	31.1 (CI 29.7-32.7)	46.7 (CI 44.7-48.9)	63.2 (CI 60.0-66.6)	79.6 (CI 74.8-84.7)		0.60 (CI 0.51-0.70)	0.40 (CI 0.33-0.48)	0.25 (CI 0.20-0.32)
	0.4 MAC isoflurane	21.8 (CI 20.8-22.9)	36.3 (CI 34.6-38.1)	53.9 (CI 51.5-56.3)	71.9 (CI 68.2-75.7)	87.4 (CI 82.2-93.0)		0.29 (CI 0.25-0.34)	0.25 (CI 0.21-0.30)	0.19 (CI 0.15-0.24)
(Savoia *et al*, 1988)+ *	Awake (n=6)		20.3 (SD 1.8)	28.6 (SD 2.9)				1.63 (SD 0.8)		
	prop. 54 ug/kg/min		24.8 (SD 2.2)	36.3 (SD 2.5)				0.31 (SD 0.13)		
	prop. 108 ug/kg/min		25.7 (SD 2.1)	37.3 (SD 2.5)				0.14 (SD 0.1)		
(Chassard *et al* 1989) +	Awake (n=6)		27.8 (SE 0.9)	30.6 (SE 1.4)				1.0 (SE 0.2)		
(Madler *et al*, 1991) + **	Awake	18.7	29.7				2.0			

Study	State	Latencies (ms)					Amplitudes (μV)			
		Na	Pa	Nb	Pb	Nc	Na	Pa	Nb	Pb
	(n=13)									
	0.3% iso.	23.4	40.6				1.0			
	0.6% iso.	27.3	44.5				0.5			
	1.2% iso.	31.7	53.1				0.3			
(Sneyd *et al*, 1992)	Before physiotherapy (n=11)			44.8 (SD 7.9)						
	During physiotherapy			41.0 (SD 6.8)						
	After physiotherapy			45.6 (SD 6.3)						
(Schwender *et al*, 1993b) +	Awake alfentanil (n=10)	20.0 (SD 1.4)	32.2 (SD 2.3)	47.1 (SD 3.2)	62.6 (SD 5.1)		1.16 (SD 0.43)	1.22 (SD 0.58)	1.15 (SD 0.65)	
	Awake fentanyl (n=10)	18.8 (SD 0.8)	30.9 (SD 2.1)	47.5 (SD 2.5)	60.5 (SD 1.9)		1.45 (SD 0.54)	1.51 (SD 1.04)	1.24 (SD 0.77)	
	Awake morphine (n=10)	19.0 (SD 1.1)	30.7 (SD 1.6)	46.7 (SD 2.3)	61.1 (SD 4.0)		1.32 (SD 0.33)	1.48 (SD 0.58)	1.21 (SD 1.06)	
(Schwender *et al*, 1993a) +	Awake (n=20)	18.6 (SD 2.3)	30.4 (SD 3.1)	47.5 (SD 8.2)	66.8 (SD 13.2)		1.64 (SD 0.73)	1.05 (SD 0.67)	0.76 (SD 0.47)	
(Schwender *et al*, 1994a) +	Awake propofol (n=10)	18.2 (SD 1.6)	31.1 (SD 2.7)				2.84 (SD 0.86)			
	After induction propofol	21.0 (SD 4.1)	39.2 (SD 6.1)				1.39 (SD 0.42)			
	Maintenance 30 min. propofol	23.6 (SD 1.7)	38.9 (SD 4.6)				0.66 (SD 0.31)			
	Maintenance 60 min. propofol	25.8 (SD 2.5)	46.7 (SD 3.7)				0.84 (SD 0.36)			
	Maintenance 90 min. propofol	22.9 (SD 2.2)	42.9 (SD 3.6)				1.51 (SD 0.50)			
	Maintenance 120 min. propofol	23.0 (SD 2.6)	42.3 (SD 4.9)				1.19 (SD 0.44)			
	Awake isoflurane (n=10)	18.3 (SD 1.61)	30.8 (SD 2.65)				2.64 (SD 0.78)			
	After induction	19.9	37.5				1.23			

Study	State	Latencies (ms)					Amplitudes (μV)			
		Na	Pa	Nb	Pb	Nc	Na	Pa	Nb	Pb
	isoflurane	(SD 3.1)	(SD 5.7)				(SD 0.41)			
	Maintenance 30 min. isoflurane	26.5 (SD 6.5)	44.8 (SD 9.0)				0.74 (SD 0.3)			
	Maintenance 60 min. isoflurane	24.5 (4.8)	43.8 (SD 6.7)				0.65 (SD 0.32)			
	Maintenance 90 min. isoflurane	24.3 (SD 5.8)	44.1 (SD 8.2)				0.64 (SD 0.32)			
	Maintenance 120 min. isoflurane	26.7 (SD 6.7)	49.7 (SD 12.7)				0.72 (SD 0.34)			
	Awake flunitrazepam (n=10)	18.5 (SD 1.8)	32.1 (SD 3.2)				2.30 (SD 0.88)			
	After induction flunitrazepam	26.8 (SD 8.0)	44.2 (SD 15.0)				0.97 (SD 0.36)			
	Maintenance 30 min. flunitrazepam	21.2 (SD 2.2)	37.6 (SD 4.7)				1.83 (SD 0.78)			
	Maintenance 60 min. flunitrazepam	22.2 (SD 2.7)	38.9 (SD 4.4)				1.40 (SD 0.56)			
	Maintenance 90 min. flunitrazepam	20.6 (SD 2.2)	38.1 (SD 3.7)				1.98 (SD 0.68)			
	Maintenance 120 min. flunitrazepam	21.5 (SD 2.7)	40.6 (SD 5.8)				1.62 (SD 0.66)			
(Schwender *et al*, 1994b) +	Awake propofol (n=10)	17.4 (SD 0.8)	30.5 (SD 4.2)	43.5 (SD 6.7)	55.8 (SD 6.2)		2.16 (SD 1.02)	1.43 (SD 0.52)	1.17 (SD 0.55)	
	Before incision propofol	21.3 (SD 2.1)	37.5 (SD 3.4)	62.9 (SD 8.5)	81.5 (SD 16.3)		1.05 (SD 0.68)	1.49 (SD 0.83)	0.98 (SD 1.21)	
	After incision propofol	22.7 (SD 3.1)	39.9 (SD 3.9)	65.4 (SD 9.1)	83.9 (SD 16.8)		0.85 (SD 0.71)	1.23 (SD 0.75)	0.69 (SD 0.62)	
	After sternotomy propofol	21.9 (SD 2.1)	39.0 (SD 3.4)	64.4 (SD 12.5)	83.5 (SD 12.0)		1.01 (SD 0.71)	0.86 (SD 0.67)	0.56 (SD 0.22)	
	Awake isoflurane (n=10)	20.1 (SD 1.0)	31.1 (SD 4.1)	44.2 (SD 5.6)	57.9 (SD 5.6)		1.77 (SD 0.97)	1.91 (SD 0.95)	2.53 (SD 3.63)	

Study	State	Latencies (ms)					Amplitudes (μV)			
		Na	Pa	Nb	Pb	Nc	Na	Pa	Nb	Pb
	Before incision isoflurane	23.2 (SD 2.7)	41.2 (SD 2.9)	64.1 (SD 9.5)	85.8 (SD 11.2)		0.62 (SD 0.70)	1.01 (SD 0.38)	0.95 (SD 0.72)	
	After incision isoflurane	22.8 (SD 2.3)	43.3 (SD 4.8)	65.3 (SD 10.2)	86.7 (SD 12.3)		0.78 (SD 0.54)	0.97 (SD 0.68)	0.70 (SD 0.65)	
	After sternotomy isoflurane	24.6 (SD 2.9)	42.2 (SD 7.5)	65.6 (SD 9.1)	89.0 (SD 8.3)		0.46 (SD 0.45)	0.91 (SD 0.60)	0.58 (SD 0.45)	
	Awake flunitrazepam (n=10)	18.7 (SD 1.6)	30.4 (SD 3.4)	43.7 (SD 5.7)	56.2 (SD 6.7)		1.57 (SD 1.09)	1.31 (SD 0.52)	1.43 (SD 0.81)	
	Before incision flunitrazepam	20.8 (SD 1.3)	35.7 (SD 4.5)	55.9 (SD 7.5)	75.8 (SD 8.9)		0.91 (SD 0.43)	1.17 (SD 0.63)	1.18 (SD 0.82)	
	After incision flunitrazepam	21.0 (SD 1.3)	36.7 (SD 3.9)	57.8 (SD 7.0)	76.9 (SD 9.1)		0.91 (SD 0.40)	1.25 (SD 0.91)	0.70 (SD 0.54)	
	After sternotomy flunitrazepam	21.0 (SD 1.9)	38.1 (SD 3.3)	61.4 (SD 6.9)	82.8 (SD 11.5)		0.79 (SD 0.35)	0.98 (SD 0.35)	0.80 (SD 0.41)	

Notes:

* = Wrong filter settings (high-pass -3 db point was set to 100 Hz).

** = Latencies and amplitude were measured from accompanying figure.

\+ = Peak-to-peak measurement between present and next peak.

CI = Confidence Interval.

SD = Standard Deviation.

SE = Standard Error.

