THE INTENSIVE CARE OF PATIENTS
FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION

Gilbert Richard Park

Doctor of Medicine
University of Edinburgh
1990
DECLARATION

This thesis has been prepared for the degree of Doctor of Medicine. The nature of the topic demands that the research can only be performed as part of a large team. In all of the original studies described within it (indicated by a title in italics) I was the principal investigator. The assistance of other investigators has been duly noted. The literature reviews are of my own composition.

Two of the studies in Chapter 11 have been submitted by Mr K Quinn as part of his thesis entitled "The Pharmacokinetics and Drug Metabolism of Morphine in Man" submitted towards the degree of Doctor of Philosophy at the University of Cambridge. These parts are indicated in the text.

G R Park
8 February 1990
ABSTRACT

This thesis describes the intensive care of patients following orthotopic liver transplantation and the studies that have explored some of the problems such patients may experience at this time.

The shortage of organs for transplantation prompted a one year study into the outcome of all patients who became brain dead in Addenbrooke’s Hospital. This demonstrated that the major causes for organs not being donated were the relatives and the coroner refusing permission for donation and medical unsuitability.

Early studies investigated the information obtained from laboratory tests of liver function in the immediate postoperative period. They concluded that changes in liver function occur slowly even after this operation and are modified by blood transfusion.

The relief of pain and anxiety is of considerable importance in this group of patients, not only for humanitarian reasons but also to facilitate weaning from artificial ventilation. There was little information about the elimination of analgesic and sedative drugs in this group of patients. Therefore, an intensive investigation into the elimination of midazolam,
morphine, alfentanil, nalbuphine and propofol in patients during either the anhepatic period of liver transplantation or in the immediate postoperative period was undertaken. Some drugs were studied in both periods. Several different patterns of metabolism were found. The use of the specific benzodiazepine antagonist flumazenil was also investigated and shown to have a useful role in the assessment of conscious level. As an alternative to systemic analgesia several methods of providing regional analgesia were also investigated.

Renal failure in this group carries a high mortality and the use of the dopaminergic agents dopamine and dopexamine to prevent this complication was investigated. Both agents appeared to confer some protection.

Postoperative bleeding is a further complication that is difficult to manage. The intraoperative haemodynamic changes associated with the release of abdominal tamponade were described. In some patients conventional haemostatic measures did not produce an improvement in postoperative bleeding; in such patients vasopressin was found to be useful.

The final chapter of the thesis reviews the causes of mortality in the 20 years that this operation has been
performed in the United Kingdom. Infection has been the major cause of death during this period, with bleeding and renal failure becoming less prominent as causes of death.
DEDICATION

Ruth,
Richard and Helen
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Many of my colleagues have assisted and encouraged me with my research. In particular I wish to acknowledge the help of the following:

Professor Sir Roy Calne - Professor of Surgery, University of Cambridge
Dr R Williams - Director, The Liver Unit, Kings College Hospital, London
Drs J V Farman, J R Klinck and M J Lindop - Consultants in Anaesthesia and Intensive Care
Drs Glazebrook, Herrick, Morris, Tolley and Turner - Consultant Anaesthetists
Messrs Jamieson, Johnston, Friend and Rolles - Consultant Surgeons
Drs Shelly, Mendel, Manara, Bodenham and Gray - Research Registrars
Mr M Smith - Senior Operating Department Technician

The trainee doctors and especially the nursing staff of the intensive care unit, all of whom have been both patient during the trials and forthcoming with constructive criticism.

Mrs P Mayoss for the many hours spent typing the manuscript.
INTRODUCTION

The work for this thesis originated from the challenge of providing intensive care to patients following liver transplantation. I was appointed Consultant in Anaesthesia and Intensive Care to Addenbrooke’s Hospital in Cambridge in 1983, at which time 148 liver transplants had been undertaken over the preceding 15 years. In the 6 years since my appointment a further 400 transplants have been performed. This rapid increase is principally due to public awareness of the benefits of transplantation, particularly since Ben Hardwick received his transplant on 23 January 1984. The rapid increase in numbers presented the opportunity, not previously available in the United Kingdom, to gain a wealth of experience in the care of these critically ill patients. At present two or three patients are treated each week after liver transplantation.

Patients presenting for liver transplantation are usually seriously ill with end stage liver failure, receiving multiple drug therapy and have gross pathophysiological abnormalities. The operation is a major procedure, which by itself is demanding, and when performed in seriously ill patients, postoperative support presents many difficulties. Some of these areas were identified as requiring further investigation and form the basis of this thesis.
The provision of appropriate postoperative analgesia and sedation was often a major problem in these patients, due to the unexpected prolongation of action of drugs. The exact mechanism for this was unknown and required an intensive programme studying the metabolism of drugs in this group of patients both postoperatively and during the anhepatic period of liver transplantation in an attempt to understand the mechanisms.

Renal failure developing in such critically ill patients has a high mortality. Its cause is multifactorial but understanding and overcoming these causes led to a reduction in the incidence of morbidity and mortality.

Care of the organ donor is crucial to the successful outcome of a transplant. There was surprisingly little in the literature on this important subject in comparison with the rapidly increasing amount of literature about the recipient operation. Similarly, little research appeared to have been done on the reasons why organs are not retrieved from potential organ donors.

Continuing postoperative bleeding following liver transplantation is one of the most difficult acute problems to deal with in the immediate postoperative period. During surgical re-exploration of the abdomen for continued bleeding the removal of 6 - 9 litres of
blood from the abdominal cavity resulted in profound hypotension despite adequate volume resuscitation; this proved to be due to vasodilation. Reoperation is not always successful in controlling continuing intra-abdominal bleeding and this led us to study the effects of vasopressin in this situation.

Although the work in this thesis has concentrated primarily on patients undergoing liver transplantation there are many common areas which can contribute to the care of other critically ill patients in this and other ICUs.

All of the original research contained within this thesis is identified by the title in bold, italics. Where this work has been published the journal, year, volume and page numbers are also given.
CHAPTER 1

THE HISTORY OF LIVER TRANSPLANTATION

The first successful solid organ transplant in humans took place in 1954 with the transfer of a kidney from one identical twin to another. This followed the first reported human renal transplant by Voronoy in 1936 and later attempts in the early 1950s (Hamilton 1984). Shortly thereafter, kidneys were successfully transplanted from non identical siblings using ionising radiation to provide immunosuppression. Since these early beginnings, many different organs have been successfully transplanted. The kidney is able to withstand periods of ischaemia at body temperature for up to one hour (warm ischaemic time) and still function satisfactorily after transplantation. This allows the removal of kidneys after the circulation has ceased unlike the heart, liver and lungs, which tolerate only short periods of warm ischaemia before irreversible cellular damage occurs. These organs must be isolated whilst the donor circulation is intact and cooled with cold perfusion fluids whilst in situ. The concept of brain stem death was coincidently becoming accepted at the same time as these needs were recognised allowing the use of beating heart organ donors.

The earliest record of liver grafting is that by Welch
(1955), who transplanted livers into dogs as an auxiliary organ and also by Cannon (1956), who performed orthotopic liver transplants. Further work by Moore (1959; 1960) and Starzl (1960; 1961), also in dogs, led the way to the first human liver transplant on 1 March 1963 by Dr Starzl, then at the University of Colorado. Five years later, the first British, human liver transplant was performed on 1 May 1968 by Professor Calne and Dr R Williams; this marked the start of the Cambridge/King’s College transplant programme.

Over the ensuing years there was continuing debate about the best site for a liver transplant. Should it be in an orthotopic or a heterotopic position, the latter providing an auxiliary liver to the patient’s own? Among the problems of heterotopic transplantation was the difficulty of finding a suitable space to accommodate such a large auxiliary organ. Should the abdominal distention produced by ascites not be of sufficient size for the transplanted organ then a pneumoperitoneum could be produced preoperatively to provide sufficient space. Alternatively the abdominal wall could be reconstructed (Fortner et al 1973). The absence of hepatotrophic factors from the blood supply to the transplanted liver was a further problem that was thought to result in poor liver function. These factors include insulin and possibly glucagon as well as others (Starzl et al 1973). Indeed, it was postulated that to
ensure these factors reached the transplanted liver the recipient’s own liver should either be removed or damaged.

The prognosis of heterotopic liver transplantation was poor. Fortner and his colleagues (1977) described 50 patients who had undergone heterotopic liver transplantation, of whom only one had survived a period of four years. In 1980 Houssin and his colleagues described a further adult survivor who had developed fulminant hepatic failure from hepatitis B infection and received a heterotopic liver transplant from a 5 year old donor. This poor prognosis contrasted with the increasingly favourable results being experienced by several centres that were performing orthotopic liver transplantation and heterotopic liver transplantation has now been abandoned by most centres.

In the early stages of the development of orthotopic liver transplantation, considerable technical difficulties needed to be overcome. One of the major problems, which still remains unresolved, is the need for the liver to function immediately following transplantation. There is no adequate prolonged artificial support for the liver should it fail, unlike the kidneys, where haemodialysis can be substituted. In such circumstances retransplantation offers the only
option for survival, if a donor organ is available.

Initially the preservation time of organs after removal from the body was short (1-3 hours), necessitating the movement of the recipient to the donor hospital or the donor to the recipient hospital to enable transplantation of organs in adjacent operating theatres. Collin's solution, which is similar to the intracellular electrolyte composition, was introduced in the USA in 1976 and a modified albumin solution was later used in the United Kingdom (Pegg 1986) for organ preservation. Both these solutions increased the preservation time for organs after removal to 10-12 hours. Recent, further, developments have prolonged preservation times to almost 24 hours, greatly easing the logistic difficulties of providing support for this operation (Jamieson 1988a,b; 1989; see also Chapter 2).

Transplantation of a donor organ into a recipient evokes a foreign body reaction and immunosuppression is necessary to prevent rejection. Initially whole-body irradiation was used and, although this method had been successfully used for marrow transplantation, when used for other organs it frequently resulted in the death of the patient from overwhelming infection. Smaller, sublethal doses of irradiation did not prevent rejection of the organ and this led to the investigation of other methods of immunosuppression. Azathioprine as the sole
agent has been used but proved unsatisfactory and is now used in combination with corticosteroids. Although the combination allows a reduced dose of azathioprine to be used it still retains some of the adverse effects, particularly marrow suppression and thrombocytopenia. Antilymphocytic globulin, derived from horse serum, has also been used, but it does not provide satisfactory immunosuppression and has resulted in severe anaphylactic or anaphylactoid reactions. In patients who are allergic to azathioprine, cyclophosphamide has been found to be a suitable substitute. Corticosteroids are frequently used in combination with other agents although the development of Cushingoid features, infection, avascular necrosis of joints, sodium and water retention and other complications limits their usefulness. Thoracic duct drainage, to deplete the body of lymphocytes, has been tried in patients after kidney transplantation but proved unsatisfactory as a means of immunosuppression after liver transplantation and requires 20-30 days of pretreatment (Starzl et al 1982). Cyclosporin A, an extract from the fungi Cylindrocarpon lucidum and Trichoderma polysporum, was described by Borel and his colleagues (1976; 1977) and was subsequently introduced into clinical practice by Calne (1978; 1979). The effect of the introduction of this drug on mortality was dramatic; it improved survival at 12 months from 33% when azathioprine was used alone to 78.6% when cyclosporin A was introduced
There are some adverse effects of cyclosporin A including pulmonary and renal toxicity, neurological complications, hepatotoxicity, gingival hyperplasia, tremor, regional flushing, vague abdominal discomfort and breast adenomas, as well as an associated increased incidence of lymphomas.

The survival rate from liver transplantation has improved (Starzl et al 1980; Calne 1981; Starzl et al 1982; Starzl et al 1984; Scharschmidt 1984; Williams et al 1985; Scharschmidt 1986; Bismuth et al 1987) and in 1983 liver transplantation became accepted as a therapeutic entity for liver failure (NIH Consensus Conference 1984). Despite improvements, the risks of liver transplantation are considerable: infection, multiorgan failure and rejection being the commonest causes of death (Cuervas-Mons et al 1986). For a patient to merit liver transplantation, death must be anticipated within the next year or life must be of such a poor quality, either because of pruritus or recurrent encephalopathy as to warrant the risk. Some palliative procedures may be undertaken to improve the quality of life in patients who have slow growing tumours which are incapacitating. The current indications for liver transplantation include (Vierling 1984):

- Extrahepatic biliary atresia. This occurs in
neonates with a frequency of 1 in 10,000. It has been defined as the partial or total absence of bile ducts between the porta hepatis and duodenum. Portoenterostomy (Kasai Procedure) will restore bile flow in 90% of children if performed before the age of 60 days. If the operation is unsuccessful or if the child develops cirrhosis later on in life, hepatic transplantation may be indicated. Similar diseases include neonatal hepatitis and intrahepatic biliary atresia.

- Primary biliary cirrhosis. This is a slowly progressive cholestatic liver disease that severely debilitates the patient. It is characterised by destruction of the intrahepatic bile ducts, leading to cirrhosis. These changes may be immunologically mediated, although the exact pathophysiological process is unknown.

- Sclerosing cholangitis. This disease is characterised by inflammation of parts of the extrahepatic bile ducts, although in some patients intrahepatic ducts may also be involved. Obstruction of biliary drainage leads to progressive cirrhosis. Since there are no markers for predicting the subsequent course of this disease, transplantation is usually delayed until deterioration makes death imminent.

Page 18
- Chronic active hepatitis. Commonly the aetiology of this disease is unknown but it sometimes follows viral infections or reactions to drugs. The pathological process involves chronic inflammation of the portal tracts with patchy areas of necrosis. In patients presenting for transplantation the liver has become cirrhotic.

- Acute fulminant liver failure. This may follow viral infections, idiosyncratic drug reactions, drug intoxication or Wilson’s Disease. O’Grady and his colleagues (1988) have described the management of this problem by liver transplantation.

- Hepatic vein thrombosis (Budd Chiari Syndrome). In some instances this follows the use of the oral contraceptive pill in young women or it may occur spontaneously. Sinusoidal congestion and thrombosis occur and progress to liver failure. Although some centres may favour procedures to decompress the portal venous system, in severe cases hepatic transplantation can be invaluable.

- Inborn errors of metabolism. There are several of these that may result in liver failure, or a combination of liver failure and failure of some other essential organ. For example, primary hyperoxaluria may result not only in damage to the
liver but also in renal failure. Wilson’s disease can present as an acute neurological emergency which, if it fails to respond to chelation, may be reversed by liver transplantation (Groth et al 1973; Sternlieb 1984). Not all inborn errors of metabolism can or should be treated by liver transplantation; $\alpha_1$-antitrypsin deficiency has approximately 20 phenotypes and only one of these (1 PiZZ) is thought to be treatable by transplantation.

- Hepatic neoplasms. There are several primary tumours of the liver that are treatable by liver transplantation, including fibrolamellar and some hepatocellular tumours. Neoplastic lesions of the biliary ducts have proved to be untreatable by this method at present. Metastatic lesions may be successfully treated by orthotopic liver transplantation if they are proved to be solitary. Starzl (1982) has reported that of 16 patients who had secondary metastasis to the liver without radiological evidence of spread to other parts of the body, all but one were successfully treated by liver transplantation. The patient who died proved to have metastases that were not detected by radiological means. Liver transplantation as a palliative procedure may be worthwhile in some patients. Diarrhoea from carcinoid tumour may be
sufficiently incapacitating to warrant this procedure and allow a comfortable existence before death from the primary tumour results.

- Alcoholic cirrhosis. Despite increasing public awareness of the hazards of excessive alcohol this remains a major cause of morbidity in both the UK and the USA. Transplantation will improve the patient’s well being but is only of benefit if the patient is no longer abusing alcohol (Schenker 1984). One year survival in this group may be as good as that for other groups of patients treated by liver transplantation (Neuberger 1989).

- Retransplantation. This is an indication in an increasing number of patients whose primary graft has failed. This may be performed as an emergency following acute graft failure, usually due to infarction, or as an elective procedure if graft failure results from rejection.

Bismuth and his colleagues (1987) studied the indications for transplantation before and after 1983 and demonstrated little change except for a decrease in the number performed for neoplasms and an increase in the number of paediatric and acute hepatic failure cases. There are currently 30 European and 50 American centres
performing this procedure. Other centres exist in Australia and in the Republic of China.

It has been estimated that there are 20 persons per million per year requiring liver transplantation (National Institute of Health 1984). The current one-year survival following liver transplantation for children is 70% and for adults slightly less at 60%. The longest survival time after a liver transplant is approximately 14 years and this patient has subsequently been through college (Calne 1985). The subsequent restoration of normal life to many other survivors testifies to the efficacy of this procedure.

The ethical, moral and economic difficulties posed by liver transplantation are increasingly complex, and are much debated. They have been reviewed in depth recently (Sabesin, Williams and Evans 1988). The Pittsburgh group demonstrated the financial, as well as clinical, advantages of this operation several years ago (Starzl et al 1982). The cost of a liver transplant at that time was US$ 55,000 (23,000 - 150,000) whilst the cost of the management of variceal bleeding was US$ 35,000 and if operative treatment was undertaken this increased to US$ 53,000. Neither medical nor surgical procedures for variceal bleeding are curative. They may need to be repeated several times on a patient who experiences continuing ill health and subsequently dies. This contrasts with liver transplantation, which can restore the
patient to an almost normal life.
Until such time as donation of livers from living humans becomes possible (McBride 1989) or animal organs can be transplanted into humans, the postoperative care of a patient undergoing liver transplantation starts when brain death has been declared in the donor. If proper care is not taken of the organs before transplantation then the postoperative course followed by the recipient may be the subject of unnecessary and avoidable morbidity. In extreme cases death of the recipient may be a direct consequence of poor donor care. Before proceeding further with this thesis it is therefore appropriate to review the care of the organ donor. Furthermore, since shortage of organ donors has been blamed on intensive care doctors not requesting consent, this subject will also be addressed. My position and that of my colleagues working in the John Farman Intensive Care Unit is uncommon in the United Kingdom. We find ourselves caring for organ donors, who are admitted as part of the general workload of the Intensive Care Unit, as well as for the recipients. This has resulted in an unparalleled opportunity to maintain an interest both in organ donation and care of the recipient. Such a situation could have caused ethical problems. These were foreseen and a system of cross cover of ICUs was developed to avoid a conflict of
interests. My neurosurgical colleagues perform brain death testing in the John Farman ICU, and I and my colleagues reciprocate in the neurosurgical ICU. The recognition of brain death allowed the use of beating heart donors and this enabled multiple organ procurement from a single donor. Suitable patients with severe brain injury resulting in brain death, who may be potential organ donors, are to be found on both neurosurgical and general intensive care units. The pathophysiological results of brain death are similar, irrespective of the underlying cause. Severe brain injury may result in the loss of temperature regulation, the development of diabetes insipidus and cardiovascular instability. The management of brain injury before death often results in abnormal fluid balance, due to fluid restriction and diuretic therapy. Other problems such as acute endocrine failure and the impact of correction of these abnormalities on ultimate organ function remain to be elucidated.

The kidney is able to withstand periods of ischaemia at body temperature for up to one hour (warm ischaemic time) and still function satisfactorily after transplantation. This allows the removal of kidneys after the circulation has ceased. The heart, liver and lungs will tolerate only short periods of warm ischaemia before irreversible cellular damage occurs. These organs must be isolated whilst the donor
circulation is intact and cooled with cold perfusion fluids whilst in situ. The concept of brain stem death was coincidently becoming accepted at the same time as these needs were recognised and this allowed the use of beating heart organ donors.

It is vital, for optimal organ function after transplantation, that the donor organs are kept in good condition (Grebenik and Hinds 1987) with particular emphasis placed on the maintenance of organ perfusion. Furthermore, if, during life, the patient wanted to donate organs then the medical team have an obligation to ensure that organs are in the best possible state for the recipient.