APPENDIX B: FIR FILTER IN PASCAL

```
program FIRDEMO;

(*************************************************************************
*                                                                        *
*                    P R O G R A M M E   F I R D E M O                   *
*                                                                        *
*          Created by Harris Mantzaridis on an Amstrad PC2286            *
*                         version 1.0   06-02-91                         *
*                                                                        *
*  Compiler: Borland Turbo Pascal version 5.0                            *
*                                                                        *
*                                                                        *
*  Mod. Record:                                                          *
*    version              comments                    date      by      *
*      1.0              Initial issue                 06-02-91   H.M.    *
*                                                                        *
*                                                                        *
* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
*                                                                        *
*    Programme information:                                              *
*                                                                        *
*  Purpose    : Demonstrate the use of FIR digital filters.              *
*                                                                        *
*  Input      : The user is prompted for the filter parameters.          *
*  Process    : The programme calculates the filter coefficients and     *
*               plots the transfer function and the coefficients. Then a *
*               dynamic array is filled with random numbers which are    *
*               filtered using an FIR filter.                            *
*  Output     : Data and results are plotted on the screen.              *
*                                                                        *
*************************************************************************)


{$N+,EE}

(*
  Use math-coprocessor.
*)

uses graph,crt;

const
  Limit         = 3999;       (* Max. length of the data array is Limit+1. *)
  MaxNoOfCoefs  =  999;             (* Max. number of filter coefficients. *)
  MaxNoOfPoints = MaxNoOfCoefs*2+1;     (* Max. number of filtered points. *)
  Xorg          =   20;    (* Origins of the graphics window on the x-axis *)
  Yorg          = round(Xorg*480/640);                  (* and the y-axis. *)
  Variance      =  300;      (* Data take random values from 0 to Variance.*)

type
  dynamarray    = array [0..Limit] of word;
  coefarray     = array [-MaxNoOfCoefs..MaxNoOfCoefs] of double;

var
  Data                  : ^dynamarray;
  Coef                  : coefarray;
  k,n,m,Maxx,Maxy,
  NoOfCoefs,NoOfPoints : integer;
  Ch                    : string;
```

```
  Flonorm,Fhinorm       : double;
  Xrange,Yrange         : real;


procedure Beep;

begin
  sound(1000);
  delay(70);
  nosound;
end;   (* Beep *)

procedure KeyIn;

(*
  This procedure waits until a key is pressed. The character read is
  stored in the string variable 'Ch'.
*)

begin
  repeat
  until keypressed;
  Ch:= readkey;
end;   (* KeyIn *)


procedure InitPlot;

(*
  This procedure initialises the graphics screen.
  It also draws the initial graph.
*)
var
  GraphDrv,GraphMde,ErrorCode                        : integer;
  NoOfCoefsStr,NoOfPointsStr,FlonormStr,FhinormStr : string;

begin
  detectgraph(GraphDrv,GraphMde);      (* Check the hardware and determine *)
                                         (* the graphics driver available. *)
  if (GraphDrv <> vga) and (GraphDrv <> ega)
                       and (GraphDrv <> ega64) and (GraphDrv <> egamono) then
    begin
      textbackground(0);
      textcolor(14);
      clrscr;
      writeln;
      beep;
      writeln('Graphics error : VGA or EGA not present');
      writeln;
      writeln('Program aborted');
      writeln;
      halt(1);
    end;   (* if *)
  GraphDrv:= vga;                 (* Make sure that the system uses a 640*350 *)
  GraphMde:= 1;                    (* EGA-compatible 16 colour 2 page screen. *)
  initgraph(GraphDrv,GraphMde,'');      (* Initialise the graphics system. *)
  ErrorCode:= graphresult;
  if ErrorCode <> grok then
    begin
      textbackground(0);
      textcolor(14);
      clrscr;
      writeln('Graphics error :',grapherrormsg(errorcode));
```

```
    writeln;
    writeln('Program aborted');
    writeln;
    halt(1);
  end;  (* if *)
Maxx:= getmaxx+1;                          (* Initialise useful variables. *)
Maxy:= getmaxy+1;
Xrange:= (Maxx-2*Xorg)/Limit;
Yrange:= Maxy/(480+Yorg);
setcolor(11);
setbkcolor(0);
setfillstyle(1,1);
bar(0,0,getmaxx,getmaxy);                  (* Start drawing the initial graph. *)
setlinestyle(0,0,3);
rectangle(1,1,getmaxx-1,getmaxy-1);
setlinestyle(0,0,1);
settextstyle(0,0,2);
settextjustify(centertext,toptext);
setcolor(14);
outtextxy(round(Maxx/2),Yorg+round(Yrange*Variance)+15,
                                'FIR filter demo');
settextstyle(2,0,4);
outtextxy(round(Maxx/2),Yorg+round(Yrange*Variance)+36,
                                'Programmed by Harris Mantzaridis');
settextjustify(lefttext,toptext);
settextstyle(0,0,1);
setcolor(11);

str(NoOfCoefs+1,NoOfCoefsStr);             (* Convert integers to strings. *)
str(NoOfPoints,NoOfPointsStr);
str(Flonorm:6:4,FlonormStr);
str(Fhinorm:6:4,FhinormStr);
outtextxy(Xorg,Yorg+round(Yrange*Variance)+60,
            'Number of filtered points           = '+NoOfPointsStr);
  outtextxy(Xorg,Yorg+round(Yrange*Variance)+60+15,
            'Number of coefficients            = '+NoOfCoefsStr);
  outtextxy(Xorg,Yorg+round(Yrange*Variance)+60+30,
            'Low cut-off frequency (Normalised)  = '+FlonormStr);
  outtextxy(Xorg,Yorg+round(Yrange*Variance)+60+45,
            'High cut-off frequency (Normalised) = '+FhinormStr);

  rectangle(Xorg-3,Yorg-2,Maxx-Xorg+1,Yorg+2+round(Yrange*Variance));
  setviewport(Xorg-2,Yorg-1,Maxx-Xorg,Yorg+1+round(Yrange*Variance)
                                                        ,clipon);
  clearviewport;
  setviewport(Xorg-1,Yorg,Maxx-Xorg-1,       (* Define the window in which *)
          Yorg+round(Yrange*Variance),clipon);   (* data will be plotted. *)
end;   (* InitPlot *)


procedure CalcCoeffs;

(*
  This procedure calculates the filter coefficients.
  The filter is a raised cosine filter.
*)

begin
  NoOfCoefs:= NoOfCoefs-1;
  Coef[0]:= 2.0*(Fhinorm-Flonorm);         (* Calculate the coefficients. *)
  for k:= 1 to NoOfCoefs do
    begin
      Coef[k]:= 1.0/k/pi*(sin(2.0*pi*k*Fhinorm)-sin(2.0*pi*k*Flonorm));
      Coef[k]:= Coef[k]*(0.5+0.5*cos(pi*k/NoOfCoefs));
      Coef[-k]:= Coef[k];
```

```
    end;  (* for *)
end;  (* CalcCoeffs *)


procedure GetNormFreq;

(*
  This procedure prompts the user for the parameters of the filter.
*)
begin
  repeat
    writeln;
    write(' Number of filtered points (it must be an odd number <= ',
                                                    MaxNoOfPoints,') : ');
    readln(NoOfPoints);
  until (NoOfPoints <= MaxNoOfPoints) and (NoOfPoints > 0)
                      and ((NoOfPoints-1)/2 = round((NoOfPoints-1)/2));
  NoOfCoefs:= (NoOfPoints+1) div 2;
  writeln;
  write(' Low cut-off frequency (Normalised)  = ');
  readln(Flonorm);
  writeln;
  write(' High cut-off frequency (Normalised) = ');
  readln(Fhinorm);
end;  (* GetNormFreq *)


procedure InitData;

(*
  This procedure initialises the data array
  with random numbers from 0 to Variance.
*)

begin
  randseed:= 12345;     (* Make sure that the data will always be the same *)
                    (* by giving randseed (=random seed) a specific value. *)
  for n:= 0 to Limit do
    Data^[n]:= random(Variance);              (* Initialise the data array. *)
end;  (* InitData *)


procedure PlotFreqResp;

(*
  This procedure plots the transfer function of the filter.
*)

const
  xref = 60;                          (* Offset from the upper left corner of *)
  yref = 30;                                    (* the current view port. *)

var
   temp,Hf,f : real;
   i,j       : integer;
   AxisStr   : string;

begin
  settextjustify(centertext,centertext);
  outtextXY((Maxx-2*Xorg) div 2,15,
                              'Transfer function');
  setcolor(4);
  settextstyle(2,0,4);
  for j:= 0 to 8 do                              (* Start plotting the grid. *)
```

```
  line(xref,yref+j*20,xref+500,yref+j*20);
for i:= 0 to 10 do
  line(xref+i*50,yref,xref+i*50,yref+160);
setcolor(11);
for i:= 0 to 500 div 50 do
  begin
    str(i/20:3:2,AxisStr);
    outtextXY(xref+i*50-5,yref+173,AxisStr);
  end;  (* for *)
settextjustify(righttext,centertext);
for j:= 0 to 4 do
  begin
    str((4-j)/4:3:2,AxisStr);
    outtextXY(xref-12,yref+j*40,AxisStr);
  end;  (* for *)
settextstyle(0,0,1);

setcolor(14);                (* Calculate and plot the transfer function. *)
f:= 0;
temp:= 0;
for k:= -NoOfCoefs to NoOfCoefs do temp:=temp+(Coef[k]*cos(2*PI*f*k));
Hf:= cos(2*temp);
moveto(xref+round(f*1000),round((Hf+0.4162)*(Yrange
                          *Variance*0.52)+(Yrange*Variance*0.15)));
f:= f+0.00125;
while (f < 0.5) and (not keypressed) do          (* Stop if f=0.5 or a *)
  begin                                             (* key is pressed. *)
    temp:= 0;
    for k:= -NoOfCoefs to NoOfCoefs do temp:=temp+(Coef[k]
                                                  *cos(2*PI*f*k));
    Hf:= cos(2*temp);
    lineto(xref+round(f*1000),round((Hf+0.4162)*(Yrange
                          *Variance*0.52)+ (Yrange*Variance*0.15)));
    f:= f+0.00125;
  end;  (* while *)

  setcolor(11);
  if keypressed then Ch:= readkey;
  beep;
  keyin;
  clearviewport;
end;  (* PlotFreqResp *)


procedure PlotCoeffs;

(*
  This procedure plots the coefficients of the filter.
*)

const
  xref = 60;                        (* Offset from the upper left corner of *)
  yref = 30;                                    (* the current view port. *)

var
   i,j                      : integer;
   AxisStr                  : string;
   MinCoef,MaxCoef,DifCoef  : double;

begin
  MinCoef:= Coef[0];                (* Calculate the variables used to plot *)
  MaxCoef:= Coef[0];                     (* the coefficients on the screen. *)
  for k:= 1 to NoOfCoefs do
    begin
```

```
    if Coef[k] < MinCoef then MinCoef:= Coef[k];
    if Coef[k] > MaxCoef then MaxCoef:= Coef[k];
  end;  (* for *)
DifCoef:= MaxCoef-MinCoef;

settextjustify(centertext,centertext);
outtextXY((Maxx-2*Xorg) div 2,15,'Coefficients');

setcolor(4);
settextstyle(2,0,4);
for j:= 0 to 8 do                                  (* Start plotting the grid. *)
  line(xref,yref+j*20,xref+500,yref+j*20);
for i:= 0 to 10 do
  line(xref+i*50,yref,xref+i*50,yref+160);
setcolor(11);
for i:= 0 to 10 do
  begin
    str(round((i-5)*NoOfCoefs/5):3,AxisStr);
    outtextXY(xref+i*50,yref+173,AxisStr);
  end;  (* for *)
settextjustify(righttext,centertext);
for j:= 0 to 4 do
  begin
    str((MaxCoef-DifCoef*j/4):6:5,AxisStr);
    outtextXY(xref-12,yref+j*40,AxisStr);
  end;  (* for *)
settextjustify(lefttext,toptext);
settextstyle(0,0,1);

setcolor(14);                              (* Start plotting the coefficients. *)
moveto(xref,round(yref+160-(Coef[-NoOfCoefs]-MinCoef)/DifCoef*160));
for k:= 1-NoOfCoefs to NoOfCoefs do
  begin
    lineto(xref+round((k+NoOfCoefs)/NoOfCoefs*250),
           round(yref+160-(Coef[k]-MinCoef)/DifCoef*160));
  end;  (* for *)
  beep;
  keyin;
  clearviewport;
end;  (* PlotCoeffs *)


procedure PlotFilterData;

(*
  This procedure filters the data array and plots the results on the screen.
*)

var
  SampleNo,CoefNo,Xtemp,Ytemp : integer;
  tempFIR                     : double;

begin
  moveto(0,round(Yrange*Data^[0]));          (* Plot the initial data array. *)
  setcolor(2);
  for SampleNo:= 1 to Limit do
    begin
      lineto(round(Xrange*SampleNo),round(Yrange*Data^[SampleNo]));
      putpixel(round(Xrange*(SampleNo-1)),round(Yrange
                                          *Data^[SampleNo-1]),4);
    end;  (* for *)
  putpixel(round(Xrange*Limit),round(Yrange*Data^[Limit]),3);

  tempFIR:= 0;    (* Filter the data array to get the first filtered point *)
  for k:= -NoOfCoefs to NoOfCoefs do      (* and move the current graphics *)
```

```
  tempFIR:= tempFIR+Data^[NoOfCoefs+k]*Coef[k];       (* pointer to that *)
moveto(round(Xrange*NoOfCoefs),round(Yrange*tempFIR));         (* point. *)

SampleNo:= NoOfCoefs+1;
while (SampleNo <= Limit-          (* Stop if SampleNo > Limit-NoOfCoefs *)
       NoOfCoefs) and (not keypressed) do       (* or a key is pressed. *)
  begin                                      (* Start the main filter loop. *)
    Xtemp:= getx;                              (* Draw the lines that show *)
    Ytemp:= gety;                               (* which part of the data *)
    setcolor(12);                              (* is currently processed. *)
    setviewport(Xorg-1,Yorg-2,Maxx-Xorg-1,Yorg+
                                  2+round(Yrange*Variance),clipon);
    line(round(Xrange*(SampleNo-NoOfCoefs)),0,round(Xrange*
                                   (SampleNo+NoOfCoefs)),0);
    putpixel(round(Xrange*SampleNo),0,0);
    line(round(Xrange*(SampleNo-NoOfCoefs)),round(Yrange*Variance)+4,
        round(Xrange*(SampleNo+NoOfCoefs)),round(Yrange*Variance)+4);
    putpixel(round(Xrange*SampleNo),round(Yrange*Variance)+4,0);
    setviewport(Xorg-1,Yorg,Maxx-Xorg-1,Yorg+round(Yrange*
                                                  Variance),clipon);

    setcolor(14);
    moveto(Xtemp,Ytemp);

    tempFIR:= 0;                                 (* Filter the data array *)
    for k:= -NoOfCoefs to NoOfCoefs do              (* and draw a line *)
        tempFIR:= tempFIR+Data^[SampleNo+k]*Coef[k];          (* to that *)
    lineto(round(Xrange*SampleNo),round(Yrange*tempFIR));      (* point. *)

    Xtemp:= getx;                       (* Delete part of the lines that show *)
    Ytemp:= gety;                                (* which part of the data *)
    setcolor(11);                               (* is currently processed. *)
    setviewport(Xorg-1,Yorg-2,Maxx-Xorg-1,Yorg+
                                    2+round(Yrange*Variance),clipon);
    line(round(Xrange*(SampleNo-NoOfCoefs)),0,round(Xrange*
                                   (SampleNo-NoOfCoefs+1)),0);
    line(round(Xrange*(SampleNo-NoOfCoefs)),round(Yrange*Variance)+4,
      round(Xrange*(SampleNo-NoOfCoefs+1)),round(Yrange*Variance)+4);
    setviewport(Xorg-1,Yorg,Maxx-Xorg-1,Yorg+round(Yrange*
                                                  Variance),clipon);

    setcolor(14);
    moveto(Xtemp,Ytemp);
    SampleNo:= SampleNo+1;
  end;  (* for *)
  if keypressed then Ch:= readkey;
end;  (* PlotFilterData *)

                    (*      MAIN PROGRAMME      *)

begin
  TextColor(14);
  TextBackground(1);
  clrscr;
  gotoxy(18,2);
  writeln('┌──────────────────────────────────────┐');
  gotoxy(18,3);
  writeln('│ FIR filter demonstration programme │');
  gotoxy(18,4);
  writeln('└──────────────────────────────────────┘');
  writeln;
  TextColor(11);
  new(Data);                                 (* Create a new dynamic variable. *)
  GetNormFreq;                          (* Get the parameters of the filter. *)
  CalcCoeffs;                        (* Calculate the filter coefficients. *)
```

```
  InitData;                                    (* Initialise the data array. *)
  InitPlot;                                  (* Initialise the graphics system *)
                                               (* and draw the initial graph. *)
  PlotFreqResp;                 (* Plot the frequency response of the filter. *)
  PlotCoeffs;                         (* Plot the coefficients of the filter. *)
  PlotFilterData;                          (* Filter and plot the data array. *)
  Beep;
  KeyIn;
  closegraph;                                  (* Close the graphics system. *)
  gotoxy(24,10);
  write(' Programme terminated normally. ');
  dispose(Data);                          (* Dispose the dynamic variable Data. *)
  delay(1000);
  writeln;
end.  (* PROGRAMME *)
```