The Diagnosis of Brain Death
The advent of modern resuscitation and intensive care facilities has changed death from an event to a process. Patients who have no hope of survival may have their vital functions supported by artificial techniques and treatments. In patients who have sustained massive brain injury the heart will stop beating unless ventilatory support is continued. The brain is unique amongst organs in being necessary for life yet having no means of artificial support or transplantation; therefore death of the brain and death of the patient are synonymous. This was first recognised by two French physicians (Mollaret and
Goulon 1959) as "Coma de Passe". Following this early
description, criteria for the diagnosis of brain death
were first described by the Harvard group in 1968
(Harvard Medical School Ad Hoc Committee 1968). At
this time organ transplantation was developing from
an experimental method of treatment to a therapeutic
modality for end-stage organ failure. Brain stem death
and organ transplantation were described at similar
times and have become associated with one another.
They are, however, independent concepts; even in the
absence of organ transplantation there would still be a
need for the recognition and diagnosis of brain stem
death in order to alleviate the suffering of relatives
and intensive care staff, as well as to prevent the
wastage of valuable intensive care resource.

The British criteria for the recognition of brain stem
death were described by the Conference of the Medical
Royal Colleges and their Faculties in the U K in 1976
and revised three years later in 1979; this resulted in
the publication of the Code of Practice. The criteria
described in the code are based on clinical findings
(Jennett 1982; Pallis 1982a,b,c) and do not include
electroencephalographic (EEG) examination and cerebral
blood flow measurements that are mandatory elsewhere
(Powner, Snyder and Grenvik 1977; Powner, Pinkus and
Grenvik 1981). It should be emphasised that this is a
code of practice; it does not have any legal authority although it has considerable moral and ethical support, having been originated by the medical profession, endorsed by the Chief Medical Officer and distributed by the Department of Health and Social Security.

The diagnosis of brain stem death is made by two clinicians, one of whom should be the consultant responsible for the patient's care or his deputy. The deputy should be of senior status and registered for at least 5 years. One other doctor is required to perform the tests. Both doctors must be suitably experienced and able to perform this test. They will usually be intensive care doctors, physicians or neurosurgeons. Involvement of a neurologist in the performance of these tests is unnecessary. Neither doctor must be a member of the transplant team. Before the tests are performed both doctors must assure themselves both of the diagnosis and of the exclusions.

Firstly the diagnosis must be certain, the patient having suffered severe and irreversible brain damage, the aetiology of which must be known and be totally dependent upon artificial ventilation. If any doubt exists then the diagnosis of brain death must not be made. Secondly, it is necessary for certain exclusions
to be made. Hypothermia (a body temperature <35°C), would also preclude testing. Similarly the presence of gross electrolyte, acid/base or other metabolic abnormalities would also exclude testing. The absence of chronic endocrine abnormalities such as hypothyroidism, which would confuse testing if it was present, should be excluded, or appropriate treatment should have been continued during the period of acute illness. Prolonged drug action (including alcohol) should always be considered. Decreased elimination of drugs, such as benzodiazepines and opiates, that may have been used therapeutically in critically ill patients is increasingly recognised (Chapters 8, 10, 11 and 12). The pharmacokinetic and pharmacodynamic effects of hypotension, hypothermia and endocrine failure on sedative and analgesic drugs has not been studied in the brain dead patient, but the possibility of delayed drug elimination must be considered. In addition 6-10% of the population have been demonstrated to have pharmacogenetic abnormalities leading to delayed drug metabolism (Dundee et al 1986; Maitre et al 1987). Measurement of plasma concentrations of sedative and analgesic drugs has been shown to correlate poorly with central effects (Bond, Hailey and Lailer 1977) and cannot be relied upon. The use of the specific opiate and benzodiazepine antagonists naloxone and flumazenil has been proposed as a test to exclude drug accumulation. Improvement in conscious level, as shown by the return of reflexes or
purposeful movements within the cranial nerve distribution, after the administration of these antagonists, disproves brain death. Conversely, with the lack of current clinical information, a lack of improvement cannot be taken as excluding residual sedative effect. If there is doubt about the presence of sedative drugs then the diagnosis of brain death cannot be made. The adverse effects of the two antagonists on haemodynamics and intracranial pressure make their use in the brain injured patient dangerous (Smith and Pinnock 1985; Chilero et al 1988). If they are to be used then this should be postponed until all other tests have demonstrated brain death. The continuing effects of neuromuscular blocking agents must be demonstrably absent. If the limbs have been seen to move then neuromuscular blockade can be excluded; if not, it can be excluded by the use of a peripheral nerve stimulator.

Ventral pontine infarction ("the locked-in syndrome"), idiopathic polyneuritis (Guillain-Barré syndrome), and brain stem encephalitis have been listed as conditions which may mimic brain death (Pallis 1982c). The "locked in syndrome" is characterised by retained consciousness, spontaneous respiration and vertical eye movements (Pearce 1987). Polyneuritis has a characteristic history and presentation; consciousness is not lost although all muscle groups may be paralysed. Brain stem encephalitis is characterised by rousable
stupor and retained purposeful limb movements (Al-Din et al 1982). All these conditions differ from the common causes of brain death (traumatic head injury, intracranial haemorrhage and cerebral hypoxia) in that they lack a defined severe cerebral injury as stipulated in the criteria. Furthermore, if a careful clinical examination is performed, patients with these conditions will not fulfil the criteria either.

These tests are repeated by each doctor. This is to ensure that there has been no observer error. The exact timing between tests is determined by the doctors and will vary from case to case. If the injury has been caused by trauma or massive intracranial bleeding then the interval may be very short. If, however, the injury is due to hypoxic brain damage the interval may be much greater (up to 24 hours). This flexibility enables the physician to tailor the tests to the patient’s condition. The time of death is legally defined as the time of completion of the second set of tests by both doctors.

No patient who has fulfilled the brain stem death criteria outlined above has ever recovered and large studies have repeatedly shown the validity of the diagnosis of brain death (Jennett, Gleave and Wilson 1981). In the United Kingdom the majority of doctors
firmly believe that further tests of brain stem death are not indicated. A small minority have expressed doubts about the validity of this method of testing and this resulted in an in-depth investigation. Expert opinion was sought from all members of the medical profession as well as lawyers, theologians and lay persons. The small minority who doubted the validity of the tests were also invited to give evidence. The outcome of this investigation was published in the Hoffenburg Report (1987). The investigation concluded that the brain stem death tests remained valid and should not be changed, nor should any more tests of brain stem function be added.

The causes of death in beating heart donors during one year (1987), as reported to the United Kingdom Transplant Service, are shown in Table 2.1.
<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
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<tr>
<td>Subarachnoid haemorrhage</td>
<td>215</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>14</td>
</tr>
<tr>
<td>Intracerebral haemorrhage</td>
<td>120</td>
</tr>
<tr>
<td>Head injury (road traffic accident)</td>
<td>188</td>
</tr>
<tr>
<td>Head injury (other causes)</td>
<td>94</td>
</tr>
<tr>
<td>Road traffic accident (associated injuries)</td>
<td>59</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>18</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>13</td>
</tr>
<tr>
<td>Meningitis</td>
<td>10</td>
</tr>
<tr>
<td>Asthma</td>
<td>11</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>11</td>
</tr>
<tr>
<td>Respiratory arrest (other causes)</td>
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<tr>
<td>Anoxia/Hypoxia</td>
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<tr>
<td>Overdose</td>
<td>6</td>
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<tr>
<td>Others</td>
<td>36</td>
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<tr>
<td><strong>Total</strong></td>
<td>815</td>
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</table>

Table 2.1. The causes of death in beating heart organ donors during 1987 (Figures supplied by the United Kingdom Transplant Service).
Once death has been declared a decision needs to be made as to whether organ donation is to occur. This is usually discussed with the relatives after the first set of brain stem death tests have been performed, so that at the time of the second set the procedure to be followed is clear. If organ donation is not to occur then the ventilator is usually disconnected at the end of the second set of tests, Apnoea results and the ensuing hypoxia leads to cardiac standstill. When organ donation is requested then treatment changes from patient care to organ maintenance.

The tests used to confirm brain death are summarised in Table 2.2.

The exact timing of the second set will vary according to the clinical condition of the patient and may be up to 24 hours from the first set. Inevitably some patients will become asystolic whilst the diagnosis is awaited but may be suitable for cadaveric organ donation if consent has been granted. Details of testing are best documented on a single form, variations of which are available in many hospitals.
Known cause of irreversible and severe brain injury.
Absence of hypothermia, electrolyte and endocrine abnormalities.
No residual sedative drug effects.
No pupillary response to light.
Absent corneal reflex.
Absent caloric responses.
No motor response within distribution of cranial nerves. No gag or bronchial reflex to a painful stimulus.
Apnoea when disconnected from the ventilator with a normal PaCO₂.

Table 2.2. Clinical criteria for diagnosing brain death in the United Kingdom.

After Bodenham and Park (1989) Intens Care Med 15; 340-348
Consent to Organ Donation

At present in the UK it is usually a senior member of the medical team looking after the patient who asks for consent. He should have previously met the relatives and discussed the poor prognosis and have the time available to discuss the question of donation. If he is unable to devote the time or feel unable to, then a transplant coordinator may be able to help (Wallwork 1989). The majority of relatives will gain some comfort from the act of donating organs and this provides some relief from an otherwise tragic situation (Morton and Leonard 1979); some may even feel aggrieved if not approached about donation. Unfortunately some relatives will refuse when asked, only to regret that decision later (Wallwork 1989). A voluntary group "BODY" (British Organ Donor Society), has recently been set up in the UK to offer help to relatives in these situations. Transplantation programmes are more successful in children than adults but are hampered by the lack of child donors under 5 years. Donation from children may cause particularly strong emotions both in favour of and against organ donation.

Consent may have been granted before death occurred, and this will usually have been recorded on a donor card. If the patient carried a donor card there is no legal requirement to discuss consent with the relatives, but it is usual and recommended practice to do so. If no donor
card has been signed permission may be obtained from relatives (although in theory the local Health Authority legally own the body and only they can give consent). Organ donation is best discussed with the relatives after the first set of tests have been performed. Waiting until after the second set of tests have been completed can result in unnecessary distress for the relatives and delay in obtaining the organs. When brain death and organ donation are being discussed with relatives, the concept of the beating heart donor should be clearly explained. This will avoid the possibility of future distress should the media highlight the issue at a later date. It is also important that multiple organ donation is discussed with them. Studies after multiple organ procurement have shown no individual difference in organ function when compared with single organ donation (Shaw, Rosenthal and Hurdesty 1984) and this is an important means of increasing organ availability. However, some relatives do not wish to donate all of their relatives organs, particularly the corneas and heart, and the opportunity must be given for them to express their wishes.

In circumstances where there are no relatives, the Hospital Administrator (as the legal possessor of the body) may grant permission to donate organs. The only occasion when the local Health Authority does not own the body is where brain stem death has been
occasioned by an act of violence or in other suspicious circumstances. In such instances the Coroner, in England, or the Procurator Fiscal, in Scotland, owns the body. Organs may then only be removed with their approval. When criminal proceedings are likely to follow the death of a patient then it is unlikely that permission for organ removal will be granted, as a full and complete autopsy may be required as evidence.

The publicity, both good and bad, surrounding the practice of organ donation has led to fluctuations in supply but there is still a large deficit of donor organs. Many people wish their organs to be donated after death but may not communicate this to their next of kin. In the UK an "opting in" system is practised, in the form of widely available donor cards. These were at one time issued as part of the driving licence. This latter practice has been withdrawn to comply with European Economic Community regulations. Donor cards have not been successful owing to low acceptance rates by the public and to cards not being carried or being lost at the time of accident or hospital admission. "Opting out" procedures have been implemented in some countries where individuals have to register on a central computer that they do not wish to donate organs.

It has been estimated that there are approximately 4000 potential donors per year in the UK but only 15-20% of
these actually donate organs (Rudge 1987; Jennett and Hessett 1981). These figures were derived from epidemiological studies of the incidence of subarachnoid haemorrhage and severe head injuries. They did not take into account regional variations in medical practice or pathology. Furthermore, this estimate was published in 1981, since when there have been improvements in car and road safety and changes in public attitudes to organ donation. There is a lack of knowledge of the true incidence of brain death, the frequency with which the question of organ donation is raised and consent is refused and the effects of changes in legislation. However, transplant surgeons have alleged that organs from many potential donors are not being made available because of reluctance of doctors to ask relatives to consent to donation. They have therefore called for new legislation requiring clinicians to ask for consent to organ donation (Chisholm 1988). "Required request" has been introduced as Federal Law in many States in the USA (Oh and Uniewski 1986; Grenvik 1988), but there is no scientific evidence that the supply of donors has increased as a result. This legislation requires that the physician looking after a potential organ donor discusses the possibility of organ donation with the relatives. A compromise has been suggested in the form of "Required discussion", where physicians must discuss potential donors with the local transplant team who could then approach the relatives (Rudge 1987). To
investigate whether "required request" would make a significant difference to the number of potential donors failing to donate organs, a prospective study was performed of all patients admitted in 1 year to the 4 intensive care units (general, paediatric, neurosurgical and neurotrauma) at this hospital who were declared brain dead or considered suitable to donate organs after circulatory arrest. This hospital was chosen because the transplant teams at Addenbrooke's and nearby Papworth are pioneers in organ transplantation. This generates much local, as well as national media interest. Awareness of transplantation is thus high in the local population and the medical and nursing staff. It might therefore be expected that consent for organ donation would be considered both by medical staff and relatives more readily than in other centres. In addition the study was used to determine the causes and complications of brain stem death in this hospital.

This study was carried out with the assistance of Dr A Bodenham and Dr J Berridge (Data collection).
Subjects and Methods

From 18 November 1987 to 17 November 1988 all cases of brain stem death that occurred were studied. At diagnosis of brain stem death the following information was collected: age, general diagnosis, duration of artificial ventilation after the declaration of death and number and type of organs donated. If organs were not donated by a potential donor then the reasons for this were examined and allocated to one of four categories: medical contraindications, consent not requested, consent denied by relatives and consent denied by the coroner. In addition, any complications directly attributable to brain death were also recorded. These included hypotension (systolic blood pressure <80mmHg, without inotropic support), diabetes insipidus (urine output > 200 ml/hr in the absence of diuretics or other causes of polyuria) and hypothermia (temperature <35°C, without warming).

Results

Forty-two patients (25 male and 17 female) fulfilled the criteria for the diagnosis of brain death during the period of study. In ten other patients, three male and seven female, circulatory arrest occurred before formal testing could be completed. The age of the subjects was
mean (SD) 37.3 (22.4) (range 0.5-89) years and the mean duration of artificial ventilation after testing was 123 (range 10-3070) minutes. The large range in duration of ventilatory support reflects the need in one instance to wait until relatives arrived from the Far East to give consent. The major causes of brain death were head injury (28 cases) and spontaneous intracranial haemorrhage (17 cases) with intracranial tumour, hypoxic brain injury and hydrocephalus the remaining diagnoses (Table 2.3).

All 52 subjects had at least one complication of brain stem dysfunction with diabetes insipidus and hypotension occurring in the majority (Table 2.4).

Consent to organ donation was obtained in 24 of the potential donors with organs being donated by 23. One subject was found to have peritonitis at operation precluding organ retrieval. In four cases consent was restricted to corneal donation leaving 19 donors of solid organs, three donating after circulatory arrest. Table 2.5 shows the number of organs donated compared with the number for which consent to removal was granted.
<table>
<thead>
<tr>
<th>Cause</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Road traffic accidents</td>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>Assault</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Other trauma</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Intracerebral haemorrhage</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Cerebral neoplasm</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Hypoxic brain injury</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2.3: Causes of fatal brain injury in 52 potential organ donors
<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Insipidus</td>
<td>34</td>
<td>65</td>
</tr>
<tr>
<td>Hypotension</td>
<td>33</td>
<td>63</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Oliguria</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Pulmonary Oedema</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2.4: Complications of fatal brain injury in 52 potential organ donors. In 22 cases more than one complication occurred.
<table>
<thead>
<tr>
<th>Organ</th>
<th>Donated</th>
<th>Consented</th>
<th>Not used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>35</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Liver</td>
<td>9</td>
<td>16*</td>
<td>6</td>
</tr>
<tr>
<td>Liver/ pancreas</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>7</td>
<td>16*</td>
<td>7</td>
</tr>
<tr>
<td>Heart/lung</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>54</strong></td>
<td><strong>70</strong></td>
<td><strong>16</strong></td>
</tr>
</tbody>
</table>

Table 2.5: Number and type of organs donated by 19 organ donors compared to number of organs with consent to be removed. (In 4 further cases consent was restricted to corneal donation) *A donor cannot donate liver and pancreas or heart and heart-lung separately.
At the donor operation one kidney was found to have been previously traumatised and was not removed. Lack of a suitable recipient prevented the removal of two kidneys, a liver and three hearts. Three livers were not utilised because of shortage of intensive care facilities for a recipient. The age criteria for hepatic and cardiac donation prevented the use of two livers and four hearts.

Twenty-nine subjects failed to donate any organs (Table 2.6). This was due to medical contraindications in 13 (profound hypotension, sepsis, trauma or renal failure). In eight cases the injuries resulting in brain death occurred in circumstances resulting in serious criminal charges being brought against another person. In such circumstances the coroner felt unable to grant permission for organ donation. There were five occasions where the relatives refused permission: in three the feeling was that the deceased had "been through enough", in one the deceased had expressed a wish not to be an organ donor and in a further case the relatives had doubts about donation. Consent was not requested in only three subjects.
<table>
<thead>
<tr>
<th>Medical</th>
<th>Consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=13</td>
<td>n=16</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Denied by Coroner 8</td>
</tr>
<tr>
<td>8</td>
<td>Denied by Relatives 5</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Failure to request 3</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Organ Trauma</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.6: Causes of failure to donate in 29 potential organ donors.
Discussion

Sixteen organs were not utilised when consent to their removal had been granted because of lack of intensive care facilities or shortage of recipients matched for blood group and cytomegalovirus status. Lack of intensive care facilities is often due to nursing shortages and is part of the increasing manpower crisis facing the health service (Bosanquet and Gerfard 1985).

In this series, organs from eight potential donors did not come to donation because the coroner would not release the body for donation, a feature others have experienced with the Procurator Fiscal in Scotland (J D Miller, personal communication). The prevalence of traumatic causes of brain death suggests that this is a nationwide feature and is unlikely to change, though individual coroners and procurators fiscal have widely differing opinions on this subject, some releasing bodies when others would not (Jennett and Gentleman 1989).

Of concern is the large proportion (a quarter) of potential donors whose poor general condition rendered them unsuitable for donation, a feature subsequently noted by others (Dennis, Ryan and Blamey 1989; Gore, Hinds and Rutherford 1989). This, coupled with the high incidence of complications, means that such patients require careful medical and nursing care with particular attention to cardiovascular function. Perhaps
by attention to these factors not only absolute numbers of donors will increase but also there will be an improvement in the condition of organs that are donated.

In this study, although solid organs were donated from only 19 of 52 patients with brain stem death, in only three of the remaining 33 cases was consent for donation not requested. This suggests that failure to request donation after brain stem death is uncommon at our hospital. If this level of requesting donation is representative of that at most other centres then legislation to make request compulsory would not considerably increase the number of organs available for transplantation. Further evidence of the ineffectiveness of required request to increase organ donation is demonstrated in a report from San Francisco (where required request has been introduced) about withholding or withdrawing support from critically ill patients (Smederia et al 1990). In this study brain death was diagnosed in 18 patients yet only five of them became organ donors. Wakeford and Stepney (1989), in a survey of attitudes to organ donation, concluded that coercive measures were less likely to increase the supply of donor organs than improved education of the public and the medical profession.

Collins (1989) has suggested that, as a means of increasing organ donors, patients who have suffered a
severe cerebral vascular accident, but who are breathing spontaneously (and therefore not brain dead), should be admitted to the ICU if their neurological condition deteriorates further. This would enable respiratory arrest to be treated promptly after which tests to diagnose brain stem death could be performed. If these confirm the diagnosis then, assuming consent has been given, organ donation can take place. There are many ethical and moral problems arising from this approach that remain to be resolved.

Organ Retrieval

The UK Transplant Service (UKTS) in Bristol maintains a computerised record of all patients in need of organ transplantation and acts as a co-ordinating centre for the use of organs. Local organisation of the surgical organ retrieval is performed by regional transplant co-ordinators. The different organs retrieved from a single donor may be used in several different centres around the UK. Organs are also exchanged within the EEC. Within Europe there are a number of different co-ordinating organisations including Eurotransplant (the Benelux countries, Federal Republic of Germany & Austria), France Transplant, Scandia Transplant, Swiss Transplant, North Italy Transplant, Barcelona Transplant and Luso Transplant (Portugal). The activities of these organisations has been reviewed in depth (Gore and Bradley 1988).
Unavoidable delays at the transplantation centre may be seen as procrastination by the donor hospital and may lead to frustration. These delays may be caused by the difficulties in organising several retrieval teams simultaneously and the frequent shortage of ICU bedspace for the recipient. Another complaint of donor hospitals is the large number of telephone calls for information from the various recipient hospitals about the donor organs. To overcome this I am designing, in conjunction with Mrs Celia Wight (Transplant Co-ordinator), a form which will contain all the information required by transplant teams. The form can be completed by the donor hospital and faxed to UKTS who have agreed to coordinate dissemination of the information.

Emotional differences may exist between the medical personnel looking after the potential donor (who feel their therapeutic efforts have failed) and the members of the transplant team (who are encouraged by the opportunity to help another patient). These differences have, on occasions, led to misunderstandings and both groups need to appreciate the other’s feelings if these problems are to be prevented in the future.

Criteria for Organ Donation
A few absolute contraindications apply to all potential donor organs including Hepatitis B infectivity, the
demonstration of antibodies to human immune deficiency virus (HIV), other known viral infections, a history of intravenous drug abuse, malignancy (apart from primary central nervous system (CNS) tumours) and concurrent bacterial sepsis (Table 2.7).

The potential donor who is known or suspected of being an active promiscuous homosexual should be carefully considered. It is possible to be infective with HIV despite negative serology (see below). The decision to use organs in these situations can only be resolved by individual discussion of each case with the surgeon responsible for the recipient operation. Age, diabetes mellitus and the presence of other disease processes are relative contraindications. Some organs which do not fulfil the usual criteria may be used if there is a desperate need, such as in a patient with fulminating hepatic failure.

**Donor Transmitted Disease**

Transmitted bacterial infection should be avoidable by careful screening of donors for clinical and laboratory signs of sepsis and the use of routine prophylactic broad spectrum antibiotics during organ procurement. Viral and protozoal infections are more of a problem owing to their silent carriage in donor organs and, once recognised, to the lack of effective drugs for their treatment.
Age <70 years
Free from transmissible disease:
Bacterial
Fungal
Protozoal
Viral infections.
   Hepatitis B antigen negative.
   HIV antibody negative.
No widespread atherosclerosis.
No trauma, infection or chronic disease in organ to be transplanted.
Free of malignant disease except primary CNS.
Satisfactory donor height, weight, abdominal girth
Liver function tests normal
No alcohol abuse

Table 2.7. General criteria for liver donation

After Bodenham and Park (1989) Intens Care Med 15; 340-348
Screening for Hepatitis B and HIV is routinely performed in potential donors. However, using currently available assays, seroconversion occurs several weeks after primary infection. Antibody titres against HIV may be diluted by massive blood transfusion and blood products may themselves transmit infection to the donor. Testing the blood samples originally sent to the transfusion laboratory for crossmatching when the patient was first admitted may be helpful in such cases. However, tests failing to demonstrate antibodies to HIV in donors cannot exclude HIV infection. Both HIV (L'Age-Sterh et al 1985) and Hepatitis B (Combined Medical Research Council and Public Health Laboratory Report 1980) have been transmitted via transplanted organs and are likely to run a fulminant course in the immunosuppressed patient.

Cytomegalovirus and toxoplasmosis gondii both exist in latent forms in the normal population and may be reactivated in the immunosuppressed patient, particularly in the presence of other infections (Editorial 1984; Ho et al 1975; Grundy, Super and Griffiths 1986). Both organisms may be transmitted to seronegative recipients either via infected donor organs or via blood transfusions and subsequently, cause a primary infection. In the immunosuppressed patient both organisms may give rise to life-threatening infections. Heart and heart–lung recipients appear particularly at
risk from these organisms; some transplant units routinely screen all donor organs for them and then avoid giving seronegative recipients seropositive organs or blood (Luft et al 1983).

**DONOR MAINTENANCE**

After the criteria for brain stem death have been satisfied and consent obtained, patient care becomes donor maintenance, and there is a change in emphasis from cerebral to donor organ protection. Failure to ensure that the organs are in optimal condition on removal may result in graft failure or malfunction in the recipient. Special problems arise when managing these donors; severe intracerebral damage can result in diabetes insipidus, disturbances of cardiovascular function and temperature regulation.

The cardiovascular system

Hypotension is a common finding in the brain dead patient. The vasomotor centre is damaged, in common with the rest of the brain stem, resulting in progressive vasodilatation. Dehydration from fluid restriction and diuretic administration is a recognised treatment for cerebral oedema and may result in hypovolaemia. Myocardial function has also been shown to deteriorate in the brain-dead baboon with increasing anaerobic
metabolism (Novitsky et al 1984). Bradycardias are common in the presence of severe cerebral injury owing to loss of sympathetic drive. The destruction of the nucleus ambiguus in the brain stem abolishes resting vagal tone, and atropine therefore fails to reverse bradycardia in this situation; this has been used as a diagnostic test for brain stem death (Ouakine 1978; Vaghadia 1986). Bradycardias continue to respond to sympathomimetic drugs, such as isoprenaline, which act directly on beta adrenergic receptors in the heart.

The first step in the correction of hypotension is to expand the intravascular volume, using central venous pressure as a guide to adequate replacement. Urine output and core-to-peripheral temperature gradients are additional useful guides in this situation. Blood losses should be replaced with whole blood or packed cells to maintain an haematocrit of 30%. This haematocrit maximises oxygen supply by optimising the balance between oxygen transport by the red blood cell mass and blood flow related to changes in viscosity (Messmer 1975). The choice of other fluids for the correction of hypovolaemia is controversial, particularly when large volumes need to be given quickly to resuscitate a hypotensive donor. At this centre a modified gelatin solution is used but it remains to be determined whether crystalloid or colloidal solutions are better in this situation. If a low blood
pressure persists after correction of hypovolaemia the circulation may be supported by infusion of an inotropic agent. Dopamine is currently the most popular drug because it causes renovascular dilatation at doses up to 5μg/kg/min. Higher doses of it and other inotropes lead to progressive renal and systemic vasoconstriction. Drugs with predominantly vasoconstrictor properties (eg aramine, ephedrine, metaraminol) should only rarely be required if the above steps are followed. Their inappropriate use may cause splanchnic vasoconstriction, reducing liver and kidney perfusion. With worsening brain damage it may well become impossible to maintain an adequate circulation (Jennett, Gleave and Wilson 1981). The blood pressure should not be considered in isolation, as a maximally vasodilated circulation may provide good organ perfusion despite low measured blood pressures.

Fluid balance
Fluid restriction and diuretic therapy are routine practice in many units looking after acute neurological injuries. Diabetes insipidus, glycosuria (due to steroid therapy), and hyperthermia (before brain death) are also common, and increase water losses. When assessing organ donors, fluid intake and losses should be calculated for the previous period of intensive care. Fluid replacement is guided by assessment of skin turgor and mucous membrane hydration, together with measurement
of peripheral temperature, urine output and central venous pressure and the laboratory estimation of plasma urea and electrolytes and haematocrit.

The urinary losses in diabetes insipidus should be replaced by 5% dextrose with added potassium (Schucart and Jackson 1976), or preferably with a solution based on the measured urinary losses of electrolytes. The inappropriate use of 0.9% sodium chloride or plasma volume expanders containing 0.9% sodium chloride over a period of days may lead to progressive hypernatraemia.

**Temperature control**

Extensive damage to the brain stem causes loss of the normal central control of body temperature, the body effectively becoming poikilothermic. Without control of the temperature by passive warming the donor temperature will fall to that of its environment. Hypothermia is harmful as it causes progressive vasoconstriction and cardiac instability as the core temperature falls. Monitoring of body core temperature should be carried out and steps taken to conserve heat. Intravenous blood and fluids should be warmed, inspired gases should be heated and humidified and the donor should be placed on a warming mattress and covered by reflective insulating blankets.
Endocrine failure

The incidence of posterior pituitary failure (manifested by diabetes insipidus) is high in brain death. Autopsy findings in such cases have shown necrosis, infarction or oedema of the pituitary as a consequence of the initial injury (Fiser et al 1987). Polyuria results from lack of antidiuretic hormone and the large volumes of dilute urine need to be replaced on an hourly basis if marked fluid depletion is not to occur. Fluid therapy is discussed elsewhere in the text. A diuresis greater than 150 mls/hr in an adult can be controlled using vasopressin or its synthetic analogues. Early use of vasopressin considerably simplifies the fluid management of these patients. Vasopressin may be effectively given as intramuscular injections or as a low dose infusion of 1-2 units per hour (Chanson et al 1987). The synthetic form dDAVP is more potent as an antidiuretic, it has a longer duration of action and has less vasoconstrictor properties.

It would be surprising if anterior pituitary function was not damaged in a similar fashion to posterior pituitary function when brain death occurs, and this has been confirmed experimentally in animals with brain stem injury (Novitsky et al 1984). Studies in humans have been less clear. Hall and his colleagues (1980) measured thyroid stimulating hormone, prolactin and cortisol in five patients with brain death, and could
demonstrate no abnormality except loss of the diurnal cortisol variation. Novitsky and his colleagues (1987) measured triidothyronine (T3), insulin and cortisol in 21 brain dead patients, and found a decreased T3 and a low or normal cortisol and insulin concentrations. On the basis of this and their animal work they gave T3, cortisol and insulin to all their subsequent organ donors and appeared to have less cardiovascular and metabolic problems in them, compared with historical controls who did not receive hormone therapy. This study was both uncontrolled and retrospective, with the attendant methodological problems, but does indicate the need for further studies in this area.

Organ Preservation

At the start of liver transplantation little was known about organ preservation and the recipient was moved, along with a support team, to the donor hospital. This had many disadvantages. The recognition of the protective effects of hypothermia, producing a 1.5-2 fold reduction in enzyme activity for each 10°C reduction in temperature, and the advent of electrolyte and later citrate-based preservative solutions allowed ischaemic periods of approximately eight hours for livers and even longer (30 hours) for kidneys (Marshall 1984; Pegg 1986). The advantages of longer preservation times have become apparent:
more distant organ procurement, less wastage and better sharing of organs; more time for tissue matching (for other organs), and the opportunity to change the practice of liver transplantation into a semielective, daytime procedure. However certain problems of storage have been identified and are shown in Table 2.8.

Although the preservative solutions described above overcame some of these problems they were not satisfactory and Belzer and Southard (1988), in Wisconsin, set out to design a solution that could be used for all organs for a prolonged period. The University of Wisconsin preservative solution uses lactobionate (to which, unlike dextrose, hepatic cells are impermeable) to prevent cell swelling and the colloid hydroxyethyl starch to increase colloid osmotic pressure. Phosphate is used to buffer any acidosis and adenosine to provide a precursor for ATP resynthesis during reperfusion. Allopurinol is included to inhibit xanthine oxidase and the production of free radicals. Similarly glutathione, which is depleted during ischaemia, is also included to enable the reduction of cytotoxic substances. Experimentally the solution has been shown to be effective in the isolated rabbit liver (Jamieson et al 1988a) and in hepatic transplantation in dogs after 24-48 hours cold storage (Jamieson et al 1988b).
<table>
<thead>
<tr>
<th>Effect of storage</th>
<th>Cause</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell swelling</td>
<td>Solution effect</td>
<td>Increase colloid osmotic pressure</td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td></td>
</tr>
<tr>
<td>Intracellular acidosis</td>
<td>Lactic acid accumulation</td>
<td>Effective buffering</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce glucose content</td>
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<td>Reperfusion injury</td>
<td>Oxygen radicals</td>
<td>Antioxidants</td>
</tr>
<tr>
<td>ATP depletion</td>
<td>Substrate depletion</td>
<td>ATP precursors</td>
</tr>
</tbody>
</table>

Table 2.8: Problems of hypothermic storage of organs for transplantation.
In humans it has been used in over 60 adults with times of up to 17 hours (Jamieson 1989)

**Ventilatory Support**

Continued artificial ventilation is necessary in the organ donor. The ventilator should be adjusted to give a PaCO\(_2\) of 5.3-5.6 kPa and added oxygen given to maintain PaO\(_2\) greater than 10 kPa. Oxygenation may be a problem if aspiration of stomach contents, acute lung injury, neurogenic pulmonary oedema or traumatic damage have occurred; arterial blood gases should be measured frequently. Positive end expiratory pressure (PEEP) should not be used unless oxygenation is not responsive to increases in inspired oxygen concentration. PEEP increases mean intrathoracic pressure, leading to decreases in thoracic venous return, with a consequent decrease in cardiac output and hepatic blood flow (Matschak, Pinsky and Rogers 1987). PEEP should therefore be avoided in the presence of haemodynamic instability and when not indicated specifically to improve PaO\(_2\). Carbon dioxide production is low in the absence of cerebral blood flow, sympathetic drive and muscle tone (Ropper, Kennedy and Russel 1981; Bruce 1986). Low minute volumes or the addition of a dead space to the ventilator circuit may be necessary to maintain normocapnia.
Reflex movements, particularly in the limbs, may occur following stimuli in the presence of brain death. The intact lower spinal cord retains certain spinal reflexes which may give rise to muscle spasms and twitches on stimulation. Superficial reflexes are more common than deep muscle reflexes (Ivan 1973). No reflexes occur in the distribution of the cranial nerves. Anxieties may arise as to the validity of brain stem death criteria, unless these changes are anticipated and understood by attending staff. True decerebrate or decorticate posturing implies intact pathways within the brain and is not seen in brain stem death. Tachycardia and hypertension may also occur after surgical incision. The neuronal pathways for these haemodynamic responses are not clear but may reflect a spinal vasoconstrictor response or a humoral mechanism such as adrenal medullary stimulation by a spinal reflex (Wetzel et al 1985).

Tubocurarine is often recommended for abolishing muscle movement but usually causes a decrease in blood pressure due to histamine release and ganglionic blockade. More cardiostable muscle relaxants, such as pancuronium or vecuronium, are a better choice, given the high incidence of hypotension in donors.
The question of the use of analgesic and anaesthetic agents is difficult. Their use depresses the possibly harmful tachycardia and hypertension related to surgical incision; otherwise their use is illogical in a brain stem dead donor. Nevertheless some experienced anaesthetists add volatile anaesthetic agents, in anaesthetic concentrations, to the inspired gases. This practice overcomes some of the objections to organ donation expressed by some clinicians but others would regard this as an illogical position (D. Hill personal communication). Most anaesthetists continue to use nitrous oxide as a carrier gas to avoid the administration of 100% oxygen from anaesthetic machines without a supply of compressed air.

Exact operative details differ between centres and the procedure described is that used at this centre (Rolles 1986). If all transplantable organs are to be removed the chest and abdomen are opened with a long midline incision from the jugular notch to the symphysis pubis. After a thorough inspection to exclude unsuspected disease all organs are dissected out until attached only by their vascular pedicles. This dissection may take up to three hours, the most frequent delay being due to the presence of accessory vessels. The liver is dissected first followed by kidneys and pancreas.

When dissection is completed heparin is given
intravenously to avoid coagulation around perfusion cannulae (15,000 units in an adult). Cannulae are then placed in the lower abdominal aorta, the inferior vena cava, and the portal vein in preparation for cold perfusion of the abdominal organs. The heart is perfused first with cold cardioplegic solution via a cannula in the aorta and fluid is vented by incising the superior pulmonary vein. Artificial ventilation is then discontinued. The liver is then perfused with ice-cold Ringer’s lactate followed by 4.5% albumin solution. The kidneys are perfused with ice-cold Marshall’s hypertonic citrate solution.

After cold perfusion the organs are removed, put in sterile bags, packed in ice and transported to the recipient. Kidneys may be stored for up to 48 hours (although organ survival after 72-96 hours has been documented), livers up to ten hours, and heart and heart/lungs for 4 hours using these techniques. However, recent advances in preservation fluids may allow longer times in the future. Successful organ retrieval requires close co-operation between the different surgical teams from different centres. Efforts are being made in some areas to organise and train one surgical team to remove all organs rather than different teams each removing one organ.

Losses of fluids by bleeding and evaporation from an
open abdomen and chest during the dissection phase are significant. Blood transfusion may be required during this dissection phase and blood should be crossmatched in anticipation.

Hypothermia may be a problem in the operating theatre when the donor has an open chest and abdomen. Open body cavities give rise to large heat losses from evaporation and radiation. Heat losses should be minimised by a warm theatre, warming all infused fluids, using heated humidifiers on ventilator circuits and using warming blankets beneath the donor.
DIFFICULTIES PERFORMING AND INTERPRETING RESEARCH IN PATIENTS UNDERGOING LIVER TRANSPLANTATION

An increasing amount of research is being performed on patients before, during and after liver transplantation. This is a reflection of the increasing survival of such patients, the rapid advances made by the pharmaceutical industry, who are producing more and better drugs (and the development of more specific and sensitive assays for their measurement), and a more questioning attitude amongst those caring for these patients. Furthermore, Iber (1987) has said that it is more ethical to perform a trial than to use treatments of unproven value. There are many treatments used in the care of these patients that are unproven and that may be of benefit, not only to this group, but also to other critically patients, and there is an obligation to evaluate them.

The complexity of the treatment, the unfamiliarity of the environment, and the fact that some patients have deranged levels of consciousness, and are thus unable to give their own consent or express any concern) means that the potential for abuse during research in patients undergoing liver transplantation is greater than for almost any other group of patients. To protect subjects participating in biomedical research, the Nuremberg code
was enunciated and updated in 1964 with the Declaration of Helsinki. This was subsequently revised in 1975 and 1983. The important principle of all of these codes was summarised by Pope Pius XII who stated that "Science is not the highest value to which all other orders of value . . . should be subordinated". In other words, no physician has the right to risk an injury to one person for the benefit of others. To protect patients all studies presented in this thesis were reviewed and granted approval by the District Ethical Committee.

Informed consent is considered to be an essential prerequisite to most trials in humans. Iber (1987) has described informed consent as "the process by which the patient and research staff come to a common understanding about what the uncertainties might be". In the elective studies described in this thesis, informed consent can be obtained preoperatively, before the patient receives any sedative drugs as premedication. Once premedicated the effects of drugs and the underlying illness mean that it is rarely possible subsequently to obtain consent in this group of patients until after they have left intensive care. Under British law consent can only be granted by the patient or someone legally authorised to do so (such as a guardian or when a patient is being compulsorily treated under the Mental Health Act). It is unusual for legal steps to be taken to grant authority to another person when a person
undergoes liver transplantation. Permission to perform a postoperative study may therefore be sought from relatives; however, even the next of kin can only give assent to a study which in British law has no value.

The amount of information which can be given to the patient or their relatives does vary. At the start of a trial there may be many uncertainties and complicated research, in itself, will carry a risk of further morbidity. Certainly the known risks are explained to the patient or their relatives and included in a written information sheet for them to take away and read when they are able. Some patients and relatives may be so anxious that they are unable to cope with the additional stress of decision about participation in a trial. Others may not want to know the hazards while some will ask very searching questions. In all studies time has been devoted to a discussion about the trial with the patient or relatives so that the appropriate amount of information is given. If after this any doubts remain about the patient participating in a trial then they have not been included.

A significant proportion of liver transplant patients come from outside the United Kingdom and do not speak English. In such patients consent has been obtained with the help of an interpreter. Additional time for explanations to these patients has to be
allowed for translation of both verbal and written information to patients.