APPENDIX C: FIR FILTER IN ASSEMBLY

```
$mod186
name   mtaall


      EXTRSEGMNT EQU 4000H

      NOOFERRORS EQU 3
      BELL       EQU 7
      BS         EQU 8
      TAB        EQU 9
      LF         EQU 10
      CR         EQU 13
      CLS        EQU 26
      ESCP       EQU 27
      SPC        EQU 32
      PROMPT     EQU '>'
      PACE       EQU '>'

      PCB        EQU 0FF00H          ;We assume PCB has not been relocated.

      A2DC       EQU 1000H

      PIO_A      EQU 1080H
      PIO_B      EQU 1082H
      PIO_C      EQU 1084H
      PIO_CON1   EQU 1086H

      DISP0      EQU 2000H
      DISP1      EQU 2002H

      RTC        EQU 3000H
      TENTHSEC   EQU RTC+00H
      SECONDS    EQU RTC+02H
      MINUTES    EQU RTC+04H
      MINALARM   EQU RTC+06H
      HOURS      EQU RTC+08H
      HOURALARM  EQU RTC+0AH
      DAYS       EQU RTC+0CH
      DAYALARM   EQU RTC+0EH
      DATE       EQU RTC+10H
      MONTHS     EQU RTC+12H
      YEARS      EQU RTC+14H
      RTCCOM     EQU RTC+16H
      WATCHDOG0  EQU RTC+18H
      WATHCDOG1  EQU RTC+1AH

      EOI        EQU PCB+02H
      I0CON      EQU PCB+18H

      INT0_TYPE  EQU 12

      T0CMPA     EQU PCB+32H
      T0CMPB     EQU PCB+34H
      T0CON      EQU PCB+36H

      T1CMPA     EQU PCB+3AH
      T1CMPB     EQU PCB+3CH
      T1CON      EQU PCB+3EH

      T2CMPA     EQU PCB+42H
      T2CMPB     EQU PCB+44H
      T2CON      EQU PCB+46H
```

```
B0CMP       EQU PCB+60H
B0CNT       EQU PCB+62H
S0CON       EQU PCB+64H
S0STS       EQU PCB+66H
S0RBUF      EQU PCB+68H
S0TBUF      EQU PCB+6AH

B1CMP       EQU PCB+70H
B1CNT       EQU PCB+72H
S1CON       EQU PCB+74H
S1STS       EQU PCB+76H
S1RBUF      EQU PCB+78H
S1TBUF      EQU PCB+7AH

GCS0ST      EQU PCB+80H
GCS0SP      EQU PCB+82H
GCS1ST      EQU PCB+84H
GCS1SP      EQU PCB+86H
GCS2ST      EQU PCB+88H
GCS2SP      EQU PCB+8AH
GCS3ST      EQU PCB+8CH
GCS3SP      EQU PCB+8EH
GCS4ST      EQU PCB+90H
GCS4SP      EQU PCB+92H
GCS5ST      EQU PCB+94H
GCS5SP      EQU PCB+96H
GCS6ST      EQU PCB+98H
GCS6SP      EQU PCB+9AH
GCS7ST      EQU PCB+9CH
GCS7SP      EQU PCB+9EH
LCSST       EQU PCB+0A0H
LCSSP       EQU PCB+0A2H
UCSST       EQU PCB+0A4H
UCSSP       EQU PCB+0A6H

INCRE       EQU 0303H
CAPAC       EQU 8000H                ;Size of memory segment is 64K.

; *** for the MTA ***

  BASE           EQU A2DC                    ;Base address of the ADC.

  LIMIT          EQU  255          ;Total number of samples is 255+1.
  EPOCH          EQU    1             ;Total number of epochs is 1+1.
  SMALLARRAY     EQU  128       ;Total number of small arrays is 128.
  SWEEPS2REJECT  EQU    7          ;Number of sweeps to reject after
                                              ;diathermy is switced off.
  DIATH_HI_DEF   EQU 4080          ;Default upper limit for diathermy
                                                  ;detection window.
  DIATH_LO_DEF   EQU   16          ;Default lower limit for diathermy
                                                  ;detection window.


; *** for the FIR ***

  NoOfCoefs EQU 18                      ;Number of filter coefficients.
  Limit_FIR EQU 256           ;Total number of smoothing array points.


; Inside the subprogram, value arguments are accessed by
; using a STRUCTURE reference, with BP as the base and the
; appropriate field name as a qualifier; e.g.: [BP].PARM3
```

```
;
; NOTE: The STRUCTURE fields for the arguments are declared
; in reverse order in which they were pushed, because the
; 80x86 stack grows toward low memory.
;
; The saved value of BP and the return address must be
; declared in the structure, since these two items are pushed
; between the arguments and the spot pointed to by BP.

DSA         STRUC

OLD_BP      DW ?                    ;Prologue code saves BP here.
OLD_DS      DW ?                    ;Prologue code saves DS here.
RETURN      DD ?                  ;Double word for FAR procedures.
PARM3       DW ?                          ;Parameter 3 is a word.
PARM2       DW ?                          ;Parameter 2 is a word.
PARM1       DW ?                          ;Parameter 1 is a word.

DSA         ENDS


data2 segment para 'data'


Inputs          DW 256 DUP(?)


      PUBLIC    SMOOPREARRAY
      PUBLIC    SMOOARRAY
      PUBLIC    SMOOMETAARRAY
      PUBLIC    COEFARRAY
      PUBLIC    SMOOTMPADD1
      PUBLIC    SMOOTMPADD2
      PUBLIC    SMOOTMPSUB1
      PUBLIC    SMOOTMPSUB2
      PUBLIC    SMOOSEGM
      PUBLIC    SMOOADDR

SMOOPREARRAY    DW NoOfCoefs-1 DUP (?)      ;Additional smoothing array.
SMOOARRAY       DW Limit_FIR DUP (?)              ;Main smoothing array.
SMOOMETAARRAY   DW NoOfCoefs-1 DUP (?)      ;Additional smoothing array.
COEFARRAY       DW 2*NoOfCoefs-1 DUP (?)            ;Coefficient array.
SMOOTMPADD1     DW ?                     ;Temporary 32-bit storage
SMOOTMPADD2     DW ?                                 ;for addition.
SMOOTMPSUB1     DW ?                     ;Temporary 32-bit storage
SMOOTMPSUB2     DW ?                                 ;for subtraction.
SMOOSEGM        DW ?                  ;Segment of curve to be smoothed.
SMOOADDR        DW ?                  ;Address of curve to be smoothed.


data2 ends


code_seg segment para 'code'

      assume cs:code_seg


PUBLIC SMOOTH

SMOOTH proc far

;This routine smooths the contents of a word
;array (with length=Limit_FIR)by using a 35 point
```

```
;low-pass FIR filter with frequency response
;0-0.0492 of the Nyquist interval.The input to
;the routine is a far pointer to the beginning
;of the array. DX contains the segment and
;AX contains the address. The output of
;the routine is a smoothed curve, which is
;stored in the original input array. The
;routine exits with all registers unmodified.

        push    ds
        mov     ax,data2
        mov     ds,ax

        assume  ds:data2

        mov     ax,offset Inputs
        MOV     BX,DS                   ;Copy the original array into SMOOARRAY.
        MOV     DX,DS
        MOV     SMOOSEGM,DX
        MOV     ES,BX
        MOV     SI,AX
        MOV     SMOOADDR,AX
        MOV     DI,OFFSET SMOOARRAY
        MOV     CX,Limit_FIR
        REP     MOVSW
        MOV     DS,BX
                                        ;Fill SMOOPREARRAY with the first word
                                                        ;of SMOOARRAY.
        MOV     AX,SMOOARRAY
        MOV     DI,OFFSET SMOOPREARRAY
        MOV     CX,NoOfCoefs-1
        REP     STOSW
                                        ;Fill SMOOMETAARRAY with the last word
                                                        ;of SMOOARRAY.
        MOV     AX,(SMOOARRAY+(Limit_FIR*2)-2)
        MOV     DI,OFFSET SMOOMETAARRAY
        MOV     CX,NoOfCoefs-1
        REP     STOSW
SMOOTH1:
        MOV     SI,OFFSET SMOOPREARRAY
        MOV     DI,SMOOADDR
        MOV     ES,SMOOSEGM
        MOV     CX,Limit_FIR
                                        ;This loop produces one filter point
SMOOTH2:                                                ;(addressed by SI).

        PUSH    CX
        XOR     AX,AX                   ;Initialise SMOOTEMPLONG* variables.
        MOV     SMOOTMPADD1,AX
        MOV     SMOOTMPADD2,AX
        MOV     SMOOTMPSUB1,AX
        MOV     SMOOTMPSUB2,AX
        MOV     CX,2*NoOfCoefs-1                ;Repeat the loop 35 times
                                                ;(once per filtered point).
        MOV     BX,OFFSET COEFARRAY
        PUSH    SI
SMOOTH3:
        MOV     AX,DS:[SI]
        MOV     DX,[BX]
        CMP     DX,7FFFH
        JNA     SMOOTH4
        NEG     DX
        MUL     DX
        ADD     SMOOTMPSUB1,AX                  ;32-bit subtraction.
        ADC     SMOOTMPSUB2,DX
```

```
        JMP SHORT SMOOTH5
SMOOTH4:
        MUL     DX
        ADD     SMOOTMPADD1,AX                    ;32-bit addition.
        ADC     SMOOTMPADD2,DX
SMOOTH5:
        INC     BX
        INC     BX
        INC     SI
        INC     SI
        LOOP    SMOOTH3

        POP     SI
        MOV     AX,SMOOTMPADD1
        MOV     BX,SMOOTMPADD2
        SUB     AX,SMOOTMPSUB1
        SBB     BX,SMOOTMPSUB2
        MOV     ES:[DI],BX
        POP     CX
        INC     SI
        INC     SI
        INC     DI
        INC     DI
        LOOP    SMOOTH2

SMOOTHEXIT:
        pop     ds
        RET

SMOOTH endp


PUBLIC    INITCOEFS
INITCOEFS proc far

;This routine initialises the 18 coefficients
;for a 35 point low-pass FIR filter with
;frequency response 0-0.0492 of the Nyquist
;interval.

        push    ds
        mov     ax,data2
        mov     ds,ax

        assume  ds:data2

        PUSH    BX
        MOV     BX,OFFSET COEFARRAY
        MOV WORD PTR [BX],0
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-11
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-47
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-103
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-161
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-186
```

```
INC     BX
INC     BX
MOV WORD PTR [BX],-135
INC     BX
INC     BX
MOV WORD PTR [BX],38
INC     BX
INC     BX
MOV     [BX],370
INC     BX
INC     BX
MOV     [BX],883
INC     BX
INC     BX
MOV     [BX],1574
INC     BX
INC     BX
MOV     [BX],2413
INC     BX
INC     BX
MOV     [BX],3342
INC     BX
INC     BX
MOV     [BX],4284
INC     BX
INC     BX
MOV     [BX],5147
INC     BX
INC     BX
MOV     [BX],5842
INC     BX
INC     BX
MOV     [BX],6292
```

```
INC     BX
INC     BX
MOV     [BX],6449

INC     BX
INC     BX
MOV     [BX],6292
INC     BX
INC     BX
MOV     [BX],5842
INC     BX
INC     BX
MOV     [BX],5147
INC     BX
INC     BX
MOV     [BX],4284
INC     BX
INC     BX
MOV     [BX],3342
INC     BX
INC     BX
MOV     [BX],2413
INC     BX
INC     BX
MOV     [BX],1574
INC     BX
INC     BX
MOV     [BX],883
INC     BX
INC     BX
MOV     [BX],370
INC     BX
```

```
        INC     BX
        MOV WORD PTR [BX],38
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-135
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-186
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-161
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-103
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-47
        INC     BX
        INC     BX
        MOV WORD PTR [BX],-11
        INC     BX
        INC     BX
        MOV WORD PTR [BX],0
        POP     BX
        pop     ds
        RET

INITCOEFS endp

code_seg ends
```

APPENDIX D: PUBLICATIONS

This appendix consists of seven sections, each relating to published material arising from work carried out during the study towards the PhD degree conducted by the author of this thesis.

The text, data and figures have been transcribed *verbatim* from the original papers, including spelling. However, the bibliographies are combined at the end of this thesis to prevent repetitions.

D.1 Title: Middle latency auditory evoked potentials during repeated transitions from consciousness to unconsciousness.

Authors: Davies, FW, Mantzaridis, H, Kenny, GN, Fisher, AC.

Source: *Anaesthesia* (1996) **51**, 107-113.

D.2 Title: Transition between consciousness and unconsciousness during anesthesia.

Authors: Kenny, GN, Davies, FW, Mantzaridis, H, Fisher, AC.

Source: *Anesthesiology* (1993) **79**, A330.