Permission for participation may be forthcoming for a variety of reasons. There is usually a genuine desire for patients or relatives not only to help themselves or their relative but also to further knowledge and benefit other patients. Occasionally it may be given because of fears that failing to please the doctor by refusing permission will result in adverse treatment. Conversely, some may feel that better care may be forthcoming because of agreement to participate. It has been stressed to patients or relatives that they are able to refuse without jeopardizing the quality of care the patient receives. To achieve this attempts have been made, wherever possible, to separate the research team from those more directly involved in the patient’s care. Finally, as the number of trials increase, patients and relatives may feel unintentional pressure during discussions in the day room by other patients and relatives who have already consented to trials. If the decision to participate in a trial is made then it has usually been obtained in writing and witnessed by a member of staff who is not part of the trial group.

Pharmaceutical companies have become increasingly involved in this area of research and have supported parts of
the research in this thesis. Although all the protocols have been designed by me the company will often prepare protocols to their own format. Contained within the protocol there may be a paragraph relating to ownership of data. Most companies will ask for sight of a paper before submission to comment upon. Regrettably some statements have been included in some studies in this thesis that I feel are both immoral and unethical; an example of which is:

"All data obtained in this study, in whatever form, (other than specific items relating to the well being or treatment of individual patients) is the property of the company and will not be disclosed to any third party without the company’s written consent."

I feel that the data generated in a trial are the patient’s property and that there is an obligation to the patient to ensure proper scientific presentation. Regrettably, some pharmaceutical companies have expressed a different view, withholding permission for publication.

These moral and ethical difficulties have not proved insurmountable. I have been greatly helped with these matters by discussion of these difficulties with my medical and nursing colleagues, at departmental meetings and with the ethics committee, which I believe is the best way of protecting the patient and ensuring that the best
possible research is done in difficult circumstances.

INTERPRETING PLASMA CONCENTRATIONS OF DRUGS

The measurement of plasma concentrations of analgesic and sedative drugs might be expected to improve the therapeutic accuracy of drug prescriptions. Regrettably this is not always the case. For example, it has been suggested that pethidine has a predictable plasma concentration/effect curve. Austin and his colleagues (1980) correlated plasma concentrations of pethidine and pain relief in nine patients after intra-abdominal or joint surgery on 95 occasions. They demonstrated only a small difference (50 ng/ml) between the mean plasma concentration at which severe pain was experienced (410 mg/ml) and the mean minimum plasma concentration of pethidine at which pain was relieved (460 mg/ml). However, interpatient variability in pain relief at these concentrations was large and in many cases effective analgesia was not obtained within this range. When Bond, Hailey and Lader (1977) studied 20 anxious patients who were treated with three benzodiazepines, barbiturates or placebo, only one of the benzodiazepines (medazepam) demonstrated any sort of relationship between plasma concentration and effect. No significant relationship could be found between plasma concentration of the remaining treatments and physiological effect.

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When the results of studies are interpreted the method of drug analysis and the specificity of the assay must be known, as metabolites may interfere with the assay. This is particularly well illustrated by the various methods of analysis used to determine concentrations of morphine in the blood. The early radioimmunoassay method described by Moore and his colleagues (1984a) cross-reacted with the metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), both initially supposed to be inactive. Subsequently M6G was shown to be highly active in man and much of the earlier work using this assay proved to be misleading (Chapter 11). This is well illustrated in a study by Ball and her colleagues (1985) which attempted to address morphine elimination by the kidney. Similarly Rigg (1978) showed a lack of correlation between plasma concentrations of morphine and its ventilatory depressant effects in a study which also used a radioimmunoassay analytical method which cross-reacted with the metabolites of morphine. When specific assays are available the metabolites should also be measured as their importance as pharmacologically active compounds are increasingly being recognised.

With refinements in assay methods there is an increasing awareness of pharmacogenetic abnormalities which may affect 6-10% of the normal population. This may result in failure of treatment or excessive sensitivity to the
medication. It is also well recognised that there may be variations not just between patient groups but also between patients in the same group. Less well recognised is the change in pharmacokinetics and pharmacodynamics that may occur in an individual patient as their condition improves or deteriorates (Chapters 8 and 12).

In addition to the difficulties described above, pharmacokinetic results based on sampling of easily accessible body fluids (blood and urine) should be interpreted with caution since they may not reflect concentrations or activity at receptor sites. Schenker (1970) hypothesised that the brain of a patient with liver disease is more sensitive to a variety of stimuli than the normal brain. This may be the result of an increase in the number of GABA receptors (Ferenci et al 1984), to which several drugs bind. Bakti and his colleagues (1987) used a variety of psychometric tests to compare the effects of triazolam on patients with cirrhosis and normal volunteers at a time when they had similar plasma concentrations. He found the cirrhotic group had a significantly greater impairment than did the control group. Since plasma concentrations were similar this could only be due to an alteration in receptor sensitivity, numbers or pharmacokinetics. How long these changes take to recover after liver transplantation is unknown.
Alteration of the receptors, resulting in drug tolerance, may also alter the response to the specified plasma concentration of the drug. A clear example of acute drug tolerance was demonstrated by Greenblatt and his colleagues (1978) in patients after a diazepam overdose. Plasma concentrations must also bear a constant relationship to the concentration of drug or its active metabolite at the receptor. An example of how benzodiazepines can have low plasma concentrations yet still have high activity at the receptors has been demonstrated using flumazenil (Bodenham et al 1988).

In this patient midazolam had been administered as part of an intensive care sedation regimen. After discontinuation the patient remained sedated and plasma concentrations of midazolam and its principal metabolite α-hydroxymidazolam were measured. Both of these were low but despite this, when flumazenil was administered the patient rapidly recovered consciousness. A further example of this, occurring with morphine, in patients after liver transplantation is shown in Chapter 9.

Application of pharmacokinetic analysis to predict the effects of drugs has proved to be reliable and accurate for only a few drugs. Even in these drugs the value of therapeutic drug monitoring has been questioned (McInnes 1989), although it may prove useful in diagnosing toxicity or the reason for therapeutic failure (Watson and Thomson 1989). Despite the attractions of drug
concentration monitoring the difficulties associated with its use have resulted in the often less satisfactory measurement of pharmacodynamic variables being adopted in clinical practice. Pharmacodynamic tests must be both sensitive and specific for the drug in question. Whilst this may be straightforward for some drugs, such as inotropes, it has been difficult to evolve such measures for other drugs such as the sedative and analgesic drugs.
CHAPTER 4.

SURGERY AND ANAESTHESIA

To understand some of the subsequent parts of this thesis it is necessary to describe the surgical procedure and the accompanying anaesthetic technique. The operation is described first, so that the nomenclature of the various phases is established. The descriptions will concentrate primarily on the techniques used in Addenbrooke’s Hospital as these are the ones used during the studies detailed in this thesis.

ASSESSMENT OF THE RECIPIENT

The recipient is assessed by a multidisciplinary team consisting of a hepatologist, a surgeon, an anaesthetist (who is also an intensive care consultant) and a sister, also from the intensive care unit. The purpose of this assessment is to make sure that the potential recipient fulfils the medical criteria for transplantation and is psychologically prepared to undergo this major operation. Once the patient has been accepted onto the transplant list they must live within 6 hours travelling time of the hospital so that when a liver becomes available they can be called from home to the hospital. With the development of air transport and fast road
travel this can now be anywhere within the United Kingdom, although in the earlier part of the programme this posed considerable logistic problems for patients who lived a long distance away.

Details of previous surgery are obtained and the patency of the portal vein assessed to anticipate difficulties with surgery. The coagulation status of the patient can also be measured so that a baseline value can be established. Should transplantation occur in the near future the results of these tests can guide appropriate replacement therapy in the immediate preoperative period.

The opportunity is also taken to assess pulmonary function. Lung function tests commonly demonstrate a restrictive defect, usually due to ascites splinting the diaphragm and spreading the lower ribs. A preoperative chest X-ray may demonstrate the presence and size of a pleural effusion. Pulmonary oedema, often due to the low plasma albumin and oncotic pressure, may also be demonstrated. Liver disease is commonly accompanied by a poorly understood increase in pulmonary arterio-venous shunting of blood; some patients may even present with central cyanosis and clubbing as the first sign of their liver disease. Arterial blood gases (ABGs) are routinely performed, with the patient breathing room air, to measure the degree of hypoxaemia.
This provides additional information about the acid/base status of the patient. Metabolic acidosis is a common feature in the more seriously ill patient, usually because the patient has significantly impaired renal function, the mechanism of which is discussed in Chapter 15.

Anaemia frequently accompanies severe liver disease. It may be macrocytic in nature and due to the liver disease or more commonly a microcytic, hypochromic anaemia usually due to variceal bleeding. It is of note that Borland, Roule and Cook (1985) found that 13 of 68 paediatric patients presenting for transplantation were anaemic (Hb <10g/l). The nutritional state of the patient requires close attention. Many of the patients are cachectic and preoperative nutrition, where appropriate, can be of great benefit in diminishing the effects of muscle wasting that occurs after liver transplantation. Any sepsis, particularly oral sepsis in adults and recurring sepsis of the ears and tonsils in children can be dealt with in the intervening time to transplantation. Technical difficulties associated with the anaesthetic procedure, especially difficulties with tracheal intubation, arterial and venous access can also be identified at this time.

Borland and Martin (1987) have shown that in unpremedicated patients immediately before liver
transplantation the cardiac output is markedly increased along with a decrease in systemic vascular resistance. A low oxygen consumption occurs, despite an increased oxygen delivery, indicating the presence of peripheral, as well as pulmonary, arterio-venous shunts. The low oxygen consumption in the presence of a high oxygen delivery may indicate poor organ perfusion. Because of the additional physiological stresses placed upon the cardiovascular system during and after the operation, patients with severe ischaemic heart disease are excluded from the transplant programme. The assessment of ischaemic heart disease is difficult and the value of multiple gated blood pool (MUGA) scanning as a predictor of perioperative problems is being assessed by Dr J Klinck in this department. Its positive predictive power appears superior to clinical electrocardiograph evaluation, although significant cardiovascular instability, which had not been predicted, still occurred in many cases. This may have resulted from factors not related to myocardial disease. Because of the high incidence of occult ischaemic heart disease in the British population it is uncommon to transplant patients above the age of 60 years.

The opportunity can also be taken by the patients to visit the intensive care unit so that when they recover consciousness postoperatively they are not in an unfamiliar environment.
The technique at this centre has been well described by Calne (1983, 1987a, 1988). Before the operation starts the surgeon satisfies himself that the donor liver has arrived and is suitable for transplantation into the recipient. The following operation is divided into three phases: the preanhepatic phase or dissection phase, when the liver is skeletonised on to its vascular pedicles; the anhepatic period, starting when the vascular pedicles are clamped and followed by removal of the liver and the anastomosis of the donor to the recipient vessels; and finally the postanhepatic phase, with the anastomosis of remaining vessels and bile duct.

Preanhepatic or Dissection Phase

The abdomen and, in case elective or emergency bypass should be necessary, the right groin are prepared for surgery. The abdomen is then opened by a wide bilateral subcostal incision with an upward extension to the xiphoid process. The chest is not opened. The liver is then skeletonised on to its vascular pedicles. Bleeding during this period can be profuse, particularly if the patient has chronic liver disease with portal hypertension and portosystemic shunting. The source of bleeding is usually vessels in the skin edges or the peritoneum. Meticulous haemostasis is necessary during this period but even so a large blood loss can
occur. Bleeding will be exacerbated if there is a pre-existing coagulopathy. It is important that the small and large bowel are properly attended to during this period. Should they be left hanging over the skin edge then they will become congested and dilated, producing difficulties with abdominal closure.

Various steps can be identified during the preanhepatic phase. The infrahepatic inferior vena cava (IVC) is first isolated and a tape placed around it, above the right renal vein. At this time the IVC is temporarily clamped to see if significant haemodynamic disturbances occur. The decrease in venous return to the heart, caused by occluding the inferior vena cava, may produce profound hypotension. This will usually respond to an increase in intravascular volume. If this manoeuvre does not restore blood pressure then veno-venous or veno-arterial bypass may be necessary. Should bypass be necessary, it is usual to start it at this time rather than to wait until difficulties have arisen later in the operation. The left triangular, falciform and coronary ligaments are next divided. This enables the liver to be mobilised and the hepatic veins, where they enter the inferior IVC, to be identified but not dissected out. Following this step the liver is separated from the diaphragm. If the patient has had long-standing liver disease there may be numerous adhesions between the
liver and the diaphragm which when divided result in profuse bleeding. Despite great care the diaphragm may also be torn.

The common hepatic and cystic duct are ligated and divided. The junction between the two is made into a funnel-shaped opening into the common bile duct for later anastomosis to the donor’s gall bladder. The two branches of the hepatic artery are then divided and this is followed shortly thereafter by the division of the infrahepatic IVC. The next vessel to be divided is the portal vein and this is then followed by division of the suprahepatic IVC.

The exact order of the above steps will vary slightly from patient to patient depending on the presence or absence of adhesions from previous surgery or the disease process. The anhepatic period starts when the blood no longer flows through the liver.

**Anhepatic Period**

Once all of the vessels have been clamped and divided the diseased liver can be removed. At this time haemostasis, particularly of the diaphragm, can be secured. The new liver is put into the place vacated by the diseased liver and the suprahepatic IVC anastomosis completed. The portal vein of the recipient and donor are aligned and anastomosed. Just before completion of
the suture line the liver is flushed to remove any air and preservative fluid in the large venous sinuses. The preservative solution has a high concentration of potassium and will also contain toxic substances released from the liver during the period of transport. Innes (1989) has measured the potassium content and changes in the acid/base status of effluent blood from donor livers, without prior flushing. He demonstrated a mean potassium concentration of 31.2 (range 13.6-65.8) mmol/l and an average base excess of -16.3 mmol/l (range -9.7 to -24.0 mmol/l) in the effluent. These grossly abnormal results may reflect the composition of the preservative fluid which is normally removed by flushing. Even with flushing, the remaining preservative fluid and old blood may increase the plasma potassium by up to 6 mmol/l above the starting value and produce cardiac arrhythmias. Human albumin solution has been used to flush the liver but since most of the solution is subsequently aspirated and wasted it was felt to be an unnecessary expense in the operation. In its place a modified gelatin solution has been substituted. Originally Haemaccel and later Gelofusine were used, the former having a potassium content (5.10 mmol/l) approximately 13 times the latter (<0.4 mmol/l). Although this difference is small some of this fluid will get to the heart and it was felt prudent to use the solution with the lowest potassium content. After flushing, the portal vein anastomosis is completed and
the portal vein clamp removed. With the suprahepatic clamp still in place the infrahepatic IVC clamp is gradually released and about 100 ml of blood let out through the infrahepatic part of the IVC. The portal vein and suprahepatic IVC clamps are removed. At this point blood again flows through the liver and the anhepatic period is ended. The infrahepatic IVC anastomosis is completed and this clamp is then removed, allowing blood to flow from the lower half of the body back into the circulation.

An alternative method of revascularisation is sometimes used. The suprahepatic IVC anastomosis is still completed first but this is followed by the infrahepatic IVC anastomosis. When these 2 anastomoses are complete, the IVC clamps are removed and blood is allowed to flow from the lower half of the body, restoring venous return and cardiac output. Following this the portal vein anastomosis is completed and the liver reperfused. This method may avoid the stress of revascularisation in the presence of a diminished venous return.

The anhepatic period lasts approximately 40-60 minutes. It is of interest that the Hannover group is now undertaking ex situ removal of neoplasms, necessitating an anhepatic period of approximately 9 hours.
Post Anhepatic Phase

Once anastomosis of the major veins has taken place the hepatic arterial anastomosis is completed. Hepatic arterial blood flow is measured following revascularisation, using an electromagnetic flow probe around the hepatic artery. A normal hepatic arterial blood flow in adult patients at this stage is in the range 200-400 ml/min. If the flow is below this level it is usually due to spasm of the artery and papaverine may be used to reverse this. In some patients hepatic arterial flow may be markedly increased, at times reaching 1 l/min. The mechanism behind this high hepatic arterial blood flow is not known but may be due to a denervated hepatic artery exposed to the effects of surgery, anaesthesia and exogenous dopaminergic stimulation.

The fundus of the gall bladder is anastomosed to the funnel previously formed from the junction of the common hepatic and cystic duct. A T-tube is inserted to allow bile to drain externally. If the donor did not have a gall bladder then duct-to—duct anastomosis can be performed. In some instances a Roux-en-Y choledochojejunostomy may be performed. To stabilise the new liver the ligamentum teres is anastomosed to the peritoneum.

Once haemostasis is achieved the abdomen is closed and
The patient taken to the intensive care unit.

**The Operation in Children**

The operative technique is similar to that in adults. Difficulties arise because of the small size, particularly of the hepatic arterial anastomosis which is prone to thrombosis. Out of 84 children transplanted at this centre, 27 have suffered an ischaemic insult to their transplanted liver. Eleven children have required retransplantation for this complication and two are awaiting a suitable donor (1989). Despite retransplantation in those for whom a donor liver became available, 16 of the 27 have died.

The difficulties in matching the size of the donor liver to the recipient have been overcome to some extent by using the technique of liver reduction described by Bismuth and Houssain (1985). An adult-sized liver is reduced in size on the operating bench by removing a lobe. The use of a rapidly polymerising gelatin-resorcinol-formaldehyde glue on the cut surface of the liver has overcome the difficulty of postoperative bleeding which used to accompany this procedure. This technique has enabled livers from adult donors to be transplanted into children whose condition is deteriorating such that further delay waiting for a donor liver matched for size is likely to result in the
child's death. The recipient IVC can be anastomosed to the donor liver above and below the liver in the usual way, although it may need to be plicated in size to match the size of the recipient. The right hepatic artery, portal vein and cystic duct of the donor liver are ligated, and the remainder of each of these trunks used for the anastomosis.

Partial Cardiopulmonary Bypass

Early experimental transplantation in dogs was made difficult by the animals being unable to tolerate the anhepatic period. Death would occur 20-30 minutes after the IVC was cross-clamped. To overcome this the portal vein was anastomosed to the IVC and a passive shunt made from the IVC to the internal jugular vein. This overcame the problems in dogs, but when it was tried in humans the results were unsatisfactory; in particular, thromboembolism resulted in the death of some patients. Following this it became apparent that humans could tolerate a sufficiently long period of cross-clamping of the IVC to allow transplantation to proceed in the majority of patients (Shaw 1986). Some patients, however, still had major haemodynamic instability during this period. Partial cardiopulmonary bypass was used in these patients to overcome these difficulties. The initial problems with the technique centred principally around the development of a bleeding diathesis. Heparin
was used as an anticoagulant, and although it could be reversed by protamine this was not invariably so. The advent of a centrifugal pump, which did not need anticoagulation, and heparin bonded tubing, in combination with a high blood flow (with most centres aiming for approximately 1 l/min as the minimum), overcame this difficulty in the majority of patients. At this centre, epoprostenol, which is thought to be superior to heparin, is used in a low dose (10 μg/kg/min) as an anticoagulant. Epoprostenol acts as an anticoagulant by decreasing platelet adhesion; its effects end approximately 2-3 minutes after discontinuation of the infusion. The low dose is only sufficient to anticoagulate the extracorporeal circulation and is not sufficient to anticoagulate the patient (Smith 1987).

Not all patients suffer significant haemodynamic deterioration during the period of IVC cross-clamping. This variation may reflect the difference between chronic disease, in which there is time for adequate collateral circulation to develop and thus venous drainage, even with the IVC cross-clamped, continues, compared with acute disease when these collaterals may not develop. Children appear to tolerate cross-clamping better than adults. Mathey and his colleagues (1989) have demonstrated that this is because paediatric patients are able to compensate for the decrease in
cardiac output by increasing their systemic vascular resistance (SVR) to a greater extent than adults and therefore maintain their blood pressure.

Some centres use femoral vein to femoral artery bypass in a similar way to standard cardiopulmonary bypass procedure (Smith 1987). However, other centres prefer femoral vein to another large vein bypass, claiming better results (Calne et al 1984). The different merits of each method require clarification in the future.