D.3 Title: Closed-loop control of anesthesia.

Authors: Kenny, GN, McFadzean, WA, Mantzaridis, H, Fisher, AC.

Source: *Anesthesiology* (1992) **77**, A328.

D.4 Title: Propofol requirements during closed-loop anesthesia.

Authors: Kenny, GN, McFadzean, WA, Mantzaridis, H, Fisher, AC.

Source: *Anesthesiology* (1993) **79**, A329.

D.5 Title: Assessment of anaesthetic depth.

Authors: McFadzean, WA, Mantzaridis, H, Kenny, GN.

Source: *Advanced Hospital Technology* (1992) **2**, 22-25.

D.6 Title: Validation of anesthetic depth by closed-loop control.

Authors: Kenny, GN, Mantzaridis, H, Fisher, AC.

Source: In: Sebel, P, Bonke, B and Winograd, E (Eds.) *Memory and Awareness in Anesthesia* (1993) pp. 225-264. Englewood Cliffs: Prentice Hall.

D.1 Middle Latency Auditory Evoked Potentials During Repeated Transitions From Consciousness To Unconsciousness

Summary

We have investigated the relationship between changes in the Middle Latency Auditory Evoked Potentials during alternating periods of consciousness and unconsciousness produced by propofol infusion combined with spinal anaesthesia for total knee replacement. Eleven patients completed the study, of whom two had recollection of events after the onset of the anaesthetic. There were no significant differences in heart rate or systolic arterial pressure between any conscious and unconscious period. With the first change from consciousness to unconsciousness, latencies of Na, Pa and Nb increased from mean (SD) starting values of 20.0 (1.4), 31.7 (1.0) and 42.8 (1.6) ms to 22.5 (2.0), 39.3 (2.1) and 57.8 (4.4) ms, respectively. During successive transitions from unconsciousness to consciousness, awake latencies were slightly higher than those of baseline awake, whereas anaesthetised latencies were similar to the ones obtained during the first period of unconsciousness. The consistent changes demonstrated, suggest that the AEP could represent a reliable indicator of potential awareness during anaesthesia.

Introduction

The objective measurement of anaesthetic depth and its implications for the production of a reliable monitor of awareness, remains a desirable but elusive goal in anaesthesia (Brighouse and Norman, 1992). Previous attempts to obtain an index of anaesthetic depth have included the use of the spontaneous electroencephalogram (Gibbs *et al,* 1937) and its processed derivatives, the cerebral function monitor (Dubois *et al,* 1978a), the cerebral

function analysing monitor (Sebel *et al,* 1983), fast Fourier transformation (FFT) and aperiodic waveform analysis (Levy *et al,* 1980). More recently, the change in lower oesophageal contractility associated with anaesthesia has been investigated and has been shown to be related to the end-tidal concentration of volatile anaesthetics (Evans *et al,* 1984). It was, however, found to be insufficiently discriminating at the interface between consciousness and unconsciousness to be used as a monitor of awareness (Isaac and Rosen, 1990), and proved to be unrelated to blood concentration of intravenous anaesthetics (Thornton *et al,* 1989b).

The most promising area of investigation has been the Auditory Evoked Potential (AEP), which appears to show specific changes in its early cortical components related to depth of anaesthesia. These changes are independent of the anaesthetic agent used (Thornton *et al,* 1983; Thornton *et al,* 1984; Thornton *et al,* 1985; Thornton *et al,* 1986; Heneghan *et al,* 1987; Thornton *et al,* 1989b) and are partially reversed by surgical stimulation (Thornton *et al,* 1988), properties thought to be necessary to qualify as an indicator of anaesthetic depth (Sebel *et al,* 1985). In a recent study (Newton *et al,* 1992), the early cortical AEP was shown to be "able to demonstrate potential awareness" under isoflurane anaesthesia. During some of those studies, a partial recovery of the AEP was observed after temporary discontinuation of the anaesthetic before the start of surgery (Thornton *et al,* 1983; Thornton *et al,* 1984; Thornton *et al,* 1985; Thornton *et al,* 1986; Heneghan *et al,* 1987; Thornton *et al,* 1989b). However, the patients were not allowed to recover completely and no quantitative data were published.

Using a purpose-built, computer-based system, capable of processing the raw EEG and obtaining the AEP in real time, we investigated the changes in AEP parameters associated with alternating periods of consciousness and unconsciousness. The specific questions we hoped to answer were:

- What changes occur to the AEP during successive conscious and unconscious periods?

- Can the AEP patterns of patients *just* awake and *just* anaesthetised be distinguished?
- How reproducible are those changes in the same patient? How great is the inter-patient variability?

Patients and methods

The study was approved by the Hospital Ethics Committee. Twelve patients were studied and written informed consent obtained. All patients were scheduled to have total knee replacement performed under spinal anaesthesia. All patients received a premedication of temazepam 10-20 mg approximately 1 hour before surgery. Spinal anaesthesia was established with the patient in the sitting position and 2.5 ml of 0.5% hyperbaric bupivacaine administered via a 26G needle.

AEP acquisition

The EEG was obtained from three disposable ECG silver-silver chloride electrodes (Medicotest M-00-S) placed on the right forehead (+), right mastoid (-) and middle forehead (reference). The position of one of the active electrodes on the forehead was dictated by the nature of the electrodes applied and has been used in other studies (Sneyd *et al,* 1992; Munglani *et al,* 1993b). It produces MLAEP signals with latencies similar to the ones produced by electrodes placed on the vertex (Ozdamar and Kraus, 1983).

The amplifier was custom-built and had a 5 kV medical grade isolation (BS 5724, IEC 601, ISO 8185). It had a Common Mode Rejection Ratio (CMRR) of 170 dB with balanced source impedance (160 dB with a 5 kOhm source imbalance), input voltage noise of 0.3 μV and current input noise of 4 pA (0.5 Hz-1 kHz rms). Input bias current was only 200 pA, and on the failure of any component it was limited to 10 μA. A third-order Butterworth analogue band-pass filter with a bandwidth of 1-220 Hz was used before the signal was presented to a high accuracy, low distortion (typical integral nonlinearity ± 1/2 LSB, maximum full scale error ± 5 LSB) 12-bit analogue-to-digital converter

(ADC). The ADC was incorporated in an IBM PC/XT/AT expansion card (model PC 27 by Amplicon Liveline Ltd).

The clicks were 70 dB above the normal hearing threshold and had a duration of 1 ms. They were presented at a rate of 6.9 Hz to the right ear only using a standard moulded earphone receiver.

AEP analysis

The amplified EEG was sampled by the ADC at a frequency of 1.78 kHz and was processed in real-time by an IBM-compatible personal computer. AEPs were produced by averaging 256 sweeps of 144 ms duration. The time required to have a full update of the signal was 36.9 seconds, but a moving time averaging technique allowed a faster response time to any change in the signal. Averaged curves were obtained at 3 second intervals. The AEPs were filtered by a digital low-pass 35-point Finite Impulse Response (FIR) filter with a cut-off frequency of 87 Hz, thus further improving the signal-to-noise ratio and eliminating EMG and other artefacts which might still have been present in the signals. The first 3 ms of the AEP were not filtered in order to preserve the click artefact and indicate correct operation of the system. The AEP was stored on the computer's hard disk, allowing re-creation of the whole session for further study. Peak latencies were measured manually.

Following the onset of spinal anaesthesia, the electrodes and earphone were applied and AEP acquisition was started. Once the baseline measurements had been obtained, a target-controlled propofol infusion system (White and Kenny, 1990; Kenny and White, 1992) was commenced. Two investigators were present in addition to the anaesthetist responsible for conducting the spinal anaesthetic. The first investigator operated the AEP monitoring system, while the second investigator recorded at 30 second intervals, the patient's response to a verbal command to squeeze the investigator's hand, and the presence or absence of an eyelash reflex. The presence of a response to verbal command and a positive eyelash reflex were taken as the

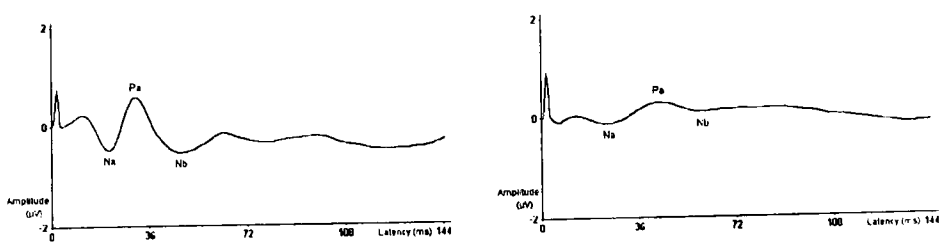
indicator of awareness and their loss was taken as the indicator of unconsciousness. The second investigator administered the propofol infusion to provide alternating periods of consciousness and unconsciousness, as defined above. The loss of both the eyelash reflex and the response to command were taken as the transition from consciousness to unconsciousness, and the return of both responses as the transition from unconsciousness to consciousness. A point 2 minutes following this transition was taken to represent a steady state (Isaac and Rosen, 1990) and AEP data were obtained for statistical analysis.

On the day after surgery, all patients were questioned about their recall of events during the procedure including any dreams or noises. They were also asked if the anaesthetic technique had been acceptable and if they would be happy to have the same anaesthetic again. Data were analysed using the *MINITAB for Windows* (version 9.2) programme. Tests used were the Friedman test and the Mann-Whitney test (two-sample Wilcoxon rank sum test).

Results

Twelve patients (5 male and 7 female) participated in the study. Their mean age was 67 years (range 51-78) and their mean weight 74 kg (range 59-100). One patient became confused and uncooperative after starting the propofol infusion. This patient was withdrawn from the study.

Figure D.1 shows typical AEP tracings produced in a single patient during anaesthesia and surgery.



A B

Figure D.1 Typical digitally filtered AEP curves as displayed on the computer screen during surgery. A: Patient conscious, B: Patient unconscious.

Figure D.2 demonstrates the effect of digital filtering and the number of repetitions on the AEP.

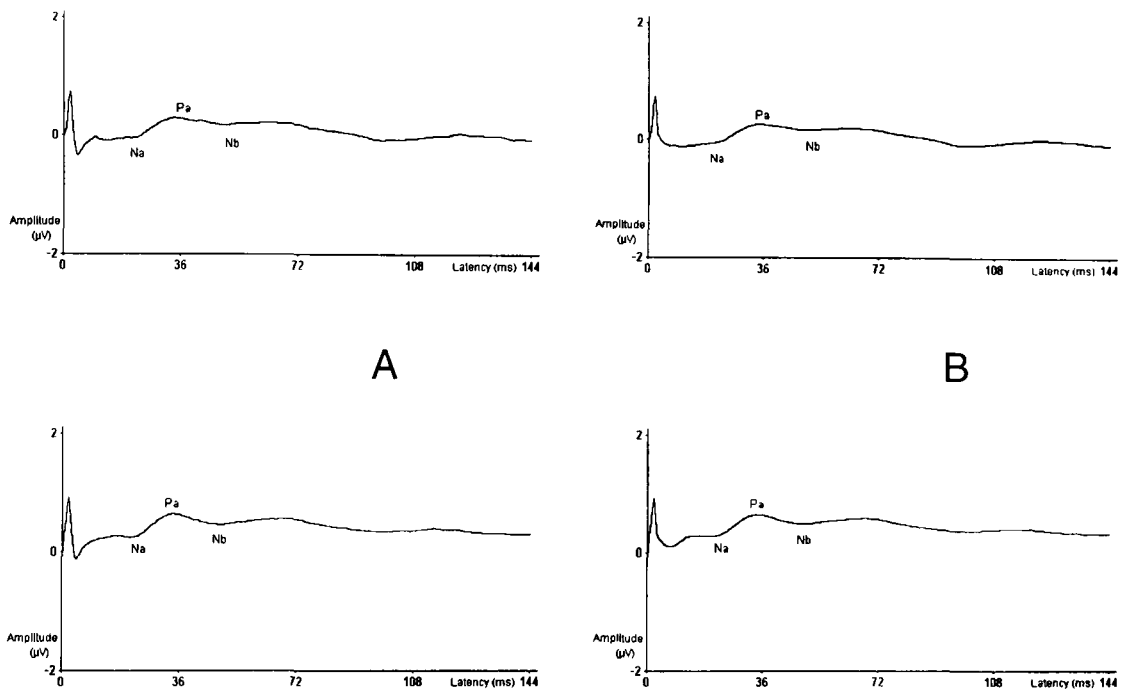


Figure D.2 Effect of number of repetitions and digital filtering on unconscious MLAEP. The curves shown in C and D are the grand average of four successive curves of 256 repetitions each obtained at intervals of 39 seconds. A: 256 repetitions without digital filtering, B: The same curve as in A (256 repetitions) but with digital filtering, C: 1024 repetitions without digital filtering, D: The same curve as in C (1024 repetitions) but with digital filtering.

The median number of periods of unconsciousness achieved during each procedure was 3 (range 1-6). The mean duration of surgery was 71 minutes (range 40-105). In a total of 38 transitions from the conscious to the unconscious state, the eyelash reflex was lost simultaneously with the response to command in 22%, response to command was lost first in 39%, and the eyelash reflex was lost first in 39%.

Latency measurements during the study are shown in Figure D.3.

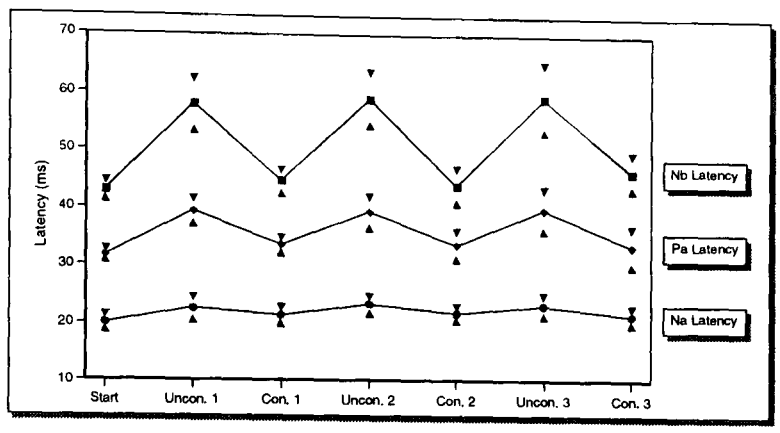


Figure D.3 Changes in AEP latencies during successive conscious and unconscious states (mean and standard deviation).

Data are represented as a mean with standard deviation. During the first transition from consciousness to unconsciousness, all peak latencies increased significantly. Thereafter, Pa and Nb showed significant changes during each transition, whereas some of the transitions between awake and unconscious were not significantly different for Na (Table D.1).

	Start (n=11)	UNCON 1 (n=11)	CON 1 (n=11)	UNCON 2 (n=10)	CON 2 (n=10)	UNCON 3 (n=8)	CON 3 (n=8)
Na (ms)	Mean 20.0	22.5	21.3	23.2	21.7	23.1	21.3
	SD 1.4	2.0	1.4	1.5	1.2	1.7	1.4
	p=0.004	p=0.136	p=0.016	p=0.035	p=0.095	p=0.065	
Pa (ms)	Mean 31.7	39.3	33.5	39.2	33.6	39.7	33.3
	SD 1.0	2.1	1.2	2.7	2.4	3.6	3.3
	p=0.0001	p=0.0001	p=0.001	p=0.001	p=0.004	p=0.009	
Nb (ms)	Mean 42.8	57.8	44.6	58.9	43.9	59.1	46.3
	SD 1.6	4.4	2.1	4.6	3.0	5.9	3.1
	p=0.0001	p=0.0001	p=0.0001	p=0.0002	p=0.0004	p=0.0009	

Table D.1 Changes in AEP latencies between successive transitions from consciousness (CON) to unconsciousness (UNCON) [mean, standard deviation (SD) and statistical significance].

During the awake stages, following recovery of consciousness, Na, Pa and Nb latencies were all increased from the baseline start values, but were not significantly different from each other (Table D.2). Values measured at loss of consciousness did not differ significantly from each other.

There were no significant differences in heart rate or systolic arterial pressure between any conscious and unconscious period.

We did not experience any problem in communicating with the awake patients while eliciting the AEP. This is in agreement with the findings of Thornton and colleagues (Thornton *et al,* 1992).

Eleven patients completed the study and were questioned on the day after surgery. All patients recalled clicks being played before administering propofol. Nine patients had no recollection of events after the onset of the propofol infusion and the remaining two patients remembered the instruction to squeeze the investigator's hand. All patients were satisfied and would be happy to have the same anaesthetic again in the future.

	Start (n=11)	CON 1 (n=11)	CON 2 (n=10)	CON 3 (n=8)
Na (ms)	Mean 20.0	21.3	21.7	21.3
	SD 1.4	1.4	1.2	1.4
	p=0.032	p=0.543	p=0.619	
Pa (ms)	Mean 31.7	33.5	33.6	33.3
	SD 1.0	1.2	2.4	3.3
	p=0.003	p=0.943	p=0.894	
Nb (ms)	Mean 42.8	44.6	43.9	46.3
	SD 1.6	2.1	3.0	3.1
	p=0.020	p=0.644	p=0.081	

Table D.2 Differences between starting latencies and latencies after patients regained consciousness (CON) [mean, standard deviation (SD) and statistical significance].

Discussion

While a device such as a non-invasive blood pressure monitor can be related to direct arterial pressure measurements, there is a fundamental problem encountered when attempting to assess the validity of a monitor of awareness, since there is no universally accepted standard with which to compare the device. We have attempted to solve this problem by using the clinical end points of consciousness and unconsciousness and relating them to simultaneously produced AEPs. The assumption is made that patients defined as conscious were aware and that those defined as unconscious were not. This assumption has been made in previous studies in which a response to command was considered as an indication of awareness (Thornton *et al,* 1989a; Newton *et al,* 1992).

It has been shown previously that awareness during surgery is possible without recall, if anaesthesia is deepened subsequently (Rupreht, 1989). This is supported by our observation that only 18% of patients had any recall of events after the propofol infusion was started, despite repeated prolonged periods of intraoperative wakefulness. The frequency of recall may have been greater in our study had consciousness been associated with fear or the pain of surgery, although patients who experienced pain during anaesthesia produced by midazolam and alfentanil in a study by Russell did not have subsequent recall (Russell, 1993).

Consciousness was lost and regained a number of times in each patient. Figure D.3 demonstrates a clear difference in AEP measurements between patients considered to be conscious and aware and those considered unconscious. We found, as did Newton and colleagues (Newton *et al,* 1992), that a significant number of transitions (22%) between consciousness and unconsciousness were rapid, without a graded change. However, retention of the eyelash reflex alone occurred in 39% of our patients and the response to command alone in 39%. It was therefore necessary to define a point for analysis where the state of awareness was similar within each patient and

between patients. The point 2 minutes following transition represented a point at which both eyelash reflex and response to command had been unequivocally lost or regained and this was chosen as the measuring point for the AEP values (Isaac and Rosen, 1990). In that way, we ensured that there would be no composite AEP curves due to the subject's level of consciousness changing back and forth from one state to the other (Newton *et al,* 1992).

No amplitude measurements were made, since it has been suggested (Thornton *et al,* 1988; Thornton *et al,* 1989a) that only latencies are related to anaesthetic depth. Amplitudes have a greater inter-individual variability and the only way that they could be used would be by comparing pre- and intra-operative values individually (Madler *et al,* 1991). The peaks selected (Na, Pa and Nb) were the ones that are generally considered as the most stable (Ozdamar and Kraus, 1983). Later MLAEP components (Pb/P_1) have been reported in various studies, but they are not as stable as Na, Pa and Nb and this could make their detection difficult, especially during the anaesthetised state.

All conscious latencies after the first transition from the conscious to the unconscious state, were similar to each other and no significant differences were found (Table D.2). Similarly, no unconscious latencies differed significantly. However, start latencies (i.e. before the administration of any anaesthetic) were lower than any other awake period. Although this did not reach statistical significance for all awake periods, it indicates that there was still some residual effect of the anaesthetic, despite the fact that the patients were responding and the eye-lash reflex was present. This is supported by the fact that only two of eleven patients had recollection of events after the onset of the propofol infusion.

Values for the latencies of Na, Pa and Nb in the conscious state are comparable to the ones found in the literature (Picton *et al,* 1974; Ozdamar and Kraus, 1983; Thornton *et al,* 1983; Thornton *et al,* 1984; Thornton *et al,*

1985; Chassard *et al,* 1989; Madler *et al,* 1991; Newton *et al,* 1992; Schwender *et al,* 1993a; Schwender *et al,* 1993b; Schwender *et al,* 1994a; Schwender *et al,* 1994b). In the unconscious state, latencies are increased and amplitudes decreased resulting in a flattening of the AEP curves. Again, latency values are similar to the results published by other groups (Thornton *et al,* 1985; Madler *et al,* 1991; Newton *et al,* 1992; Thornton *et al,* 1992; Schwender *et al,* 1994a; Schwender *et al,* 1994b).

The mean start Na latency was 20.0 ms. It increased during all anaesthetised periods and it returned to values slightly higher than 20.0 ms during the conscious periods. However, the fact that some of those changes failed to reach statistical significance, may indicate that Na is not sensitive enough to differentiate between *just* unconscious and *just* conscious states. Both Pa and Nb were better in this respect, since all successive transitions were statistically significant. Once again, start latencies were slightly lower than consecutive awake ones.

The mean Nb latency before the administration of any anaesthetic was 42.8 ms and it remained close to that value during successive transitions from unconscious to awake. This is in line with the findings of Thornton and colleagues (Thornton *et al,* 1989a). In that study, Nb latencies were compared with responses to Tunstall's isolated forearm test. A threshold Nb latency of 44.5 ms was chosen to discriminate between positive responses, indicating awareness, and no response, indicating lack of awareness. Although these were slightly different from the results obtained during a later study (Newton *et al,* 1992), they suggest that there are characteristic AEP patterns which indicate potential awareness.

The effects of premedication on the AEP and its relevance have yet to be determined. Previous authors have demonstrated that changes in the AEP with anaesthesia are related to anaesthetic depth and unrelated to anaesthetic agent (Thornton *et al,* 1984; Thornton *et al,* 1988; Thornton *et al,* 1989b). It is not yet possible from this study alone to predict AEP peak

latencies above which loss of awareness is *guaranteed*. This may however be possible in the future given the consistent changes noted in the present study. The view that the AEP can be used as a clinical monitor of potential awareness during anaesthesia (Thornton *et al,* 1989a; Newton *et al,* 1992) is supported by this study.

In conclusion, we have demonstrated that computer processing of the AEP may offer a reliable indicator of change from light anaesthesia to awareness and *vice versa*. Analysis of the AEP latencies demonstrated a consistent change with transition from awareness to unconsciousness and from unconsciousness to awareness. The AEP would therefore appear to represent a reliable indicator of potential awareness during anaesthesia.

D.2 Transition Between Consciousness And Unconsciousness During Anesthesia

A single numerical parameter derived from the Auditory Evoked Response[3] (AER) has been reported as sufficiently reliable to control the administration of closed-loop propofol anesthesia (Kenny *et al,* 1992). We examined changes in this signal during the transition between consciousness and unconsciousness in 11 patients scheduled to undergo hip replacement under spinal anesthesia following temazepam premedication. Informed consent and approval of the Ethics Committee were obtained.

Auditory evoked responses were obtained by recording the EEG from electrodes attached to the mastoid and forehead for 144 ms after applying clicks at a rate of 6.9 Hz to the right ear. The EEG signal was amplified and connected to a microcomputer via a 12-bit analog to digital converter. A Level of Arousal Score[4] (LAS) was derived from analysis of a 3-second moving time average of 256 EEG sweeps.

Baseline LAS was measured before inducing anesthesia with a target-controlled infusion which used a pharmacokinetic model (Kenny and White, 1992) to deliver a target blood propofol concentration. This infusion system was used to increase and decrease blood propofol concentrations and so alternate between periods of unconsciousness and consciousness. Patient response to a verbal command to squeeze the investigator's hand, and the presence or absence of an eyelash reflex were determined every 30 seconds. The presence of a response to command and a positive eyelash reflex were taken as indicating awareness and their loss was taken to indicate loss of consciousness.

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[3] The Auditory Evoked Response (AER) in this and subsequent papers is equivalent to the Auditory Evoked Potential (AEP) described in this thesis.

[4] The Level of Arousal Score (LAS) in this and subsequent papers is equivalent to the Auditory Evoked Potential Index (AEPidx) described in this thesis.

The median number of periods of unconsciousness achieved during each procedure was 3 (range 1-6) with a total of 38 transitions from the conscious to the unconscious state. The initial LAS was normalized to 100% and subsequent values are shown in the table as mean and 95% confidence intervals. In all patients, the LAS decreased with the transition from consciousness to unconsciousness and increased with the transition from unconsciousness to consciousness. In contrast, there were no significant differences in heart rate or systolic arterial pressure between consciousness and unconsciousness. Patients were questioned on the day after surgery. All recalled clicks being played before induction of anesthesia but 9 patients had no recollection of events after the onset of the propofol infusion and all patients were satisfied with the anesthetic technique.

The consistent reduction in the LAS found with the transition from awareness to unconsciousness, and the consistent increase from unconsciousness to consciousness suggest that analysis of the AER may provide a method for detecting awareness during anesthesia.

	Con	**Uncon**	**Con**	**Uncon**	**Con**	**Uncon**
LAS (mean)	100	56	92	56	94	57
95% CI		(50-62)	(83-100)	(49-64)	(83-105)	(49-65)

D.3 Closed-Loop Control Of Anesthesia

Auditory Evoked Response (AER) appears to fulfill most of the requirements for a depth of anesthesia index such as being valid for different types of anesthetic agents (Thornton *et al,* 1984) and for the response to surgery (Thornton *et al,* 1988). We report that the novel technique of closed-loop anesthesia during surgery in non-paralyzed patients has been implemented using a single numerical parameter from the auditory evoked response to control an intravenous anesthetic.