Despite the widespread use of these techniques, with some centres routinely employing veno-venous or veno-arterial bypass during every operation, there is no scientific evidence to support the use of bypass. Advantages and disadvantages resulting from its use are shown in Table 4.1. At this centre we have not found the advantages to outweigh the disadvantages in the majority of cases. However, since it is difficult to predict which patient will bleed excessively, a perfusionist is available whenever surgery is performed on a patient with chronic cirrhosis with severe portal hypertension. It is usually apparent soon after opening the peritoneal cavity that excessive bleeding is likely to occur and at that time bypass is instituted. Similarly, bypass may also be started if haemodynamic instability occurs when the trial IVC clamping is made.
### Advantages:
- Decreased blood loss
- Decreased intestinal congestion and swelling
- Improved renal function
- Improved cardiovascular stability

### Disadvantages:
- Increased complexity
- Loss of platelets in the extracorporeal circuit
- Loss of heat
- Additional wounds
- Thromboembolism
- Air embolism
- Right heart strain (veno-venous)

**Table 4.1:** The advantages and disadvantages of using bypass during liver transplantation.
When bypass is necessary a veno-arterial or veno-venous system is used and it is possible, with a Y-connection, to cannulate the portal vein and decompress the portal system.

**ANAESTHESIA**

The operation of liver transplantation provides one of the greatest challenges for anaesthetists. Hypnosis, analgesia and muscle relaxation, the conventional triad of anaesthetic practice, are but a small part. Complex metabolic changes occur during the anhepatic period and these can be compounded by sudden torrential blood loss. The method of anaesthesia at this centre has been well described in several publications (Carmichael, Lindop and Farman 1985; Lindop and Farman 1987; Carmichael and Lindop 1988).

The usual anaesthetic team consists of a consultant and senior registrar, a clinical measurements technician and a senior operating department assistant. Porters are necessary to fetch blood and deliver specimens to the laboratories. Full biochemical and haematological laboratory support is essential during the procedure. Anaesthesia for children presents other problems that will be discussed as the description proceeds.

Wherever possible the patient is visited immediately
preoperatively, on the ward, by the anaesthetist. He will have seen the anaesthetic and intensive care assessment from the previous admission. At this time any quickly correctable abnormalities such as coagulation deficiencies, hypokalaemia and anaemia are dealt with. Unnecessary delay at this particular period is usually unacceptable since the donor organ is being retrieved at the same time and only a finite period of cold ischaemia is possible.

Premedication
Unless the patient is encephalopathic some form of premedication is usually desirable. In adults this is usually a short acting benzodiazepine such as oral temazepam with some anaesthetists adding oral atropine. Intramuscular premedication is not usually prescribed because it offers little advantage in these circumstances over oral premedication. Furthermore the patient’s pre-existing coagulopathy may predispose them to haematoma formation from an injection. In some instances and for some studies, particularly those involving benzodiazepines, papaveretum with or without scopolamine was used. For children trimeprazine syrup is administered orally.

Induction of Anaesthesia
For the majority of patients thiopentone 2-5 mg/kg is used to induce anaesthesia. Should a patient present as
an emergency with an unstable cardiovascular system, etomidate or ketamine are used. If the anaesthetist is sure the patient has an empty stomach then neuromuscular blockade to facilitate tracheal intubation is usually achieved using a bolus dose of atracurium. In an emergency or when the patient has a full stomach a rapid sequence induction technique utilising preoxygenation, cricoid pressure and suxamethonium (1-1.5 mg/kg) is used. In some centres it is usual practice to administer cyclosporin A orally in fruit juice in the immediate preoperative period. In such instances all patients presenting for anaesthesia will have full stomachs necessitating appropriate precautions. McArdle (1940) demonstrated that the plasma concentration of pseudocholinesterase is reduced in patients with liver disease and others have shown that its concentration changed depending on improvement or deterioration of liver function (Hunt and Lehmann 1960; Evans and Lehmann 1971). However, any resulting prolonged duration of suxamethonium is not important during liver transplantation as the patient is artificially ventilated both during the procedure and postoperatively. Furthermore, the large blood transfusion which usually accompanies this operation will dilute any suxamethonium remaining in the plasma compartment and the fresh frozen plasma (FFP), given routinely to correct coagulopathies, will provide pseudocholinesterase to break down any remaining in the
plasma and at the neuromuscular junction.

Maintenance of Anaesthesia

Anaesthesia is maintained with a narcotic (usually fentanyl) and a volatile agent, currently isoflurane. Minimal metabolism of isoflurane in humans, with only 0.2% being broken down compared with halothane’s 20%, is considered a major advantage. In addition, it has been shown in the guinea-pig that halothane decreases oxygen delivery to a greater extent than isoflurane, for equal decreases in mean arterial pressure (MAP) (Hursh, Gelman and Bradley 1987). Similarly, in pigs Noldge and his colleagues (1989) have shown that oxygen availability to the liver decreases less with isoflurane (14%) than with enflurane (51%) or halothane (37%). Furthermore they also demonstrated that liver PO$_2$ also decreases less with isoflurane than with enflurane and that isoflurane increases hepatic arterial blood flow by 42% compared with a decrease with both enflurane (37%) and halothane (14%). Other volatile agents that were used, particularly in the early part of the series, include trilene and enflurane.

The use of nitrous oxide for part or all of the procedure is controversial and it is not my practice to use nitrous oxide during liver transplantation. The disadvantages of this agent include:

**Bone Marrow Depression**

Nitrous oxide has been implicated in the production
of megaloblastic haemopoiesis and leukopenia (Skacel et al 1983; Nunn 1987). Furthermore, Amos and his colleagues (1982, 1984) have shown that its use during anaesthesia may increase mortality in critically ill patients. This problem is also discussed in Chapter 5.

Hepatic Blood Flow

In the rat, nitrous oxide has been shown to decrease portal venous blood flow without a compensatory increase in hepatic arterial blood flow (HABF), possibly due to interference with the normal regulatory mechanisms (Seyde, Ellis and Langnecker 1968). Decreases in HABF, whilst of little significance in normal livers, may compromise flow through a recently anastomosed vessel and contribute to thrombosis. In addition hepatic oxygen delivery may also be decreased.

Bowel Distension

Since nitrous oxide is more soluble than nitrogen it will diffuse into air-containing spaces more rapidly than nitrogen can diffuse out, resulting in a two or three fold increase in size (Eiger 1980). Bowel distension will therefore occur from the moment that nitrous oxide is used and can make closure of the abdomen difficult.
Air Embolism

Air may gain access to the circulation from the large transfusion lines, monitoring lines or a bypass system if used. During the operation, if there is a low venous pressure and a large vein (skin vessel or the IVC) is inadvertently opened to atmosphere, air may also enter the circulation by this route. Large volumes of air gaining access to the circulation may completely obstruct blood flow through the heart. Small quantities of air may also gain access to the systemic circulation, via the pulmonary and systemic arterio-venous anastomoses and become lodged in an essential arterial supply such as the cerebral or coronary circulation (Starzl et al 1978). If nitrous oxide is in use during this period the volume of this embolus will rapidly increase and its effects be more disastrous.

During surgery most neuromuscular blocking agents can be used but the use of bolus doses may produce periods of hypotension and inadequate muscle relaxation during the procedure. Farman, Turner and Blanloeil (1986) have described the use of an atracurium infusion during liver transplantation which has now become universally accepted. They also demonstrated only a small reduction in the need for muscle relaxation during the anhepatic period, a reflection of the novel method of breakdown of
atracurium by Hoffmann degradation.

MONITORING DURING ANAESTHESIA AND SURGERY

Since the successful management of the cardiorespiratory system depends upon correctly calibrated and accurate monitoring equipment, the assistance of a technician to maintain and recalibrate the equipment throughout the procedure is essential.

Artificial Ventilation
Continuous monitoring of SaO\textsubscript{2} and E\textsubscript{T}CO\textsubscript{2} provide valuable continuous noninvasive monitoring of the respiratory system. In addition E\textsubscript{T}CO\textsubscript{2} can also give rapid warning of the occurrence of an air embolus. A ventilation failure alarm is used to warn of accidental disconnection of the ventilator, the recognition of which can otherwise easily be delayed if many other events are taking place.

Arterial blood gases are measured intermittently to assess oxygenation, ventilation and acid/base status. They are usually measured at the same time as the biochemical variables described below.

Cardiovascular
A continuous ECG is displayed to enable recognition of arrhythmias and also to look at changes in the height of
T waves so that hyperkalaemia can be rapidly detected.

An arterial line is introduced percutaneously into the left radial artery for pressure recording and blood sampling for both clinical and research purposes. A central venous line is usually introduced through the right internal jugular vein (although at times it may be placed in the right subclavian vein or other sites if there is difficulty). Triple lumen central venous catheters are used to enable separate lumens to be used for the infusion of mannitol and dopamine, the injection of drugs and for monitoring purposes. There is little left- and right- heart disequilibrium during liver transplantation, but changes in pulmonary capillary wedge pressure (PCWP) are slightly more sensitive to hypovolaemia than alterations in right atrial pressure (RAP) (Carmichael, Lindop and Farman 1985). Despite this, pulmonary artery flotation catheters are not routinely used. One of the prerequisites for recipients is the absence of significance ischaemic heart disease. In such circumstances the benefits of pulmonary artery catheterisation are limited, a view held by others when dealing with children (Borland and Martin 1987). In patients in whom pulmonary artery catheterisation is considered unnecessary, it is common practice to insert a pulmonary artery catheter introducer so that if a situation arises where one is necessary it can be introduced rapidly.
Biochemistry

Plasma urea and electrolytes, ABGs, blood glucose and plasma ionised calcium are routinely measured prior to induction, one hour after induction, after the major vessels have been clamped, when the flow through the liver is restored (portal vein to IVC), when all the remaining vascular clamps have been removed and at the end of the procedure. It may be necessary on specific occasions to measure some or all of these values at other times.

Miscellaneous

Renal function is monitored by a Foley catheter inserted into the bladder. Urine flow commonly decreases during the anhepatic period when the IVC is cross-clamped.

Temperature is usually measured with a temperature probe at the midpoint of the oesophagus. Some centres use an oesophageal temperature probe with a stethoscope to permit monitoring of breath sounds. This is particularly useful in children. If a pulmonary artery catheter is being used then pulmonary artery temperature can be measured in place of an oesophageal temperature probe.

Coagulation is monitored in the operating theatre by an in vitro determination of whole blood clotting time using the "Hemochron" System which measures the

SPECIFIC INTRAOPERATIVE PROBLEMS

Major Blood Loss
The average blood loss during an adult operation is 7.7 litres, with a range of 700 ml to 130 litres (Carmichael and Lindop 1988). Preoperatively it is impossible to predict accurately which patients will bleed profusely. Therefore each adult patient is routinely cross-matched for 30 units of blood and each child below the age of six is cross-matched for ten units of blood. All transfused blood is filtered using a 40 micron filter to remove any microaggregates and warmed. Two 12 gauge peripheral venous cannulae are inserted, one into each arm, and used solely for transfusion purposes. A cell saver system (Haemonetics Cell Saver 4) has proved successful in decreasing the amount of banked blood that may be necessary when a large blood loss occurs (Dale et al 1986). More recently we have been using the Haemonetics Rapid Infuser device which has a large reservoir into which cell-saved or banked blood along with FFP can be stored and infused at rates of up to 1.5 l/min. The system also incorporates a heat exchanger with the result that the patient’s temperature does not
fall during massive blood transfusion (Sassano 1986).

Throughout the operation blood loss is estimated by the weighing of swabs and the measurement of blood aspirated into the suction apparatus. However, the value of this is questionable since a considerable amount of blood is spilled on to the floor and surgeons. In cases of torrential blood loss the swab weight and suction loss estimate of blood loss are ignored and the patients are transfused according to their cardiovascular variables.

Heat Loss

Body temperature may fall as a consequence of the administration of large volumes of cold fluids, evaporation of water from the abdominal cavity, and because respiratory gases may not be adequately warmed and humidified. Finally, when the liver (which has been cooled to 4°C) is reperfused, a decrease in core temperature of 1°C occurs.

The decrease in body temperature seen throughout the operation may be minimised by placing the patient on to a warming, ripple mattress and by warming all of the fluids. The use of a heat and moisture exchanger (Shelly, Lloyd and Park 1988) can prevent some of the heat loss from the respiratory tract. In addition, if a heat and moisture exchanging filter is used it will prevent microbiological organisms from gaining access to the
patient from the ventilator circuit.

Coagulation Changes
These have been described by several authors (Owen 1987; Lewis et al 1986; Kang 1986). Coagulation abnormalities may be due to four factors.

Liver Diseases
The pre-existing coagulopathy of severe liver disease consists typically of a decrease in platelet count (due to hypersplenism) and in all coagulation factors except factors I and V (due to a decrease in the liver’s synthetic ability). These deficiencies will result in a prolonged prothrombin time (PT) and kaolin partial thromboplastin time (KPTT). If the coagulopathy is severe it may require correction in the immediate preoperative period with platelets and FFP, in order to facilitate the safe placement of the various monitoring lines and to reduce the bleeding during the initial dissection period.

Intraoperative Changes in Coagulation
Of particular note is the haemostatic abnormality that occurs immediately following revascularisation of the liver. Although this rapidly reverses (usually within one hour), it can result in torrential bleeding at this time, which may in turn
lead to other coagulation abnormalities. Part of the coagulation deficiency during revascularisation may be due to activation of the fibrinolytic system and the judicious use of inhibitors such as epsilon amino kaproic or tranexamic acid may be beneficial. Heparin-like substances have also been described as appearing at this time and protamine can be effective in reversing the coagulopathy. Kang (1986) recommends that the use of any of these agents should be monitored by the thromboelastograph.

Changes in physiological variables
Coagulation may be altered by a number of physiological variables during the procedure. Metabolic acidosis, hypothermia, hypocalcaemia and hypokalaemia all exert an adverse effect on coagulation, which improves when they are corrected.

Replacement Therapy
A further contributor to the coagulopathy seen during the operation is the dilutional effect of replacement therapy. Stored blood does not contain a significant amount of platelets and is low in coagulation factors V and VIII (Gilbertson 1985). Veno-venous or veno-arterial bypass, used during the anhepatic period, will also contribute. The resulting thrombocytopenia usually necessitates...
treatment with platelet concentrate if the platelet count falls below 50 x 10⁹/l.

Citrate Intoxication

Each unit of blood contains approximately 3 g of citrate as anticoagulant. In normal circumstances it is rapidly metabolised by the liver. In an early study Bunker, Bendixen and Murphy (1962) infused sodium citrate into 6 anaesthetised humans and 9 anaesthetised dogs. At plasma concentrations of citrate seen during massive blood transfusion in both dogs and humans (2 - 4 mmol/l), cardiac output and blood pressure decreased by up to 40%. This was a result of myocardial depression caused by the concomitant hypocalcaemia, as citrate binds free calcium, and it was corrected by the administration of calcium chloride. The Birmingham group have studied the effects of blood transfusion on the plasma concentrations of citrate and calcium during liver transplantation. During the dissection phase plasma citrate concentration (normal range 0.08-0.12 mmol/l) increased from the mean preoperative value of 0.09 mmol/l to 1.57 mmol/l as blood was transfused. However, during the anhepatic period citrate metabolism did not occur and plasma citrate concentrations increased further, reaching a maximum of 3.2 mmol/l. When the donor liver was revascularised, and metabolism of citrate again took place, the plasma concentration decreased to 1.17 mmol/l. Ionised calcium
concentrations decreased to 0.68 mmol/l (normal range 1.18-1.29 mmol/l) as citrate concentrations increased (Gray et al 1986). During liver transplantation these changes result in a reduction of myocardial contractility (Bunker, Bendixen and Murphy 1962; Ludbrook and Wynn 1958) with a consequent decrease in cardiac output and hypotension. These adverse effects can be treated either empirically by the administration of calcium chloride if the patient becomes hypotensive and is not hypovolaemic, or on the basis of measured low plasma ionised calcium concentrations (Ickx, Walker, Farman 1987). Although it has been suggested that calcium gluconate is less effective than calcium chloride (owing to the need to metabolise the former) this has not been proven and if equimolar quantities of each are given no difference can be shown (Heining, Band and Linton 1984). However, hypocalcaemia during liver transplantation is routinely treated at this centre with 13.4% calcium chloride (10 ml of which contains 0.913 mmol/ml calcium) rather than calcium gluconate which only contains 0.225 mmol/ml calcium.

Calcium is also an essential part of extrinsic and intrinsic coagulation pathways. A bleeding diathesis associated with hypocalcaemia is uncommon, since cardiac arrest is said to occur before the plasma concentration decreases to a level that affects coagulation (Marquez 1986). Other authors dispute this and have reported
interference with coagulation before cardiac arrest (Kang 1986), although at the level reported (0.5 mmol/l) profound myocardial depression must have occurred.

Citrate is metabolised to bicarbonate and may produce a profound alkalosis postoperatively. Because of this it is usual to leave uncorrected any minor degree of metabolic acidosis occurring towards the end of the anhepatic period. Hypercalcaemia, complicating a hormone secreting tumour of the liver, has been reported (Sealey 1985).

Haemodynamic Changes
These have been described by Carmichael, LindopandFarman (1985). During cross-clamping of the IVC, mean arterial pressure decreases by 24%, PCWP by 42%, CVP by 26% and cardiac output by 48% compared with baseline values. There are compensatory increases in the SVR (66%), pulmonary vascular resistance (PVR) (44%) and heart rate (17%). Following revascularisation, PCWP, CVP, SVR and PVR rapidly return to their baseline values although cardiac output and MAP take some time to return.

First-degree heart block and sinus bradycardia are common immediately after revascularisation and there is often a period of hypotension (Martin et al 1984; Martin 1986; Marquez and Martin 1986). These adverse haemodynamic changes may be due to several factors
including:

- Hyperkalaemia (the potassium being released from the hepatic cells and also from any remaining preservative solution).
- Citrate intoxication.
- Hypovolaemia.
- Air embolus.
- A sudden decrease in the temperature of blood returning to the heart.
- Small molecular weight, toxic substances released from liver cells during storage which are toxic to the cardiovascular system.
- During the anhepatic period the bowel may become congested with blood, interfering with its normal ability to maintain a bacterial barrier between bowel contents and the circulation. When blood flow is restored hyperaemia may occur with toxins being released from the bowel into the systemic circulation.

Martin and his colleagues (1984) studied 23 patients during revascularisation. Eleven of the patients were pretreated with 1 g. of calcium chloride which prevented the decrease in cardiac output but not the hypotension or arrhythmias seen in the untreated patients. In the treated group a significant decrease in SVR must have occurred. Hypotension may occur at other times during
the procedure and may be due to:

- Hypovolaemia
- Low ionised calcium.
- Surgical manipulation (traction on the liver resulting in a decrease in the venous return)
- Vigorous retraction of the xiphoid process resulting in pressure on the inferior pericardium
- Development of arrhythmias.
- Pre-existing disease.

Respiratory Changes

The observation during an orthotopic liver transplant operation that the arterial blood oxygen tension \( (PaO_2) \) remained low despite increasing the inspired oxygen concentration \( (F_{I}O_2) \) until removal of the liver, when a dramatic increase in \( PaO_2 \) was noticed, prompted a review of the anaesthetic records of the twenty liver transplant operations prior to this observation. This suggested an improvement in arterial oxygenation during the anhepatic phase. Forty consecutive patients undergoing liver transplantation were therefore prospectively studied and their alveolar-arterial oxygen difference \( (A-aDO_2) \) was measured at various stages during the procedure.

Continued postoperative bleeding results in intra-abdominal distension, and high pressures may develop when the
abdomen is allowed to tamponade (Chapter 16). This is frequently accompanied by arterial hypoxaemia. Extrapolation from the reverse situation during this study, when there is no cephalad displacement of the right hemidiaphragm (ie minimal abdominal distension), might help to understand the cause of the hypoxaemia observed during abdominal distension.

I was assisted with this study by Dr K R Burchett (Senior Registrar in Anaesthesia, data collection), Mr M F Smith (Senior Technician, data collection) and Dr Pat Altham of the University of Cambridge Department of Pure Mathematics and Mathematical Statistics (statistical advice).