Auditory evoked responses were obtained from patients by recording the EEG from electrodes attached to the mastoid and forehead for 144 ms after applying clicks at a rate of 6.9 Hz to both ears. The EEG signal was amplified and connected to a microcomputer via a 12-bit analog to digital converter. A Level of Arousal Score (LAS) was derived from analysis of a 3-second moving time average of 256 EEG sweeps and used as the input to a Proportional-Integral (PI) controller. The controller altered the predicted blood concentration of propofol to minimize the difference between the measured and target LAS. The new value for the predicted propofol concentration was transmitted to the infusion system which used a 3-compartmental pharmacokinetic model to achieve and maintain the predicted value (Marsh *et al,* 1991). Anesthesia was induced automatically in 27 patients scheduled to undergo body surface surgery by using a predetermined series of increasing predicted blood propofol concentrations until the required LAS was obtained. Thereafter, anesthesia was maintained automatically by the PI regime. Informed consent was obtained and the study was approved by the Hospital Ethics Committee.

During maintenance of anesthesia, patients breathed a mixture of 66% nitrous oxide in oxygen and received an infusion of alfentanil. Arterial oxygen saturation, respiratory rate and end-tidal carbon dioxide concentration were monitored continuously and blood pressure, heart rate, degree of sweating

and tear formation were used to calculate anesthetic scores (Evans *et al*, 1987) every five minutes. LAS was normalized to 100% for each patient before induction of anesthesia. The median value required during surgery was 40 (range 35-44). Anesthetic PRST scores during surgery did not exceed 1 in any patient. Three patients moved but the movements were slight and did not interfere with surgery. Twenty two patients maintained satisfactory spontaneous respiration throughout the procedures and 5 required assisted ventilation for less than 5 minutes after induction of anesthesia. At the end of anesthesia, propofol, nitrous oxide and alfentanil were discontinued. Median LAS was 101 (range 87-111) at recovery of consciousness. No patient reported awareness during anesthesia and all were prepared to have the same anesthetic in future.

The system described here is the first enabling closed-loop control of anesthesia from induction, during surgery to recovery in non-paralyzed patients. The principal requirement of a closed-loop system is a reliable input signal. The use of LAS as the input for closed-loop control of propofol anesthesia validates it as a reliable index of anesthetic depth with this technique. Clearly, other anesthetic agents and patients must be assessed to determine whether this index of anesthetic depth can be applied more widely.

D.4 Propofol Requirements During Closed-Loop Anesthesia

Closed-loop control systems provide unbiased measurement of drug requirements (Colvin and Kenny, 1989c) and we have reported previously a closed-loop anesthetic (CLAN) system using the Auditory Evoked Response (AER) as an input signal (Kenny *et al,* 1992). We report the use of a CLAN system to assess propofol requirements in patients breathing spontaneously during surgery.

Twelve patients scheduled to undergo body surface surgery were anesthetized with the CLAN system. Informed consent was obtained and the study was approved by the Hospital Ethics Committee. Patients were premedicated with temazepam 20-30 mg and a target blood concentration of alfentanil 15 ng ml^{-1} was achieved before anesthesia was induced. After induction of anesthesia, patients breathed a mixture of nitrous oxide 66% in oxygen. The AER was calculated from 256 EEG sweeps of 144 ms duration using a click frequency of 6.9 Hz and a moving time average was obtained every 3 seconds. The AER was differentiated to obtain a Level of Arousal Score (LAS). Anesthesia was induced with a predetermined series of target blood propofol concentrations until the selected LAS value was achieved. Thereafter, anesthesia was maintained by a proportional-integral controller which compared the measured with the selected LAS, calculated a new target propofol concentration and transmitted this new value via an RS-232 interface to the target-controlled propofol infusion system (Kenny and White, 1992).

Quality of anesthesia provided by CLAN was judged to be satisfactory in that slight movement occurred in one patient during insertion of the final sutures but did not disturb the operation. The highest PRST score recorded was 1 and the median maximum decrease in systolic arterial pressure was 25%. Respiration was assisted after induction in two patients for less than 5

minutes but otherwise all patients breathed spontaneously during surgery and no patient experienced dreams or recalled any event during the procedure. The relationship between predicted and measured blood values was: measured = 0.81 + 1.1 predicted (r=0.89) with a bias of 29.1% and a precision of 34.5%. The median, maximum and minimum predicted and measured blood propofol concentrations required during surgery are shown in the table (medians and ranges).

The maximum blood propofol concentration required to control anesthesia for each patient was divided by the minimum value to calculate the percentage variation during surgery. Median variation in the predicted propofol concentrations was 225% (range 132%-422%) and 273% (range 122%-539%) for the measured values.

The precision of the propofol concentrations is a measure of the degree of scatter of the data about the line of perfect prediction and reflects the variability between patient pharmacokinetics. CLAN provides an objective assessment of the variation in propofol requirements within patients. It has demonstrated that the median intrapatient variation in propofol requirements during surgery was 6-7 times greater than the median interpatient pharmacokinetic variability.

	Median	**Maximum**	**Minimum**
Predicted ($\mu g\ ml^{-1}$)	3.5 (0.9-10.9)	4.0 (2.9-10.9)	2.4 (0.9-6.1)
Measured ($\mu g\ ml^{-1}$)	4.2 (1.0-11.4)	6.2 (4.0-11.4)	3.1 (1.0-4.3)

D.5 Assessment of anaesthetic depth

General anaesthesia involves a reversible depression of the central nervous system such that consciousness is lost with no awareness or recall of events. Response to stimulation should be minimal and should not interfere with the surgical procedure. The anaesthetic state has been defined as that "which ensures the suppression of the somatic and visceral sensory components and thus the perception of pain" in response to the noxious stimulation of surgery (Prys-Roberts, 1987). When patients breathe spontaneously during surgery, movement provides an indication of inadequate anaesthesia but with the administration of neuromuscular blocking agents, awareness under anaesthesia may occur (Winterbottom, 1950), although its incidence would appear to be decreasing (Liu *et al,* 1991).

Our "gold standard" for adequate anaesthetic depth is that a patient breathing spontaneously without muscle relaxation and not moving during surgery is sufficiently anaesthetised. However, one case of awareness under these conditions has been reported, although it did involve a difficult intubation and no monitoring of the end-tidal vapour concentration (Saucier *et al,* 1983). Therefore, there is a need for a reliable and accurate means of monitoring anaesthetic depth. The requirements of such an index are:

- There should be a similar signal for different anaesthetic agents at equipotent doses.
- The signal values at induction of anaesthesia should be consistent with those measured at recovery.
- The system should respond appropriately to alterations in the level of stimulation.
- The signal should not be affected by vasoactive drugs or hypotension.

Clinical Signs

In 1934, Guedel described the clinical signs associated with di-ethyl ether anaesthesia. This allowed the recognition of four stages of anaesthesia and the subdivision of the third stage into four planes. The signs related to a progressive increase in muscle paralysis and an abolition of reflex responses and much of this work can be applied to our practice today. After commencement of surgery, the anaesthetist is guided by the patient's residual autonomic and somatic responses. These can be subdivided into the following:

Respiratory and skeletal muscle activity

Frequency and depth of respiration are useful indicators of anaesthetic adequacy and any skeletal muscle response in relation to surgical stimulation by itself indicates insufficient anaesthesia. However, as described previously, these signs are lost in a paralysed patient and other indicators are required.

Cardiovascular stability

Heart rate and blood pressure are the most commonly recorded signs of a patient's well-being during general anaesthesia. An increase in either or both of these measurements is usually taken as an indication of insufficient anaesthesia. Peripheral circulation, monitored by digital plethysmography, can also be used to assess anaesthetic depth. Johnstone (1974) has suggested that the dose of halothane necessary for surgery in a paralysed patient may be defined as that required to block the vasoconstrictor response.

Pupillary signs

The diameter of the pupil is no longer considered to provide an accurate reflection of anaesthetic depth. Although there is a close relationship between pain and pupillary dilatation, the interpretation of pupillary signs may

be extremely difficult. Volatile and intravenous anaesthetics, opioids and other drugs all have different and sometimes conflicting effects on the pupil. Large pupils may indicate light or deep anaesthesia. The presence of a pupillary light reflex is generally taken as an indicator of light anaesthesia, but in the presence of miosis, for example, after opioid administration or mydriasis following atropine, it may prove difficult to detect. Ocular microtremor is the smallest movement made by the human eye. In 1976, Coakley demonstrated that the resting frequency decreased with the induction of anaesthesia. However, the sensitivity of this response to muscle relaxants has reduced its value as a monitor of anaesthetic depth.

Lacrimation

Tear formation is another sign of insufficient anaesthesia and can be assessed quantitatively. However, any interference with the eye can also produce increased lacrimation.

Sweating

Clinically, sweat production is taken as another indicator of light anaesthesia. Maryniak (1987) evaluated the production of sweat and its correlation with changes in heart rate in patients undergoing cystoscopy. He found a close relationship between the two and suggested that it might be used as an indicator of the degree of sympathetic activity during surgery.

It is apparent that no one clinical sign can be used to assess anaesthetic depth reliably in all cases. However, if these measurements are used in combination, then an overall assessment of the patient's anaesthetic state can be obtained. Evans and Davies (1984) have introduced a scoring system into clinical practice which allows a global score to be obtained. The PRST score is based on four variables: systolic blood pressure, pulse rate, sweating and tear formation. A score is allocated to each variable and a total calculated (minimum 0, maximum 8).

A score of 0-2 would be considered evidence of sufficient or excessive anaesthesia, 2-4 acceptable and that of 5-8 inadequate. However the clinical signs of lightening anaesthesia are not specific and can also be produced by other conditions, including hypoxia and hypercarbia.

Movement of a non-paralysed hand

In 1979, Tunstall used an isolated forearm technique to communicate with patients during the initial stages of Caesarian section. A pneumatic cuff was inflated above systolic pressure before administration of the neuromuscular blocking agent. This allowed the anaesthetist to assess the patient's depth of anaesthesia and ask direct questions concerning the sensation of pain or fear. The patient answered by squeezing the anaesthetist's hand. In this way, Tunstall was able to show a significant reduction in wakefulness in patients who received a higher percentage of nitrous oxide at the beginning of the anaesthetic. However, other researchers were unable to correlate clinical signs of light anaesthesia with the isolated arm movement technique (Breckenridge and Aitkenhead, 1981).

Measurement of lower oesophageal contractility

In humans, the upper part of the oesophagus is composed of striated muscle and the lower half of smooth or non-striated muscle. In between these zones is a transitional area. The lower oesophagus, therefore, is not affected by muscle relaxants. Oesophageal activity is described as peristaltic (primary and secondary) or non-peristaltic (tertiary). Tertiary activity is thought to be a reflex mediated through the brainstem. This is therefore stress related and its contractility has been suggested as a guide to depth of anaesthesia. Evans (1984) used an oesophageal probe with three separate pressure sensing balloons to show two forms of oesophageal activity during light anaesthesia: non-propulsive tertiary and provoked secondary peristalsis. Deepening anaesthesia resulted in progressive suppression of lower oesophageal contractility.

However, a later study (Sessler *et al,* 1989) was able to predict movement in response to skin incision in patients anaesthetised with halothane but not in those anaesthetised with nitrous oxide and alfentanil. In addition, not all patients demonstrate lower oesophageal contractility despite inadequate anaesthesia (Cox and White, 1986) and so this appears to be a limited indicator of anaesthetic depth.

Electromyography

In 1961, Fink described electromyography as an adjunct to the close observation and monitoring of anaesthetised patients. The introduction of equipment able to monitor Spontaneous Frontalis Muscle Activity (SEMG), which is resistant to neuromuscular blockade, allowed this technique to be investigated (Kay, 1984). Depression of this muscle activity is associated with a deepening of anaesthesia. However, the variability in the mean level of activity during surgery, makes it almost impossible to differentiate between the awake and anaesthetised state (Edmonds, Jr. and Paloheimo, 1985).

EEG analysis

The EEG monitors neuronal electrical activity by recording from paired electrodes placed symmetrically in standard positions on the scalp. The potentials recorded bear a general relation to the level of cerebral blood flow and oxygen metabolism. Each record consists of signals of varying frequencies (0-50 Hz) and amplitudes (10-100 microvolts). These are nominally divided into five bands: Delta, Theta, Alpha, Beta and Gamma. With deepening anaesthesia, there is a general slowing of the dominant frequency of the EEG and ultimately total electrical silence, or an isoelectric EEG, occurs. Intermittent silent periods broken up by episodic electrical activity is termed burst suppression. Both these patterns are seen with the administration of central nervous depressant drugs such as barbiturates.

Gibbs and his co-workers (Gibbs *et al,* 1937) observed graded EEG changes in three volunteers under ether anaesthesia. They suggested that the EEG

might be useful in assessing anaesthetic depth and by the late 1950's, the effects of several anaesthetic agents on the EEG had been documented. A classification of EEG changes associated with an increasing dose of anaesthetic was constructed , but the scale of changes in the EEG was not suitable to predict accurately the depth of anaesthesia and interpretation of the data was extremely difficult.