**CHANGES IN ALVEOLAR-ARTERIAL OXYGEN DIFFERENCE DURING ORTHOTOPIC LIVER TRANSPLANTATION**

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**Patients and Methods**
The anaesthetic technique used was at the discretion of the anaesthetist, and consisted of artificial ventilation using either air/oxygen and isoflurane or nitrous oxide/oxygen with isoflurane and/or fentanyl. Neuromuscular blockade was maintained by an infusion of either atracurium or vecuronium.

As part of the routine monitoring of these patients
arterial blood samples were taken and immediately analysed for oxygen (\( \text{PaO}_2 \)) and carbon dioxide (\( \text{PaCO}_2 \)) tensions (Corning 178 pH/blood gas analyser) at the following stages during the procedure: (A) after induction of anaesthesia, and before the start of surgery; (B) during the dissection of the patient’s liver; (C) at the beginning of the anhepatic phase; (D) at the end of the anhepatic phase (after unclamping of the suprahepatic IVC and the hepatic portal vein; (E) after full restoration of inferior vena cava flow, and (F) during abdominal closure. The inspired oxygen concentration (\( F_{\text{I}} \text{O}_2 \)) was measured continuously throughout the operation (Engstrom Eliza Duo \( O_2/CO_2 \) analyser). The values for \( \text{PaO}_2 \) and \( \text{PaCO}_2 \) were corrected for the patient’s core temperature at the time of sampling using a standard nomogram (Kelman and Nunn 1966), and the alveolar oxygen tension was estimated using the formula \( \text{P(A)}_2 = F_{\text{I}} \text{O}_2 - (\text{PaCO}_2/R) + (\text{PaCO}_2.F_{\text{I}} \text{O}_2/(1-R)/R) \) The respiratory quotient, \( R \), was taken to be 0.8, and it was assumed that \( \text{PACO}_2 = \text{PaCO}_2 \).

Changes in blood volume and composition were minimised by utilising invasive haemodynamic monitoring and measurements of packed cell volume at each time point.

Statistical evaluation was performed using Student’s paired t test adjusting for the Bonferroni inequality (Miller 1977). Four comparisons were made (A to B, B to
Results
Complete records were available for 26 female and 13 male patients, with a mean age of 33 (Range 1 to 63) years. The results from these patients are shown in Figure 4.1 and Table 4.2. There was an initial increase in A-aDO\(_2\) during dissection of the patient’s liver (A to B) from [mean (SEM)] 16.0 (1.5) to 19.1 (1.6) kPa. This increase failed to reach statistical significance. During the anhepatic phase there was a decrease in A-aDO\(_2\), which continued to a nadir at D [14.3 (1.6) kPa]. After revascularisation of the donor liver the A-a gradient again increased, and this continued through E [15.1 (1.5) kPa] to abdominal closure at F [19.1 (1.8) kPa]. The difference between B and D, E and F, and that between D and F were all significant at the 1% level. No correlation was found between the changes in A-aDO\(_2\) and the anaesthetic technique used.

Packed cell volume and the amount of fluid transfused at each time point are shown in Table 4.3. Systolic blood pressure is also shown in this table as an indicator of the presence or absence of hypovolaemia for the purposes of this study. PCWP or RAP were also measured, but not recorded. Despite the large volumes transfused there was little change in systolic blood pressure.
<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₁O₂</td>
<td>0.42(0.02)</td>
<td>0.42(0.01)</td>
<td>0.43(0.02)</td>
<td>0.44(0.01)</td>
<td>0.43(0.01)</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>3.9(0.13)</td>
<td>4.0(0.14)</td>
<td>3.8(0.11)</td>
<td>4.8(0.11)</td>
<td>4.5(0.12)</td>
</tr>
<tr>
<td>PaO₂</td>
<td>21.4(1.61)</td>
<td>18.5(1.64)</td>
<td>22.5(1.53)</td>
<td>24.2(1.21)</td>
<td>23.0(1.2)</td>
</tr>
</tbody>
</table>

Table 4.2: Mean (SEM) F₁O₂, PaO₂, PaCO₂ for the 39 patients
A = after induction of anaesthesia; B = during the dissection phase; C = at the beginning of the anhepatic phase; D = at the end of the anhepatic phase; E = after the inferior vena cava is unclamped; F = on completion of the operation
Figure 4.1: Mean (SEM) changes in \( (P_{A02} - P_{O2}) \) during liver transplantation in 39 patients. A = After induction of anaesthesia; B = During the dissection phase; C = At the beginning of the anhepatic phase; D = At the end of the anhepatic phase; E = inferior vena cava anastomosis; F = abdominal closure. Statistically significant differences (\( P < 0.01 \)): *B-D and D-F; †E-F
### Table 4.3: Mean (SEM) packed cell volumes, systolic arterial pressure and volume of fluid transfused.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV (%)</td>
<td>30.9(1.1)</td>
<td>32.1(1.1)</td>
<td>36.6(0.9)</td>
<td>39.0(1.0)</td>
<td>33.8(1.2)</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>111(3.2)</td>
<td>116(3.1)</td>
<td>105(3.0)</td>
<td>106(4.5)</td>
<td>111(4.6)</td>
</tr>
<tr>
<td>Fluid (ml)</td>
<td>226(87)</td>
<td>1420(219)</td>
<td>3345(456)</td>
<td>5339(649)</td>
<td>6278(739)</td>
</tr>
</tbody>
</table>

A = after induction of anaesthesia; B = during the dissection phase; C = at the beginning of the anhepatic phase; D = at the end of the anhepatic phase; E = after the inferior vena cava is unclamped; F = on completion of the operation.
The haematocrit increased during the anhepatic period, owing to the infusion of blood with a high haematocrit from the cell saver system used for autotransfusion (Dale et al 1986).

**Discussion**

The increase in $A-aD_0$ during routine, uncomplicated anaesthesia is a well recognised feature, and is attributed to a 20% decrease in functional residual capacity (FRC) and an increase in ventilation/perfusion (V/Q) mismatch. The reduction in FRC with general anaesthesia occurs whether the patient is artificially ventilated or breathing spontaneously, but increasing the FRC following induction of anaesthesia does not reverse the abnormal gas exchange.

Atelectasis occurs in the dependent parts of the lung; the low compliance of this part and the immobility of the adjacent portion of the diaphragm prevent full expansion of the dependent lung (Jones 1987). The $A-aD_0$ is also increased by a decrease in cardiac output, an increase in $PAO_2$ or a decrease in haemoglobin concentration (Nunn 1977). The increase in $A-aD_0$ seen during the dissection phase and towards the end of the procedure during abdominal closure could be explained by an initial decrease in FRC due to a cranial shift of the diaphragm, leading to atelectasis in the dependent parts of the lungs and consequent increase in V/Q mismatch.
Once the liver has been removed (during the anhepatic phase) this process may be reversed because of the reduction in abdominal contents and surgical retraction, allowing freer movement of the diaphragm. These mechanisms result in an increase in FRC and/or a decrease in atelectasis in the dependent part of the lung which may account for the gradual improvement in the A-aDO₂ gradient. These factors would be reversed once the donor liver was in place, and could explain the subsequent increase in A-aDO₂. The decrease in cardiac output at the beginning of the anhepatic phase as the vena cava is cross-clamped (Carmichael, Lindop and Farman 1985) would be expected to increase the A-aDO₂, but the reduction in oxygen consumption of some 25% seen on removal of the patient’s liver (Svensson et al 1986) may balance this to some extent. If the reduction in oxygen consumption results in an increase in the mixed venous oxygen content, and if there is a significant pulmonary shunt, then there should be an increase in arterial oxygenation (and fall in A-aDO₂) since the oxygen tension in the shunted blood would have risen and would have a smaller effect in reducing the PaO₂. It is, however, more likely that the reduction in cardiac output will result in a decrease in the mixed venous oxygen saturation, albeit less than expected because of the decrease in oxygen consumption. If this is so then presumably the improvement in the A-aDO₂ gradient is due to a marked improvement in the V/Q ratio because of the
freer movement of the diaphragm. It is also possible, though unlikely, that the liver is secreting a vasoactive substance which is affecting the pulmonary vasculature. It would appear that several factors that affect the A-aDO₂ may operate simultaneously. The balance of these factors leads to a decrease in A-aDO₂ during the anhepatic phase, and these factors are reversed with the insertion of the donor liver. When an increase in intra-abdominal pressure occurs, such as when the abdomen is tamponaded with blood, the increase in A-aDO₂ can be expected to be more pronounced.

Biochemical Changes During Liver Transplantation

Glucose

Early reports suggested that hypoglycaemia was common during liver transplantation (Aldrete, Levine and Gingrich 1969). Since this initial description this problem has not been observed by any other author. It is, however, surprising that hypoglycaemia does not occur in view of the lack of hepatic gluconeogenesis. This absence of hepatic gluconeogenesis appears to be compensated for by renal gluconeogenesis (Brobeck 1973), in addition to a decreased peripheral utilisation of glucose, and by the infusion of dextrose contained in blood and other fluids. Plasma glucose consistently increases during liver transplantation in adults and children (Dyer, Blanloeil and Farman 1987). The only
adverse effect of intraoperative hyperglycaemia appears to be polyuria. To start an insulin infusion in these circumstances may represent an unnecessary complication with little benefit.

Potassium
Plasma potassium concentration may change rapidly during hepatic transplantation, with ranges of 2.5-8 mmol/l during the operation being common. The most dramatic increase follows revascularisation, after which plasma potassium rapidly decreases as the liver takes up more potassium. Hypokalaemia is common towards the end of the operation and in the early part of the intensive care, and requires replacement therapy.

Sodium
Hypo- and hypernatraemia may occur in the preoperative period due to the use of diuretics and sodium restriction. Dyer, Blanloeil and Farman (1987) have compared changes in sodium in paediatric patients aged <10 years (Group A) and those >10 years of age (Group B). They demonstrated that the children in Group A had a much greater increase in plasma sodium than those in the older age group. This was attributed to the greater transfusion requirements, principally of blood which contains large quantities of sodium. A summary of their results is shown in Table 4.4.
## Table 4.4: Changes in plasma sodium concentration, transfusion requirements and duration of operation in 31 children undergoing orthotopic liver transplantation.

Group A are children under 10 years and Group B those greater than 10 years of age. After Dyer, Blanloeil and Farman (1987).

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&lt;10 yrs</td>
<td>&gt;10 yrs</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td><strong>Plasma Sodium (mmol/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Start of operation</strong></td>
<td>&lt;135</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>&gt;145</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Finish of operation</strong></td>
<td>&lt;135</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>&gt;145</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Transfusion Requirements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mls/kg [mean (SEM)]</td>
<td>302 &lt;64&gt;</td>
<td>149 &lt;47&gt;</td>
</tr>
<tr>
<td><strong>Duration of Operation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mins [mean (SEM)]</td>
<td>333 &lt;10.6&gt;</td>
<td>383 &lt;28.3&gt;</td>
</tr>
</tbody>
</table>
Similar changes in sodium are seen in adults, particularly those who are very ill and who may be profoundly hyponatraemic. If these patients become acidotic intraoperatively and they receive large quantities of sodium bicarbonate, sudden changes of plasma sodium to normal (or greater than normal) values may occur. This may result in an acute encephalopathy characterised, in the postoperative period, by fits. The encephalopathy does not appear to improve as time progresses.

Duration of Operation

The complex nature of this operation means that it will take a considerable period of time. Ickx, Walker and Farman (1987) reported the following times [mean (SEM)] for each of the different phases of the operation:

- Preanhepatic 148 (57) mins
- Anhepatic 48 (20) mins
- Postanhepatic 88 (32) mins

In 1988 4% of the operations took 2-4 hours, 46% took 4-6 hours, 38% took 6-8 hours, 7% 8-10 hours and a further 7% in excess of 10 hours (M F Smith - personal observation). The significance of these long and demanding operations should not be underestimated. If they occur during the day then they are likely to interfere with routine operating lists and if they occur during the night then the anaesthetic team is usually unfit for safe anaesthetic practice the following day.
CHAPTER 5.

INTENSIVE CARE AFTER LIVER TRANSPLANTATION

There is little that is unique to the intensive care of patients following liver transplantation. However, the frequent admission to the intensive care unit of critically ill patients who have undergone major surgery and the length of their stay (average 6.1 days) has important implications. Since the management of these patients incorporates every aspect of the care of critically ill patients, it has enabled the initiation of new procedures, the rapid development of treatment regimens and the investigation of the patients' altered pathophysiology and their response to pharmacological agents. This has led to a major impact on the management, not only of patients following liver transplantation, but also of other patients admitted to the intensive care unit.

The ICU stay, in uncomplicated patients, may be divided into two phases. The initial phase, covering the first hours following the procedure, is a period of stabilisation and, effectively, a continuation of the intraoperative management, with close cardiorespiratory and biochemical monitoring. The second phase is a period of recovery, dominated by the need for pain relief and resumption of respiratory function. The
latter stage is characterised by important metabolic changes, associated with the return of liver function in a patient who may previously have been in end-stage liver failure. The postoperative period is sometimes marked by the late effects of massive blood replacement. All are factors which can influence the function of the liver, kidneys and other organs.

Ventilation
During transfer from the operating theatre to the intensive care unit, cardiovascular monitoring is continued and ventilation maintained using a volume-controlled fluid logic ventilator that allows air entrainment. This avoids the use of 100% oxygen with its attendant high risk of absorption atelectasis (Park and Johnson 1982; Park et al 1989). Humidification of the inspired gases during transfer is achieved using a heat and moisture exchanger. Because of concerns about microbiological contamination of the ventilator and the subsequent transfer of these organisms to patients, a heat and moisture exchanger combined with a microbiological filter is used (Shelly et al 1986).

On arrival in the intensive care unit the patient is artificially ventilated with a volume-controlled ventilator, although more recently SIMV has been used to allow patient triggering at an early stage. Positive end expiratory pressure of 5 cm water is applied. The
use of PEEP helps maintain arterial oxygenation with a low \( F_1 O_2 \) by preventing the development of areas of atelectasis. The decrease in hepatic blood flow seen when PEEP is used is directly related to the decrease in cardiac output (Winso et al 1986) but this can be overcome by increasing intravascular volume to maintain cardiac output (Matuschak, Pinsky and Rogers 1987). The small decrease in renal function (Berry 1981) that occurs with PEEP of this level does not appear to be clinically significant. The ventilator is adjusted to maintain normocarbia, since both hyperventilation and hypoventilation have deleterious effects on hepatic oxygen consumption and splanchnic blood flow (Epstein et al 1966; Hughes et al 1979; Cooperman et al 1986).

A heat and moisture exchanging filter, identical to the one used on a transport ventilator is used to provide humidification during the initial period of artificial ventilation.

In the uncomplicated patient, weaning from artificial ventilation is now usually accomplished easily within the first 8-12 hours, providing that the patient has satisfactory gas exchange, good renal function and no major complications such as abdominal bleeding or pyrexia. Effective analgesia is vital during weaning and is discussed elsewhere in this thesis. The routine use of postoperative ventilatory support is in contrast to the first 27 patients who were transplanted at this
centre, when it was not used. However 6 of these 27 patients who did not receive elective ventilatory support required emergency assistance during their postoperative period because of respiratory failure, and a further 4 were artificially ventilated for a variety of reasons immediately postoperatively (Farman et al 1974).

If after tracheal extubation the patient develops respiratory insufficiency, reintubation of the trachea and the reinstitution of ventilatory support should not be delayed. Patients rarely tolerate a period of inadequate ventilation and eventually ventilatory support will be required as an emergency procedure. In the meantime the recently transplanted liver may be unnecessarily damaged by hypoxia.

Lung water increases following major surgery and may result in pulmonary oedema in both adults and children. Riegle and her colleagues (1984) reported the development of radiographically proven pulmonary oedema in 44% of their paediatric patients after liver transplantation. The Birmingham group have also commented on the sensitivity of patients with chronic liver disease to fluid loads (Sealey and Gray 1985). The factors responsible for this include a large intraoperative blood transfusion, fluid shifts and hormonal changes in response to stress. Surgical trauma
results in tissue oedema which will continue to accumulate for several hours after the end of the operation and which will later be absorbed into the circulation. Antidiuretic hormone is increased because of the raised mean intrathoracic pressure due to artificial ventilation and the application of PEEP.

Opioids, administered for analgesia, will also lead to water retention (Papper et al 1957), further exacerbating the increase in lung water.

The clinical diagnosis of fluid overload is difficult in patients receiving controlled ventilation; fine crackles are heard only when extreme pulmonary oedema exists. Right atrial pressure and pulmonary capillary wedge pressure may be artificially elevated during artificial ventilation and can only be accurately measured if the patient is temporarily disconnected from the ventilator; these measurements are, in any case, of dubious value in the diagnosis of non-cardiogenic pulmonary oedema. Although radiology may help it can be difficult to diagnose the presence of early pulmonary oedema on a portable supine chest X-ray in a patient receiving artificial ventilation. It was hoped that the lung water computer might provide a solution to the diagnosis of excessive lung water. This device uses changes in diffusible or nondiffusible indicators to calculate extravascular lung water.

The diffusible indicator utilises alterations in thermal conductivity while 3% saline, chromium-tagged red
cells, albumin or indocyanine green are used as the nondiffusible indicator (Noble and Severinghaus 1972). However this device requires both pulmonary and femoral artery catheterisation and has not proved reliable.

Owing to the difficulties in diagnosing pulmonary oedema it has become our practice to give a small intravenous dose of frusemide (5 mg in the adult, 1 - 2 mg in the child). This produces a prompt and large diuresis (Figure 5.1) in those patients who are water and probably salt overloaded.

It is of note that both the Pittsburg and Birmingham groups have a similar protocol for their patients and commonly use frusemide if there is the slightest suspicion of pulmonary oedema. The large diuresis following small doses of frusemide prompted us to perform a dose-response study in patients following liver transplantation and other critically ill patients, in an attempt to avoid the adverse effects of an unnecessarily large diuresis (Lowe et al 1979). I was assisted with the data collection by Dr D Tew (ICU SHO).
Figure 5.1: Effect of a 5mg intravenous bolus of frusemide on hourly urine output in 1 patient immediately prior to weaning from controlled ventilation.
LOW DOSE FRUSEMIDE ADMINISTRATION
IN CRITICALLY ILL PATIENTS
Clinical Intensive Care (1990) 1:187

Fifty-two critically ill patients admitted to this intensive care unit were studied. They were 30 male and 22 female patients, with a mean age of 53.2 years (range 17 to 85 years). All patients had a urinary catheter in place as a routine part of their intensive care. Patients were excluded from the study if they were known to be in renal failure (elevated plasma urea and creatinine), if the urinary specific gravity was less than 1010 or if they were clinically hypovolaemic (in no patient was the central venous pressure less than 3 mmHg).

Each patient received 5, 10 or 20 mg of frusemide intravenously, either to prevent fluid overload or in the management of pulmonary or peripheral oedema. Eight patients received frusemide at more than one dose strength. Pre-existing treatment was not changed in any patients and some may therefore have been receiving a renal dose of dopamine (Chapter 15).

The volumes of urine passed in the 4 hours before and 4 hours after frusemide administration were measured, and the percentage increase of postdose over predose volumes was used as an index of diuretic response. If the postdose volume was less than the predose volume...
this was analysed in the results as a negative percentage. No additional diuretic was administered during this period. The change in urine volumes was assessed statistically using a one-way analysis of variance. Urine was collected in an accurately calibrated urimeter (Vygon Products Ltd).

Results
The percentage increase in urine output at the respective doses of intravenous frusemide is shown in Table 5.1. The increase in urine output was significantly different at each dose (p<0.05). When the change in urine output was compared with the dose of frusemide expressed as mg/kg body weight, the dose-response relationship was highly significant (p<0.001). The urine output increased by 133% for each 0.1 mg/kg of frusemide administered.

Discussion
Others have previously reported that the oral administration of 20 mg of frusemide produced a significant diuresis in water-loaded normal volunteers (McClean, Baird and Longhurst 1972). This study demonstrated significant increases in urine output with small doses of frusemide. These increases were greater than those seen by McClean and his colleagues and reflect the different routes of administration. In their study frusemide was given orally and in ours intravenously. Thus it is not surprising, because of the difference in bioavailability, that we observed a greater diuresis.
<table>
<thead>
<tr>
<th>Dose of frusemide</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean increase in</td>
<td>90(19.3)</td>
<td>147(22.3)</td>
<td>190(27.3)</td>
</tr>
<tr>
<td>urine output(SEM)</td>
<td>(-44 to 550)</td>
<td>(-29 to 295)</td>
<td>(96 to 310)</td>
</tr>
<tr>
<td>(range)%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>36</td>
<td>17</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 5.1: Change in urine output after 5, 10 and 20 mg frusemide administered intravenously to 52 critically ill patients (eight patients received more than one dose).
Johnston and his colleagues (1982) have shown that the non-diuretic haemodynamic effects of frusemide (venodilation) are minimal at doses as low as 5 or 10 mg, so small doses of frusemide may be safer. Only if an unsatisfactory response is seen should larger doses be used.

Following tracheal extubation, opacification of the right lower zone on the chest X-ray has been common. The factors contributing to this include:

**Pleural Effusion**

Surgical trauma to the right hemidiaphragm results in a sympathetic effusion. In addition, ascitic fluid, often present preoperatively as part of the severe liver disease, recollects postoperatively and drains through the peritoneal-pleural channels in the right hemidiaphragm into the pleural space. This was illustrated in a patient admitted to the intensive care unit prior to liver transplantation, in whom 6 litres of ascitic fluid was drained when a right internal jugular line was inadvertently placed into his pleural cavity. Vargus-Tank and his colleagues (1984) have also demonstrated the existence of peritoneal-pleural connections in seven out of 65 autopsies and two out of eight patients. They used air in the cadavers and a radiotracer method in the
patients.

**Surgical Retraction of the Diaphragm**
This causes atelectasis due to direct pulmonary trauma.

**Paralysis of the Right Phrenic Nerve**
In approximately 10% of patients the clamp applied to the suprahepatic IVC may pinch the right phrenic nerve, paralysing the diaphragm. Recovery is usually seen over 2-4 weeks.

**Liver Size**
The donor organ is, wherever possible, matched for recipient size, although because of the difficulties of donor availability a perfect match may not always be possible. When a large donor liver is transplanted into a small recipient then the diaphragm will be elevated and will interfere with ventilation at the right base. Bronchial breathing may be heard on auscultation of the chest in such circumstances and is an indicator of compression of the lung rather than collapse.

**Intra-abdominal Collections**
Perihepatic collections of blood, or in some instances pus, will also elevate the hemidiaphragm, leading to collapse of the right base of the lung.
Pain

If adequate analgesia is not provided then patients will not cough, expectorate or adequately expand the lower parts of the lung. This results in pulmonary atelectasis and segmental collapse.

This problem of basal pulmonary opacification has almost completely disappeared from our practice with a more aggressive approach to analgesia and the institution of Intermittent Positive Pressure Breathing (IPPB) and physiotherapy 4 times a day. Although IPPB has been shown to be of little benefit in the prophylaxis and treatment of atelectasis in patients following routine surgery (Becker et al 1960), this study was performed in patients after widely differing operations as opposed to our more homogenous group. It is now quite noticeable that right basal atelectasis is an almost invariable occurrence when a patient does not receive IPPB after early tracheal extubation.

Fluid Balance

Maintenance of fluid balance is of great importance particularly in the early postoperative period. In the intensive care unit, as during the preceding surgery, the numerical values of fluid input and output can be misleading and fluid balance is best assessed from the measurement of cardiovascular parameters and urine output.
On return from the operating theatre the patient will require fluid additional to the measured losses. This is partly accounted for by vasodilatation, as rewarming occurs, expanding the intravascular volume. There may be a period of continued ooze of blood from dissected surfaces which may not drain externally, but will necessitate additional blood transfusion. An often underestimated loss is the exudate from the area of dissection left after skeletonisation of the liver. This occurs even in the absence of bleeding and can be an appreciable volume. The patients who appear to lose the largest volumes of exudate are those who have undergone extensive previous surgery or those with sclerosing cholangitis; both groups have large raw areas after extensive dissection. A further group in whom exudative losses are seen are those patients with polycystic disease. In this group of patients the discrepancy in size between the large diseased liver and the small donor liver results in little tamponade effect on the bleeding or oozing surface.

The recently transplanted liver can be expected to have a diminished synthetic capability for many substances, including albumin. Because of the high protein content of the exudate loss and diminished synthetic ability of the transplanted liver it is routine to give all adult patients 1 litre of 4.5% HAS on the first postoperative day and a further 500 ml on the second postoperative
day, rather than wait for the inevitable decrease in plasma concentrations of albumin. Severe blood loss may continue into the postoperative period and this is discussed in Chapter 16.

Fluid replacement is guided by RAP or PCWP, the haematocrit and the plasma albumin concentration. If a patient is hypovolaemic and the haematocrit is low then blood is transfused. If, however, the haematocrit is high and the plasma albumin low then 4.5% HAS is transfused. If both the haematocrit and plasma albumin are high then hetastarch will be used in its place. The haematocrit is maintained in the region of 0.3-0.35, as this is the optimal figure for oxygen carriage and tissue delivery (Messmer 1975). The increase in cardiac output necessary to cope with a haematocrit at this level is one of the reasons why patients undergoing liver transplantation require good cardiac function. A haematocrit in excess of 0.35 is considered to be potentially dangerous since blood is more viscous, and flow through small vessels, particularly around the hepatic arterial anastomosis, may be sluggish, resulting in thrombosis. Should this occur then serious damage to the graft may follow. If the haematocrit increases above 0.35 in the postoperative period then the patient is venesected to decrease it to a more acceptable level.
Electrolyte and Acid Base Balance

Plasma potassium is usually low on return from the operating theatre. Although banked blood has a high potassium content and might be expected to result in hyperkalemia, the potassium is rapidly absorbed by the transplanted liver after revascularisation. Indeed if hyperkalaemia is seen postoperatively then there is almost certainly hepatic or renal dysfunction.

In the postoperative period plasma glucose continues to be elevated, a consequence of stress, the metabolism of citrate and the administration of exogeneous steroids and glucose. It is measured each hour by the nurse using a reflectance meter and hyperglycaemia is treated by a sliding-scale infusion of insulin.

Ionised calcium concentrations are maintained intraoperatively by the administration of large amounts of calcium chloride to replace that lost by chelation with citrate transfused in the blood. High ionised calcium levels have been reported postoperatively as the citrate is metabolised by the transplanted liver (Gray et al 1986); however, these rapidly return to normal.

Autologous blood transfusion is used during the operation. This process heparinises blood collected from the operative field, then separates the red blood cells by centrifugation, and washes and resuspends
them in saline with a haematocrit of 60% (Orr 1982; Ibister and Davies 1980). The infusion of large amounts of washed red cells suspended in 0.9% saline may lead to biochemical abnormalities such as hypernatraemia and hypokalaemia. There is controversy in the literature over the existence (Sharp, Stark and Donovan 1981; Silva et al 1984) or not (Warnock et al 1982) of a coagulopathy due to heparin being reinfused along with activated clotting factors. Any abnormalities that do exist should be particularly apparent in patients following liver transplantation when impaired liver function limits the body’s ability to inactivate heparin and activated clotting factors. Although the intraoperative biochemical and haematological changes of cell-saving systems (Orr and Blenko 1978) and liver transplantation (Carmichael, Lindop and Farman 1985) have been described separately, little attention has been given to postoperative effects; which were therefore studied. Dr L Mendel (Research Registrar) and Mr M Smith (Senior Operating Department Assistant) assisted me with the data collection for this study.

**LACK OF HAEMATOLOGICAL AND BIOCHEMICAL CONSEQUENCES OF AUTOLOGOUS BLOOD TRANSFUSION**

*Anaesthesia* (1986) 41: 1259-1260

On admission to the Intensive Care Unit immediately after liver transplantation the following routine
investigations are performed on arterial blood: urea and electrolytes, haemoglobin concentration, platelet count, clotting screen and blood gases.

The results of 20 adult patients were reviewed. All had received a similar amount of stored (citrate, phosphate, dextrose and adenine) blood intraoperatively. In addition, 10 of these patients had received between 0.67 and 4.3 litres of cell-saved red blood cells. Details of blood loss and administration are shown in Table 5.2. The postoperative biochemical and haematological results are shown in Table 5.3.

The results were compared between the two groups using a Student’s t-test, and no significant difference could be demonstrated. The use of a red cell washing and reinfusion system of this type would appear not to cause significant haematological or biochemical derangements in patients following liver transplantation. It is therefore unlikely to cause significant changes in other groups of patients.
<table>
<thead>
<tr>
<th></th>
<th>Cell-saved group (n=10)</th>
<th>Non cell-saved group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood loss</td>
<td>7.4 (4.09)</td>
<td>4.5 (1.77)</td>
</tr>
<tr>
<td>Total transfusion</td>
<td>7.88 (3.08)</td>
<td>6.25 (1.32)</td>
</tr>
<tr>
<td>(banked + cell saved)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banked blood</td>
<td>6.23 (2.63)</td>
<td>6.25 (1.32)</td>
</tr>
<tr>
<td>Cell-saved red blood cells</td>
<td>1.65</td>
<td>NIL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Range 0.67-4.3)</td>
</tr>
</tbody>
</table>

Table 5.2: Mean (SD) blood losses and transfusion requirements (1) in twenty patients during orthotopic liver transplantation.
<table>
<thead>
<tr>
<th></th>
<th>Cell-saved group(n=10)</th>
<th>Non cell-saved group(n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogen ion (mmol/l)</td>
<td>36.4 (5.95)</td>
<td>34.2 (4.91)</td>
</tr>
<tr>
<td>Base Excess (mmol/l)</td>
<td>2.7 (4.79)</td>
<td>2.3 (5.09)</td>
</tr>
<tr>
<td>Potassium ion (mmol/l)</td>
<td>3.2 (0.48)</td>
<td>3.0 (0.52)</td>
</tr>
<tr>
<td>Sodium ion (mmol/l)</td>
<td>136 (3.59)</td>
<td>137 (4.07)</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>20.7 (9.86)</td>
<td>14.7 (7.22)</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>9.8 (7.06)</td>
<td>6.0 (3.64)</td>
</tr>
<tr>
<td><strong>Haematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (G/dl)</td>
<td>13.8 (1.59)</td>
<td>13.4 (2.28)</td>
</tr>
<tr>
<td>Platelets (x10⁹/l)</td>
<td>116 (54.49)</td>
<td>181 (85.43)</td>
</tr>
<tr>
<td>Prothrombin ratios*</td>
<td>1.47 (0.19)</td>
<td>1.37 (0.15)</td>
</tr>
<tr>
<td>Partial thromboplastin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>time ratios*</td>
<td>1.45 (0.50)</td>
<td>1.15 (0.08)</td>
</tr>
<tr>
<td>Thrombin time ratios*</td>
<td>1.24 (0.15)</td>
<td>1.12 (0.14)</td>
</tr>
</tbody>
</table>

Table 5.3: The effect of using cell-saved blood on biochemical and haematological results [mean (SD)] obtained in patients after liver transplantation. * Patient/control
Gastrointestinal Bleeding

Stress ulceration is a serious complication in critically ill patients. The exact aetiology is unclear but certain risk factors have been identified including artificial ventilation, major surgery, sepsis, hypotension, inotropic support, liver failure, and parenteral nutrition (Knight and Bihari 1985). Following liver transplantation patients are at further risk of gastrointestinal bleeding for a number of additional reasons. The coagulopathy often encountered postoperatively increases the risk of bleeding from any source, and correction of this reduces the risk of bleeding. Many patients will have portal hypertension and, as a consequence, oesophageal varices. Although portal blood pressure returns to normal postoperatively, the oesophagus remains friable. Trauma to oesophageal varices can be reduced by the use of a small diameter (12 FG) silicone coated nasogastric tube, this being the least traumatic size that still allows aspiration of gastric contents. Previously, problems arose when large nasogastric tubes were used: one patient exsanguinated from an ulcer at the lower end of his oesophagus, and two further patients had repeated bleeding from their oesophagus.

Further down the gastrointestinal tract, additional factors predisposing to this complication include the presence of bile acids in the stomach, the
administration of high-dose steroids for immunosuppression and the lack of food in the stomach.

In patients with fulminant liver failure, antacids have been found to be less effective in preventing stress ulceration than the $H_2$ receptor antagonists (McDougall et al 1977). Following liver transplantation prophylaxis against this complication was initially provided with intravenous ranitidine (Knight, Bihari and Tinker 1985; Shapiro et al 1986), rather than cimetidine, since it is thought to have fewer side-effects than cimetidine, which inhibits hepatic microsomal enzymes (Henry et al 1980). Ranitidine is metabolised in the liver and excreted unchanged by the kidneys but delayed metabolism and excretion have been demonstrated in renal disease (Martin et al 1982), and the dose is halved if this complication arises.

The efficacy of $H_2$ blockers was monitored by serial measurements of nasogastric pH, which was kept above 4 but below 7, as an alkaline pH encourages bacterial overgrowth and the possibility of increased risk of pulmonary infection.

In 1988 we changed our prophylaxis against stress ulceration to sucralfate. This agent, a nonabsorbable aluminium salt of sucrose octa sulphate, works by increasing the synthesis of mucosal prostaglandins,
stimulating mucus and bicarbonate production and increasing mucosal cell renewal; it does not change gastric pH.

H₂ antagonists increase the gastric pH which allows bacterial overgrowth to occur. When this happens, retrograde pharyngeal colonisation with Gram negative and anaerobic organisms may result. Subsequently these may be aspirated past a cuffed tracheal tube and result in a nosocomial pneumonia. Since sucralfate does not increase gastric pH the incidence of bacterial colonisation of the stomach and nosocomial pneumonia are lower than in patients treated with ranitidine (Driks et al 1987; Tryba 1987). Furthermore sucralfate is easier to give, does not require regular pH monitoring of the nasogastric aspirate and is cheaper. Sucralfate prophylaxis does however have one disadvantage; because gastric pH is not increased, if pulmonary aspiration of stomach contents occurs following tracheal aspiration then Mendelson's Syndrome may develop. It is therefore routine to administer ranitidine intravenously one hour before tracheal extubation to prevent this complication.

The relative efficacy of each group of drugs has been the subject of controversy (Borrero et al; Hanson and Gazzard 1987), although recent opinion is more in favour of sucralfate (Editorial 1989).
Pinkleton and Hadzima (1983) have shown that enteral alimentation is protective against gastrointestinal bleeding, and is superior to both antacids and \( \text{H}_2 \) receptor antagonists. Enteral nutrition may act by inducing a dilutional alkalisation of stomach contents or by maintaining nutrition better than parenteral feeding. Once patients are established on to either full nasogastric feeding or an adequate diet, then prophylaxis against stress ulceration is discontinued.

**Nutrition**

Many patients are malnourished preoperatively and periods without nutritional support should be as short as possible. Parenteral nutrition is usually commenced as soon as haemodynamic stability is achieved, usually within the first 24 hours postoperatively.

Parenteral nutrition is started with carbohydrates (dextrose or glucose) and conventional amino acid solutions; their concentrations are increased over the first 24-48 hours to provide 2000 kcal as carbohydrate and 14 g nitrogen per day. The patient's energy expenditure (Smith, Kennedy and Park 1984) and nitrogen requirements (Park 1980) can be estimated if required. Hyperglycaemia, should it occur, is treated by increasing the insulin sliding scale. If excessive amounts of insulin are needed (>8 units/hr) to control the blood sugar then the amount of glucose is decreased.

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Fat emulsions have not been routinely used as an energy source in this group because of concerns about them precipitating cholestatic jaundice. A study by Benjamin (1980) in infants and children, and a further one by Wolfe and his colleagues (1988), have both shown parenteral nutrition to have no demonstrable effect on hepatic histology. Any changes that were noted were attributed to the prolonged fasting or underlying disease process. Furthermore Kuse and his colleagues (1989) have shown that increasing amounts of fat emulsions (50g twice a week, 0.7 g/kg/day and 1.5 g/kg/day) does not lead to significant deterioration in hepatic function or to a fatty liver. Unfortunately this study did not include a control group receiving carbohydrate solutions alone. The Newcastle group (Burgess et al 1987) have also demonstrated the beneficial effects of daily administration of a fat emulsion on hepatic drug oxidation. They compared the metabolism of antipyrine in four groups of patients after elective gastrointestinal surgery; the first group received no parenteral nutrition, a second group received 2000 kcal all as dextrose, a further group received only 1600 kcal all as dextrose and a final group received 2000 kcal but with 25% of the calories being provided by a fat emulsion. In both groups receiving energy only in the form of dextrose, antipyrine clearance decreased by 34% compared with the control group. This was not seen in the group that
received the fat emulsion. Since hepatic function needs
to be as good as possible in patients following liver
transplantation, Intralipid is now routinely added to the
total parenteral nutrition of these patients.

When bowel function returns, enteral feeding is started.
Bowel sounds and the passage of flatus are indicators of
returning gastrointestinal function. However, in
patients with a complicated postoperative course who
require artificial ventilation bowel sounds are an
unreliable guide to return of bowel motility (Shelly and
Church 1987). In such patients nasogastric
feeding is started when nasogastric aspirate
decreases to below 20 ml per four hours.
Water is first instilled and if this is tolerated
without nausea, large volumes of nasogastric aspirate or
abdominal distension, enteral nutrition is commenced
with a proprietary feed. This is increased in volume and
concentration until the patient is receiving adequate
nutrition or until a normal diet is resumed.

Nitrous Oxide
Nitrous oxide when used over several days to provide
sedation and analgesia for patients suffering from
tetanus was shown to produce an aplastic anaemia (Lassen
et al 1956). The authors of this report, in addition to
several case reports, retrospectively examined the
records of 13 patients and found that 6 of these
patients had developed granulocytopenia and/or thrombocytopenia and they were the only ones who had received nitrous oxide. Amos and his colleagues (1982) prospectively studied 70 critically ill patients of whom 50 had received nitrous oxide. Acute megaloblastic bone marrow changes were present in 22 of the 70 patients, 18 of whom had received nitrous oxide for 2-6 hours during anaesthesia. Sixteen of the 18 patients who had received nitrous oxide died. All patients were also investigated with a deoxyuridine suppression test on the bone marrow aspirate which indicated interference with the function of vitamin B₁₂ and subsequent folate deficiency. Skacel and his colleagues (1983) studied serial bone marrow changes in nine surgical patients requiring artificial ventilation who received nitrous oxide for 4-36 hours, compared with three patients who did not receive nitrous oxide. In the group that received nitrous oxide gross megaloblastic changes were seen after 24 hours which took one week to return to normal. No such changes were seen in the group that did not receive nitrous oxide. The rapidity of onset and similarity to animal work have been confirmed by Koblin and his colleagues (1982).

The mechanism for these effects appears to be the irreversible interaction of nitrous oxide with vitamin B₁₂. This is an essential coenzyme for the enzymes methionine synthetase and methyl malonyl CoA mutase.
These enzymes are essential for the synthesis of methionine and tetrahydrofolate (Nunn 1987) and, since they are inhibited following nitrous oxide anaesthesia, plasma methionine levels will decrease. Methionine is needed for methylation reactions and to produce, from folate, 10-formyl tetrahydrofolate, itself essential for the production of deoxythymidine and thence DNA. It is the inability to produce DNA that leads to the bone marrow changes.

Since the defect is centred on the hepatic enzyme methionine synthetase, concern was expressed about the use of nitrous oxide in liver transplant patients. However, the London group (Amos et al 1984) have shown that the administration of 5-formyl tetrahydrofolinic acid can overcome the interaction with Vitamin $B_{12}$, if given in sufficient doses. Although replacement therapy is given to recipients because they may have received a nitrous oxide anaesthetic it may also be required because the donor may have received nitrous oxide as well, either at hepatectomy or as part of the initial management. It is now therefore routine practice to give all liver recipients folinic acid and vitamin $B_{12}$ postoperatively.