Processed EEG

The next development was the introduction of automated EEG processing devices such as the Cerebral Function Monitor, Cerebral Function Analysing Monitor and the Anaesthesia and Brain Monitor. These transform the raw EEG into more easily understood formats by deriving frequency and amplitude data from the raw EEG signal. During signal quantification some of the information contained in the original EEG is lost whilst other aspects may be enhanced. Processing an EEG signal consists of four basic steps: data acquisition, signal amplification, signal quantification and display of the processed signal.

The Cerebral Function Monitor (CFM) amplified, filtered, compressed and rectified the original signal to produce a trace on a slow speed semi-logarithmic chart. The trace was dependent on the frequency and amplitude of the original signal and produced a pattern which had two main characteristics: a lower border giving an indication of overall cerebral activity and a width reflecting the variability of this activity.

The Cerebral Function Analysing Monitor (CFAM) is a derivative of the CFM which had proved to be a robust and reliable machine. The CFAM differs from the CFM in that EEG amplitude and frequency content are analysed and displayed separately. The amplitude distribution is smoothed over 20 seconds and plotted on a logarithmic scale as the mean, 10th and 90th centiles of the derived value. Low amplitude traces and periods of burst suppression are recorded. Frequency information is expressed as a

percentage of the total in each of the conventional frequency bands, very low frequency waves being plotted separately. Evoked potentials to sensory stimuli may be averaged and displayed on the same chart as may the raw EEG signal itself.

The Anaesthesia and Brain Monitor (ABM) allows both analysis of EEG and EMG. The signals are amplified, filtered, rectified and integrated with respect to time each second. The averages of successive 10 second intervals are displayed graphically on a semi-logarithmic scale.

EEG processing converts an analogue signal into a digital value which may be described by a single number. Some of these numbers have been used in the assessment of anaesthetic depth, of which two have clinical significance: Spectral Edge Frequency (SEF) and Median Frequency (MF).

Spectral edge frequency is the frequency below which lie 95 per cent of the energy in the processed EEG. A progressive reduction in this value has been demonstrated with increasing concentrations of anaesthetic agents. However, this does not appear to be a satisfactory technique to assess anaesthetic depth as during the transition from deep to light levels of anaesthesia, the relationship between spectral edge and drug concentration was very poor (Arden *et al,* 1986). In contrast, the same study showed median frequency to correlate well with drug concentrations in both the uptake and elimination phases. This was supported further in a subsequent report (Schwilden and Stoeckel, 1987) which concluded that a median frequency of 5 Hz signifies an adequate level of anaesthesia.

Auditory evoked responses

Sensory evoked potentials are the electrophysiological response to the stimulation of peripheral or cranial nerves. They are believed to arise during the propagation of impulses centrally and demonstrate the functional integrity of the specific sensory pathway under investigation. Auditory, visual or somatosensory stimuli may be used but Auditory Evoked Responses (AER)

have been investigated most thoroughly with respect to depth of anaesthesia.

These stimulus specific, event related potentials represent only one per cent of the amplitude of EEG activity but can be extracted from the background noise by averaging techniques. Click stimuli are applied to the ears and the EEG signal recorded using three silver-silver chloride disc electrodes. Several hundreds or thousands of EEG sweeps are recorded to obtain a stable AER.

AER may be subdivided into three sections. The first six peaks (I-VI) occur in the first 15 ms and are believed to arise from specific anatomical sites from the acoustic nerve to the medial geniculate body (brainstem component). The second five waves (No, Po, Na, Pa and Pb) recorded at 15-80 ms are the result of neural activity between the thalamus and the cortex (early cortical or middle latency component). The third section recorded at 80-1000 ms represents wide spread activation of the frontal cortex (late cortical component).

The latency and the amplitude of the responses have been shown to have a close relationship to different anaesthetic agents at different concentrations and to surgical stimulus (Thornton *et al,* 1984; Thornton *et al,* 1988). Unlike other techniques, AER would appear to provide a reliable and reproducible guide to anaesthetic depth for a variety of anaesthetic agents.

Closed-loop anaesthesia

Any measurement of anaesthetic depth should provide the necessary information to enable satisfactory anaesthesia to be achieved in patients breathing spontaneously during surgery. Satisfactory anaesthesia includes adequate cardiorespiratory function, minimal or no movement during surgery and avoidance of awareness during the procedure. A valid test of any anaesthetic depth index is that it can be used to control anaesthesia automatically via a Closed-Loop Anaesthesia (CLAN) system. Closed-loop

control of propofol anaesthesia in volunteers has been described using the median frequency of the EEG as the input signal (Schwilden *et al*, 1989). However, the anaesthetic conditions produced would have proved inadequate for surgery.

We have developed a CLAN system based on a standard microcomputer which controls the administration of propofol anaesthesia. The input signal is obtained from an average of 256 EEG sweeps each of 144 ms duration. A completely new AER is obtained every 37 seconds but a moving time average is updated every three seconds which improves the response time of the system. A Level of Arousal Score (LAS) is derived from the AER and transferred to a proportional-integral control algorithm which is designed to minimise the difference between the measured LAS and the value selected by the anaesthetist.

The output from the control algorithm is a target blood concentration of propofol which is transmitted to a separate computer-controlled infusion device. The pharmacokinetic parameters for propofol are incorporated into this infusion system which calculates the elimination and distribution of propofol every few seconds. The required target blood propofol concentration transmitted from the control algorithm is achieved and maintained by this infusion system.

The CLAN system (Figure D.4) has been used successfully for automatic control of anaesthesia from induction through to recovery in non-paralysed adult patients undergoing surgery. The ability of the system to control anaesthesia satisfactorily in patients breathing spontaneously suggests that the AER can be used to derive a reliable index of anaesthetic depth during propofol anaesthesia (Figure D.5). However, further studies are required to assess this index of anaesthetic depth with other agents and types of patients but it offers considerable promise for future monitoring in anaesthesia.

Figure D.4 Overall view of the CLAN system in use during surgery. The trace on the computer screen is the level of arousal score which provides the input signal for the control system.

Conclusion

As yet, there is no universally accepted objective test in routine clinical use by which an anaesthetist can assess a patient's depth of anaesthesia. The anaesthetist's experience, together with the often unreliable non-specific responses of blood pressure and pulse alterations or the formation of sweat and tears, are all that are available. With the advent of neuromuscular blocking drugs, patient movement was also abolished and an invaluable sign lost. This has lead to the problem of patient awareness under anaesthesia. The AER would appear to offer the most likely advance in the search for a depth of anaesthesia index. The use of a derivative of AER as the input signal for closed-loop anaesthesia has validated this measurement as a reliable assessment of anaesthetic depth during propofol anaesthesia.

Further evaluation is necessary to determine its value with other anaesthetic agents.

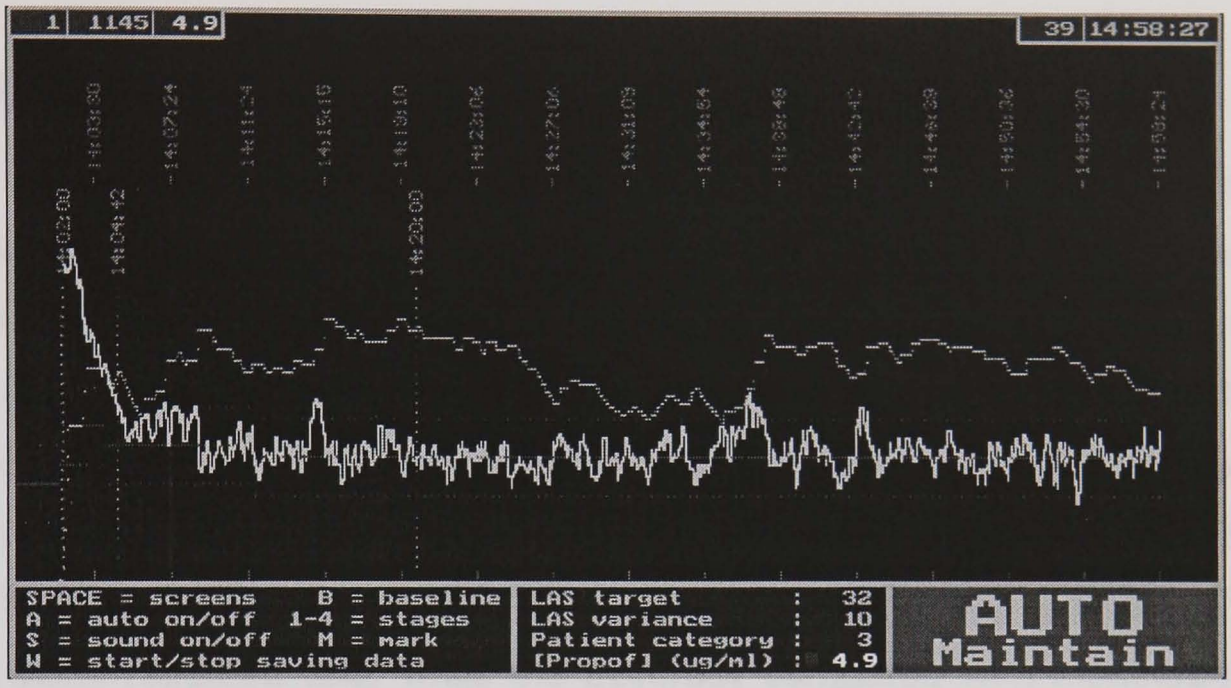

Figure D.5 Screen display of CLAN from induction of anaesthesia. The white trace is the level of arousal score and the grey line represents the target blood propofol concentration. At 14:35 the patient was turned on her side for a second procedure and the resulting stimulation led to a marked increase in the target blood propofol concentration.

D.6 Validation Of Monitoring Anesthetic Depth By Closed-Loop Control

Assessment of a new monitor

Any new technique for monitoring must be compared with an accepted standard technique. For example, the development of non-invasive monitoring of blood pressure led to many comparative studies with the accepted standard of invasive intra-arterial monitoring. The results of these studies confirmed that non-invasive monitors could, in most cases, be considered sufficiently accurate to justify their routine use in anesthesia. Similarly, the relative accuracy of end-tidal CO_2 in reflecting arterial PCO_2 has been validated and, while the accuracy compared with measurements from arterial samples varies with the percentage dead space, it has proved a valuable instrument during routine anesthesia. Pulse oximetry introduced a new dimension into the monitoring of oxygen delivery to the patient and validation of SpO_2 against the accepted standard of intermittent measurement of PO_2 and saturation from arterial blood samples showed it to be sufficiently accurate for clinical use.

Monitoring anesthetic depth

In terms of assessing the depth of anesthesia, there is no accepted standard available. Clearly, any consideration of anesthetic depth must refer to general anesthesia and the aim must be to assess any proposed index of anesthetic depth against some acceptable standard. Any monitor of anesthetic depth must be able to provide sufficient information to enable satisfactory general anesthesia to be produced during surgery. When muscle relaxants are employed, the most valuable sign of inadequate anesthesia, which is movement, is lost. Therefore, any monitor of anesthetic depth should allow the anesthesiologist to deliver good quality anesthesia in a non-

paralysed patient. In addition, the information provided should be adequate to permit satisfactory conditions in a patient breathing spontaneously while undergoing a surgical procedure. Satisfactory anesthesia requires:

- Adequate cardiovascular and respiratory stability.
- No or minimal patient movement.
- No awareness or recall of events during the procedure.

These conditions form the basis of a standard against which any monitor of the depth of anesthesia can be judged. In addition, the monitor should provide similar signals when different types of anesthetic agents are used, should alter its signal appropriately during surgical stimulation, and should result in a similar signal when the patient has recovered from anesthesia to that recorded before induction of anesthesia. There should be no effect caused by cardioactive drugs and, ideally, there should be an obvious, marked transition from awake to asleep and *vice versa*.

Clinical signs

Most anesthetists are familiar with the use of clinical signs to provide an estimate of the adequacy of anesthetic depth (Johnstone, 1974; Maryniak and Bishop, 1987). Where muscle relaxants have not been administered, patient movement is probably the most important clinical sign and can be taken to indicate an inadequate level of anesthesia. It should be remembered that the MAC of a volatile anesthetic is the concentration at which 50% of patients make a gross, purposeful movement in response to surgical stimulation but they do not generally have recall of the event. However, when relaxants have been administered, movement is lost as a sign of inadequate anesthesia and reliance must be placed on indirect signs of the patient's arousal.

An attempt to quantify the degree of sympathetic stimulation in paralysed patients has been made by Evans and colleagues (1984) who developed the PRST scoring system. This allocates scores for changes in blood Pressure,

heart Rate, Sweating and Tear formation. The lower the score achieved, the less evidence there is for sympathetic stimulation and for the possibility of awareness during anesthesia. A score of 0-2 would be considered evidence of sufficient or excessive anesthesia and that of 5-8 indicates inadequate anesthesia. However, the clinical signs of a decreasing level of anesthesia are not specific and can also be produced by other conditions such as hypoxia and hypercarbia. There are several reports where simple clinical signs have failed to guarantee lack of awareness (Winterbottom, 1950; Saucier *et al*, 1983; Liu *et al,* 1991) and attention has been turned to alternative methods of assessing depth of anesthesia.

Tunstall (1979) proposed the isolated forearm technique to detect patient awareness during the use of muscle relaxants. Before administration of the relaxant drug, a tourniquet is placed on the patient's arm and inflated above systolic blood pressure. This prevents the relaxant drug from paralysing the forearm below the tourniquet and during the procedure, the patient is instructed to clench their hand on response to command. Obeying the command indicates awareness with possible recall. This technique is attractive and simple in concept but has not proven to be a universally reliable method for detecting awareness and recall (Breckenridge and Aitkenhead, 1981).

Lower Oesophageal Contractility (LOC) has been suggested to correlate with depth of anesthesia and a commercial system was developed to monitor this activity. Evans (1984) used an oesophageal probe to show two forms of oesophageal activity during light anesthesia: non-propulsive tertiary and provoked secondary peristalsis. Deepening the level of anesthesia resulted in progressive suppression of LOC. However, while this measurement appeared to correlate well with the end-tidal concentration of volatile anesthetic agents (Evans *et al,* 1987), it has not proved as successful with intravenous agents in that a later study (Sessler *et al,* 1989) was able to predict movement in response to skin incision in patients anesthetized with

halothane but not in those anesthetized with nitrous oxide and alfentanil. In addition, not all patients demonstrate LOC despite inadequate anesthesia (Cox and White, 1986) and the signal can be affected by the administration of atropine. LOC therefore appears to be an extremely limited indicator of anesthetic depth.

Compressed Spectral Array (CSA) is a technique which provides a measure of the distribution of power in the EEG. Discreet time periods of EEG such as 2 or 8 seconds are recorded and then subjected to fast Fourier transformation which calculates the total power contained within different frequencies. The power in the different frequencies may be displayed graphically as a series of valleys and peaks but single numbers can be extracted from the CSA and have been proposed as measures of the central effect of anesthetic agents.

The spectral edge is the frequency below which is contained 95% of the total power in the CSA and is an attempt to quantify the upper edge of the power spectrum. A gradual reduction in this value has been demonstrated with increasing concentrations of anesthetic agents. However, this does not appear to be a satisfactory index of anesthesia since during the transition from a deep to a light level of anesthesia, there may be a poor correlation between the spectral edge and the concentration of the drug (Arden *et al,* 1986). The Median Frequency (MF) is a value which is derived from the CSA and represents the mid-point of the power distribution. It is the frequency below and above which lies 50% of the total power in the EEG. The MF has been suggested to be an accurate indicator of depth of anesthesia in that it appears to have a close relationship with drug concentrations in both the uptake and elimination phases (Arden *et al,* 1986). It has also been reported that a satisfactory level of anesthesia occurs at a MF of 5 Hz (Schwilden and Stoeckel, 1987). However, varying patterns of CSA are obtained when patients are anesthetized with different types of anesthetic agents and the

recording of discreet time periods of EEG can lead to difficulties in analysis during burst suppression activity in the EEG.

The Auditory Evoked Response (AER) has been reported to be a more reliable indicator of anesthetic depth. Measurement of the AER involves supplying a series of 'clicks' to earphones at a frequency of between 6-12 Hz and recording the raw EEG waveform for a period of 80-150 ms immediately after each click. The AER is lost in the noise of the background EEG activity of each sweep but by averaging many individual sweeps, this background EEG can be eliminated and the AER revealed. Generally, between several hundred and several thousand sweeps are recorded to obtain a satisfactory signal-to-noise ratio for the AER. The poorer the quality of initial signals, the more sweeps have to be averaged but this means that the time to produce a useful AER is increased. The AER appears to produce alterations in the signal value which are similar for equipotent doses of different volatile (Thornton *et al,* 1984) and intravenous (Thornton *et al,* 1989a) agents. Surgical stimulation has been reported to cause changes in AER which are consistent with increased patient arousal (Thornton *et al,* 1988).

Closed-loop control systems

Any closed-loop control system requires a valid input signal in order to function satisfactorily. For example, the principal problem in producing closed-loop control of blood pressure is to ensure that the arterial signal is valid. Artifacts such as zeroing or flushing the line can cause inappropriate signals to be delivered to the control system and considerable efforts have been made to develop suitable algorithms which can detect artifacts and ensure a valid input signal. Several closed-loop systems are now in use which can control blood pressure more accurately than nursing staff (Reid and Kenny, 1987b).

The ultimate proof for the accuracy of a measurement for depth of anesthesia is that the signal should be capable of controlling automatically

the delivery of an anesthetic agent so as to produce satisfactory anesthesia as defined previously in a patient breathing spontaneously during surgery. Closed-Loop Anesthesia (CLAN) using the systolic arterial blood pressure as the input signal has been described by Robb and colleagues (1991). This system altered the administration of a volatile agent during surgery and advised on the need for supplementary morphine but the system was used only when satisfactory anesthesia had already been established and in patients who were paralyzed during surgery. The median frequency of the CSA has also been used to control the administration of intravenous anesthetics. However, the use of this CLAN system has only been reported in volunteers and the depth of anesthesia achieved would have been inadequate for surgical procedures in that not all of the volunteers lost their corneal reflexes (Schwilden *et al,* 1989).

We have developed a closed-loop control system based on the AER which has been used to control the delivery of propofol in patients breathing spontaneously during surgery (McFadzean *et al,* 1992). The system uses a 386-based microcomputer to deliver clicks to earphones at a frequency of 6.9 Hz. EEG activity is recorded by the computer from three standard EKG electrodes placed on the scalp for 144 ms after each click using a purpose-built, high quality amplifier. A total of 256 EEG sweeps are filtered and averaged to produce the AER. A completely new set of data is obtained every 37 s but a moving time average is calculated every 3 s and improves the response time of the system. The AER is analysed on-line to produce a Level of Arousal Score (LAS).

The LAS is transferred into the control algorithm which attempts to minimize the error between the measured LAS value and the value selected by the anesthetist. The controller calculates a predicted or target blood concentration of the intravenous anesthetic agent, propofol, and transmits the required value to a separate propofol infusion system. The infusion system controls the target blood concentration of propofol by delivering to

the patient a rapid infusion to achieve the desired blood concentration and then calculates and delivers the necessary infusion rates to maintain this value (White and Kenny, 1990). When a lower target blood concentration is required, the infusion system stops delivery of the drug until the predicted concentration has declined to the new value and then restarts drug delivery at the appropriate rates. Thus, the infusion system handles the attainment and maintenance of the predicted propofol concentration determined by the control algorithm.

Each patient is assessed in terms of overall fitness before induction of anesthesia. Three grades are used at present:

1 = Unfit patient, such as one receiving cardiac medication.

2 = Intermediate level of fitness.

3 = Fit, healthy patient.

The grading of the patient determines the initial target blood concentration of propofol selected by the CLAN system, the time delay before increasing the target and the increment by which the target concentration is increased. A baseline value of LAS is measured before induction of anesthesia and subsequent measurements are calculated as a percentage of the baseline value. The target LAS is entered into the computer and the stepped blood concentrations of propofol are achieved until the target LAS is achieved. Thereafter, a proportional-integral control algorithm is used to maintain the measured LAS close to the target value.

We report the use of the CLAN system to control the induction and maintenance of anesthesia in 27 spontaneously breathing patients who underwent body surface surgery. Alfentanil was infused to achieve a predicted plasma concentration of 15 ng ml^{-1} before induction of anesthesia and this value was maintained during surgery. After insertion of a Brain laryngeal mask, patients breathed a mixture of 66% nitrous oxide in oxygen. PRST scores were recorded every 5 minutes and did not exceed 1 in any patient (Table D.3).

Spontaneous repiration	22
Respiration assisted for <5 minutes	5
Highest PRST score	1
Movement during surgery	3
Disturbance of surgery	0
Awareness or recall	0
Willing to have same anesthetic again	27

Table D.3 Quality of anesthesia obtained during CLAN in 27 patients breathing spontaneously during body surface surgery.

Patient movement occurred in three patients but was insufficient to disturb surgery. End-tidal carbon dioxide increased above 8 kPa in five patients after induction of anesthesia and ventilation was assisted in these patients for less than 5 minutes until spontaneous respiration resulted in values below 8 kPa. The median LAS value required during surgery was 40 (range 35-44) and at recovery of consciousness was 101 (range 87-111; Table D.4).

LAS at induction	100
During Surgery	40 (33-45)
Recovery	101 (87-111)

Table D.4 Level of Arousal Scores recorded from 27 patients breathing spontaneously during body surface surgery.

All patients were visited postoperatively and questioned about their memory of the perioperative period. There was no occurrence of awareness during the surgical procedures in any patient. The last memory all patients had before loss of consciousness was the clicks being played through the

earphones but none of the patients was concerned by the clicks and all were prepared to have the same anesthetic in the future.

This is the first reported CLAN system operating from induction, during surgery to recovery in patients breathing spontaneously. The quality of anesthesia was controlled within acceptable limits as assessed by satisfactory PRST scores and the occurrence of only minimal movement during surgery. While most patients had satisfactory values of end-tidal carbon dioxide during the entire procedure, five required assisted ventilation for a short time. Apnea following induction with propofol is quite common but it is also possible that excessively low values of LAS were selected in an attempt to avoid patient movement.

Balance of analgesia and anesthesia

The CLAN system has also been used to induce and maintain anesthesia successfully in patients in whom the surgical area has been blocked with local anesthetic and in those receiving muscle relaxants including some patients undergoing cardiac surgery who have received much higher doses of alfentanil. It has become clear that the process of anesthesia involves the balance of surgical stimulation with the level of arousal. Analgesia reduces the level of surgical stimulation while hypnotics, such as propofol, reduce the level of arousal (Figure D.6).

When general anesthesia is supplemented with local anesthesia, the amount of hypnotic required to produce satisfactory anesthesia is greatly decreased. Indeed, with careful psychological preparation of the patient, no general anesthesia may be required at all and the patient will remain quiet during surgery with no disturbing movements or evidence of increased sympathetic activity. Similarly, when high doses of opioids are used as part of the anesthetic technique, relatively small doses of hypnotic are required for acceptable anesthesia but the patient is then unable to breathe spontaneously. For adequate spontaneous respiration during surgery without

the use of a local block, only small doses of opioids can be used and the blood concentrations of propofol required to produce satisfactory anesthesia are then increased.

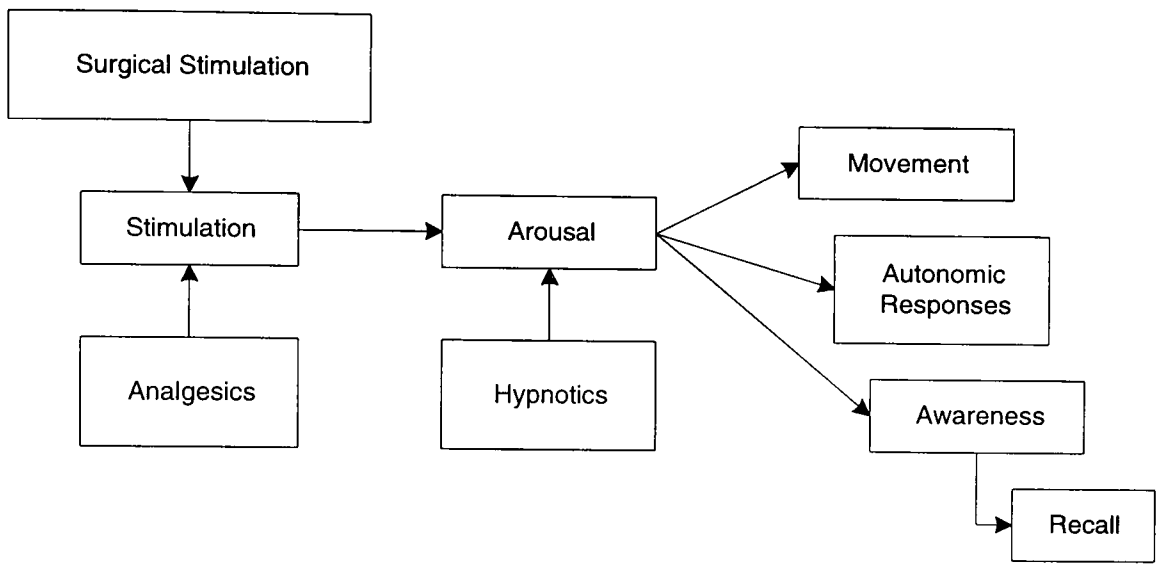

Figure D.6 Surgical stimulation leads to an increased level of arousal. Analgesia decreases surgical stimulation while hypnotic agents reduce the level of arousal directly. The same end result can be achieved therefore either with a technique which uses a low level of analgesia and a high dose of hypnotic or with a technique which achieves high levels of analgesia supplemented by a low dose of hypnotic agent.

Conclusion

While there is as yet no universally accepted index of the depth of anesthesia, some standard is required against which to compare any suggested monitoring system. Any index should provide information which enables the anesthetist to deliver satisfactory anesthesia in a non-paralysed patient breathing spontaneously while undergoing a surgical procedure. The ultimate test of any index is that it should be able to be used as the input signal in a closed-loop anesthesia system which provides acceptable anesthetic conditions in spontaneously breathing patients during surgery. The CLAN system we have developed appears to function satisfactorily in this respect and validates the LAS as an index of anesthetic depth during

propofol anesthesia. Clearly other anesthetic agents must be studied in CLAN to determine if this is a universal finding.

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