Infection
This remains one of the major causes of morbidity and mortality following liver transplantation. To reduce
the incidence prophylactic antibiotic therapy is started preoperatively and continued for 48 hours postoperatively. Regular microbiological screening is performed on drainage fluids and swabs are taken frequently so that should the patients become infected it is detected early. In addition, the tips of all intravenous monitoring lines, drains, tracheal tubes etc are sent for culture when they are removed from the patient. Despite these precautions infection may still occur, particularly since the patients are immunosuppressed. In an early review, infection was noted to occur in over 70% of patients following liver transplantation (Schroter et al 1976).

A high fever occurring postoperatively with or without leukocytosis may be difficult to diagnose. Rejection, infection and infarction will all result in both a pyrexia and an increase in white cell count. Infarction and rejection may be characterised by a deterioration in liver function and an increase in serum transaminase concentrations. Although infection is associated with liver dysfunction (Murray and MacSween 1983) it tends to be predominantly cholestatic in nature. Diagnostic difficulties when deterioration in liver function is observed may be encountered because not all infections result in a fever. This may be due to immunosuppression, the severity of illness or liver failure. Similarly an increase in white cell count does
not always occur with infection (Fagan et al 1989).

Infections may be bacterial, fungal or viral. The high incidence reported by Schroter and his colleagues (1976) during the early part of Starzl’s series reflects difficulties with the biliary drainage and immunosuppression. Cuervas-Mons (1986) reviewed the main causes of death in 48 patients and found infection to be the major cause in 21 of them. Of the group in whom infection was the primary cause, 9 had bacterial, 7 fungal and 1 a viral infection. The majority of our postoperative bacterial infections are either chest infections or intravascular line associated infections. Ho (1986) has recently reviewed the microbiological course of 62 patients after liver transplantation. Twenty-six patients developed 30 episodes of severe fungal infections (superficial infections were excluded). Twenty-two of these were due to candida, six to aspergillus, one to a cryptofungus and a further one to a mucor fungus. Aspergillus infection is particularly serious in the immunocompromised patient (Park et al 1982) and in Ho’s series all the patients with this infection died. Aspergillus spores are ubiquitous and may gain access to the systemic circulation via the portal system. The Kupffer cells normally prevent this but they may be compromised both by the severity of illness (Nolan 1978) and the immunosuppression.
Viral infections commonly include herpes simplex and cytomegalovirus infection. They may represent re-activation or primary infection from a source such as donated organ or blood products. Ho (1986) feels that a primary infection is more serious than one resulting from re-activation. The increasing recognition of viral and fungal infections has resulted in routine, weekly storage of serum. When a viral or fungal (aspergillus) infection is suspected this serum can then be examined for rising titres.

All patients with liver disease, particularly transplant recipients, should be screened for hepatitis B antigen. The presence of the surface antigen (HBsAg) indicates potential infectivity. Those patients with the e Antigen or no e markers in the presence of HBsAg are potentially highly infectious; special precautions should be taken to prevent infection of the attending personnel and other patients. Patients with HBsAg who are anti-HBe positive can be regarded as low risk. The absence of HBsAg, anti-HBs and/or anti-HBc is associated with immunity and loss of infectivity.

Cardiovascular System
Bradycardias are sometimes a feature in the more severely ill transplant patients. They may be caused by the higher than normal concentrations of bile salts, bilirubin and toxic substances that accumulate in liver failure
(Weston et al 1976). Alternatively, since they are particularly common during tracheal suction they may represent an increase in sensitivity of the vagus. The bradycardia responds rapidly to atropine or glycopyrrolate. Repeated doses of atropine in patients with renal failure may allow the accumulation of its breakdown product, tropic acid, which is centrally active. Fits have been observed on at least one occasion in a patient following liver transplantation when multiple doses of atropine were used for recurrent bradycardias. Propofol, currently under evaluation for sedation of critically ill patients, has been observed to cause a decrease in heart rate in this situation (Aitkenhead et al 1989) and in patients with ischaemic heart disease (Patrick et al 1985). In deeply jaundiced patients, with a predisposition to bradycardia, this adverse effect is more pronounced. On one occasion the resulting bradycardia following an infusion of propofol necessitated a right ventricular pacing wire to control the arrhythmia.

Postoperative hypertension, particularly in children, may occur in up to 81% of patients (Riegle et al 1984). The exact mechanism is not known, but it responds to treatment with IV labetalol or sublingual nifedipine.

**Drainage**

The T-tube drainage is observed for both quantity and
quality of bile. Usually copious quantities of dark green or brown bile are seen. If the amount decreases and particularly if the colour turns to orange then rejection or some other cause of liver dysfunction may be occurring.

**Wound Drains**

Postoperative abdominal drainage fluid is commonly dark red in colour. Initially it was assumed that this was blood and it was replaced with similar quantities of blood. During one of the early postoperative morphine studies, in a patient who had undergone liver transplantation for polycystic disease of the liver, it became apparent that haematocrit was rapidly increasing as the early samples were removed. This led to the realisation that the drainage fluid, whilst it was blood-stained, had a low haemoglobin content and consisted principally of an exudate. When the haematocrit of this and other patients was measured it was found to be between 2 and 10%, depending on the stage in the postoperative course. Subsequent investigation led to the finding that if it is greater than 10% then it is usually an indicator of postoperative bleeding and transfusion with blood is appropriate.

**Coagulation**

In the postoperative period, when liver function recovers and abdominal bleeding stops, coagulation usually returns
to normal. However, if liver function deteriorates then all of the coagulation changes associated with acute liver failure will develop (increased PT and KPTT, and a decreased fibrinogen concentration and platelet count). The increase in prothrombin time may be used as a measure of liver function. Postoperative bleeding necessitating continued postoperative blood transfusion indicates that the dilutional coagulopathy seen intraoperatively is continuing. Treatment of both forms of coagulopathy is similar. Thrombocytopenia (<50 x 10^9/l) is treated with platelet transfusion. If the plasma urea is elevated because of renal failure then dDAVP and cryoprecipitate may be administered to improve platelet function. Clotting factors are replaced with FFP, and if fibrinogen is low then factor VIII concentrate may be given. Vitamin K (10 mg) is also given to replace any deficiency.

Activation of the coagulation cascade resulting in a consumptive coagulopathy is increasingly recognised. Low antithrombin III levels have been found in some paediatric patients after liver transplantation and may be a contributory factor in hepatic artery thrombosis. Furthermore, low levels of antithrombin III may also be a factor in the cause of renal failure.

**Budd-Chiari Syndrome**

In the Budd-Chiari syndrome, thrombosis of the donor
liver is a significant risk. Subcutaneous heparin is started as soon as postoperative bleeding stops. This is followed over the next 24-48 hours by systemic heparinisation and eventually oral anticoagulation.

**Immunosuppression**

In the early stages of liver transplantation prednisolone and azathioprine were used throughout the postoperative period. With the advent of Cyclosporin A (See Chapters 1 and 17) this agent was introduced into the immediate postoperative period. However, adverse pulmonary, neurological (Powell-Jackson et al 1984) and renal (Whiting, Simpson and Thompson 1983) effects were noted when it was administered at this time. One contributory feature to the pulmonary toxicity of cyclosporin A may have been administration through a centrally placed venous line. At this time the measurement of CVP utilised a water column. This resulted in pulsed drug administration each time CVP was read during cyclosporin A administration, with the pulmonary circulation being intermittently exposed to very high concentrations of the drug. To prevent this and to ensure that only low concentrations reach the lungs (and other tissues) cyclosporin A is now administered through a peripheral line using a syringe driver. These adverse effects have led to its introduction on the second or third postoperative day when the effects of the operation have subsided. If renal function is
poor then its use is further delayed. The current immunosuppressive regimen starts during the operation when 500 mg of methylprednisolone is administered either following induction of anaesthesia or at hepatectomy. On return to the ICU, prednisolone or methylprednisolone 1 mg/kg and azathioprine 1.5 mg/kg are given. The prednisolone is gradually reduced to 0.2 mg/kg at 3 months (O'Grady and Williams 1989). If thrombocytopenia or other evidence of marrow suppression is found then the azathioprine dose is reduced. Cyclosporin A is introduced as described previously.

The patient may suffer early rejection when a high fever is seen (up to 40°C). Urgent liver biopsy is performed, with platelet and FFP cover, if necessary, to obtain a histological diagnosis and to differentiate it from infarction and infection. If rejection is proven then pulses of high doses of hydrocortisone are administered for the next five days.

Mobilisation

Early in the series patients were nursed completely flat and moved as little as possible for the first 24 hours following surgery, in an attempt to reduce intra-abdominal bleeding. More recently this period has been shortened to improve respiratory function; the patient is now turned and allowed to sit up when any abdominal bleeding has ceased and haemodynamic stability
has been achieved. As soon as patients are well enough they are encouraged to sit out of bed.
A large part of this thesis is devoted to pharmacology. This chapter reviews some of the factors occurring in liver disease that may influence drug action. It also explains the rationale for pharmacological studies in the perioperative period of liver transplantation. Finally, studies on the measurement of liver function after liver transplantation are described.

THE EFFECTS OF LIVER DISEASE ON DRUG ACTION

The liver metabolises lipophilic, nonpolar drugs to hydrophilic, polar substances in the endoplasmic reticulum of the hepatocyte. Most drugs are rendered inactive, but some may have active metabolic products. Liver disease may affect drug pharmacokinetics and consequently pharmacodynamics in five main ways:

-reduced synthesis of albumin may reduce plasma binding sites for the drug and increase the free drug fraction.

-the hyperdynamic circulation of liver disease may lead to an increase in the plasma and extracellular fluid volumes with a consequent
increase in the volume of distribution for some drugs.

-reduced liver blood flow and therefore clearance may result in prolonged elimination half-lives for drugs extensively metabolised by the liver.

-changes in hepatocyte function will alter the rate with which drugs, particularly those with a low extraction ratio, are eliminated. If hepatocyte function deteriorates, such as by a reduction in the number of hepatocytes or hypoxic cell damage, then elimination will be delayed, whereas if it is enhanced (eg by enzyme induction) elimination will be increased.

-portocaval shunting may increase the bioavailability of orally administered drugs, by reducing first-pass metabolism.

The patient with liver disease may have an altered response to drugs. In general a drug can be expected to produce a more profound and prolonged effect than normal. The effects of centrally acting agents may be particularly pronounced in patients with hepatic impairment owing to a change in the sensitivity of receptors (Bakti et al 1987, Ferenci et al 1984).
In the critically ill patient after liver transplantation drug metabolism may change (Chapters 7, 8, 11, 12, 13). Unfortunately these changes are usually unpredictable. Antipyrine has been extensively studied as a marker of hepatic oxidative metabolic activity. Mirvis, Buchanan and Eyberg (1979) studied the elimination of antipyrine in 12 critically ill patients on two occasions four days apart and demonstrated a decrease in antipyrine clearance over this time. There was also a change in volume of distribution over this time which was attributed to varying states of hydration. Two studies (Cumming 1976; Branch, Herbert and Reid 1973) have shown that, when patients are hypoxic, the half-life of antipyrine increases. Burnett and his colleagues (1976) demonstrated similar changes in viral hepatitis, whilst Reitbrock and his colleagues (1981) observed that the half-life of hexobarbitone in critically ill patients was initially normal and then decreased in sepsis with an increase in clearance.

With many drugs, as therapy continues, there may be an increasing dose requirement to produce the same effect. This may be a reflection of tolerance to the drug or an increase in its elimination (Chapter 3) as the patient’s condition improves.

The study of patients following liver transplantation may provide information enabling some of the questions
about drug metabolism in the critically ill, which would be difficult to obtain from other groups of patients, to be answered. Furthermore, additional invasive sampling catheters are not required in this group since they are already in place as an essential part of the anaesthetic technique or the postoperative intensive care.

RATIONALE FOR STUDIES OF DRUG METABOLISM IN THE PERIOPERATIVE PERIOD OF LIVER TRANSPLANTATION

Three periods are identifiable when studies on acute changes in drug metabolism due to liver disease can be undertaken.

The Immediate Postoperative Period

Studies in this period can address alterations in the elimination of drugs following acute surgery. The donor liver has been subjected to not one but two major surgical procedures (donor hepatectomy and recipient operation). Both of these procedures can be long and associated with profound and sudden haemodynamic changes. In some instances the liver may have suffered an insult before the donor operation because of the initial trauma and any subsequent operation. Additionally, there is a period of warm ischaemia during removal of the liver from the donor and cold ischaemia during transport of the donor liver which will result in
further hepatic injury. In the early part of the series the period of warm ischaemia was prolonged by the need for some bench work, particularly on the biliary anastomosis, before the donor liver was transplanted into the recipient. Although the organ had been perfused with cold preservative solution whilst still in situ, uniform and thus complete cooling at this time had not occurred and as a consequence further warm ischaemic damage resulted. Currently, any work of this nature is now performed concurrently with the recipient operation, at which time cooling will be complete and warm ischaemic damage will be reduced. The hepatic injury sustained during liver transplantation, although severe, is standard, and studies in this group can be expected to demonstrate changes that might be more difficult to demonstrate in other groups.

Studies in this period are of further interest because it is possible to collect simultaneously blood, urine and bile from patients. Controlled ventilation is also a necessary part of the initial postoperative care so, should respiratory depression occur with a sedative or analgesic drug, it will not hazard the patient. Studies during this period are usually uncomplicated to perform in the controlled atmosphere of an intensive care unit. A finding of a normal metabolic pattern of drug metabolism at this time would suggest adequate
hepatic function in the newly transplanted liver. However, an altered metabolic pattern would illustrate the need for additional caution in drug administration in the immediate postoperative period following liver surgery and possibly in other patients with other forms of liver disease.

The Anhepatic Period

It was not until 1986 that there was sufficient confidence to perform the first study during the anhepatic period of liver transplantation. During this period of the operation there is considerable activity in relation to both the surgical procedure and the associated cardiovascular and metabolic changes (Chapter 4). During the time when all of the vascular clamps are in place and until they are released there are no hepatocytes connected to the patient and hepatic blood flow is zero. This situation therefore represents an extreme example of liver failure. It lasts for approximately 40-60 minutes after which a functioning liver is connected.

If a drug is injected during the anhepatic period then any metabolites that are detected must be from extrahepatic sites of metabolism. Furthermore, since liver function is absent, the small metabolic contribution of other organs can easily be studied since the metabolites from these sites will not be inundated
by the large amounts of metabolites made by the liver. One study in this thesis uses this feature to define the importance of the pulmonary metabolism of propofol (Chapter 10).

There are potential difficulties in the interpretations of these results, besides those discussed in Chapter 3. Metabolites formed by organs distal to the infrahepatic IVC clamp may not be detected in blood sampled from the radial artery due to the discontinuity of the inferior vena cava. In patients with chronic liver disease this should not occur, since profuse anatomoses develop. However, in patients with acute liver disease it is theoretically possible that metabolites produced in organs distal to the infrahepatic IVC (eg the kidney) may not reach the systemic circulation, since these patients have not had sufficient time to develop portal anastomoses. Studies presented in this thesis demonstrate that this would appear not to be the case (Chapters 8).

In Hannover ex situ resection of liver tumours is performed. The anhepatic period in these patients lasts for 8-9 hours and should provide this group with the ability to perform some interesting studies.

Preoperative Studies

In the immediate preoperative period, the majority of
patients will have end-stage liver failure. Since hepatic transplantation is imminent this might appear an ideal time to study the pharmacology of sedative and analgesic drugs since they could be used as premedication. However, studies at this time have not proved practicable since patients are usually at home when a donor liver becomes available and often only arrive shortly before the operation. The preoperative period is a time of great activity and anxiety which preclude studies. In recent years daytime transplantation has become increasingly common and this would necessitate studies being performed at night. One study (Chapter 11) has been performed preoperatively on children following anaesthesia but before surgery. Although information from this study was useful, repeating the study protocol with other drugs has not been thought to be of value.

THE POSTOPERATIVE MONITORING OF LIVER FUNCTION

Immediately after liver transplantation hepatic metabolism is altered, the newly transplanted liver having been subjected to a variety of insults as described above. Liver function is monitored postoperatively to detect adverse trends. This is of particular importance in patients following liver transplantation who, in addition to the usual problems faced by the critically ill, may have episodes
of rejection, infarction or infection. The ideal test would be both sensitive, to allow early detection of deteriorating liver function, and specific, in order to indicate the underlying cause of abnormal liver function. Additionally the test needs to be simple to perform and relatively inexpensive. Because of the liver’s complex metabolic functions it is unlikely that any single test will ever be described which can assess all of these functions.

Conventional liver function tests are easily measured in the routine biochemistry laboratory but alterations in enzymes and bilirubin may be relatively nonspecific. The interpretation of these tests following liver transplantation may be difficult owing to several factors, including episodes of rejection, haemolysis and sepsis, the normal metabolic responses to trauma, and the effect of treatment (especially albumin transfusion and perioperative exchange transfusion). Whilst albumin provides an accurate assessment of liver function overall, it has a half-life of 14 days. Bilirubin levels reflect several factors including hepatic ischaemia (Nunes, Blaisdell and Margaretten 1970), blood transfusion reaction, elimination of excess bilirubin, haematoma reabsorption, and rejection. Alkaline phosphatase is a poor guide to the metabolic activity of the liver, the plasma concentration being affected by many factors such as
bilary obstruction and bone disease, and it has a relatively long half-life of 40 hours. Alanine aminotransferase may provide a more useful assessment of hepatocyte function, regeneration from cold ischaemia starting to occur within 24 hours. Aspartate aminotransferase is not measured at this centre, but it tends to parallel changes in alanine aminotransferase. Gamma glutamyl transferase is more complex; changes in its concentration parallel those seen with both alkaline phosphatase and alanine aminotransferase as well as being altered by the administration of enzyme-inducing agents.

Despite these measurements little was known of the typical course of conventional liver function tests following liver transplantation. The postoperative course of 38 patients who underwent liver transplantation was therefore reviewed. I cooperated in this study with Dr J V Farman, Dr J P Lancon and Dr M J Lindop.

**EARLY METABOLIC CHANGES AFTER LIVER TRANSPLANTATION**

Care of the Critically Ill (1987) 3: 31-33

**Patients and Methods**

The preoperative diagnoses of the 38 patients studied are shown in Table 6.1 and their preoperative investigations are shown in Table 6.2.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No</th>
<th>%</th>
<th>Deaths</th>
<th>LOS (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary biliary cirrhosis</td>
<td>9</td>
<td>24</td>
<td>2</td>
<td>3.5 (1)</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>6*</td>
<td>16</td>
<td>1</td>
<td>4.3 (2.5)</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
<td>5</td>
<td>13</td>
<td>2</td>
<td>9.5 (7.8)</td>
</tr>
<tr>
<td>Liver tumour</td>
<td>4</td>
<td>11</td>
<td>1</td>
<td>2.7 (0.5)</td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>3</td>
<td>8</td>
<td>0</td>
<td>5.7 (3.3)</td>
</tr>
<tr>
<td>Retransplantation</td>
<td>3**</td>
<td>8</td>
<td>1</td>
<td>7.5 (1.5)</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>5.5 (2.5)</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>4.0 (1)</td>
</tr>
<tr>
<td>Polycystic disease</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>7.0 (2)</td>
</tr>
<tr>
<td>Others</td>
<td>2***</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6.1: Diagnoses, number of deaths and lengths of stay (LOS) in the ICU in 38 Patients [mean (SD)]. * Wilson’s Disease 2, antitrypsin deficiency 2, Crigler-Najar’s Disease 1, tyrosinosis 1. ** Acute rejection 2, (48 h, 20 days), chronic rejection 1. *** Biliary atresia 1, Budd-Chiari syndrome 1.
<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35</td>
<td>16</td>
<td>(3-55)</td>
</tr>
<tr>
<td>Liver score</td>
<td>9.3</td>
<td>2.7</td>
<td>(5-14)</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.3</td>
<td>1.8</td>
<td>(6-15)</td>
</tr>
<tr>
<td>White cells (x10^9/l)</td>
<td>8.8</td>
<td>4.7</td>
<td>(3-19)</td>
</tr>
<tr>
<td>Platelets (x10^9/l)</td>
<td>232</td>
<td>175</td>
<td>(45-748)</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>26</td>
<td>8</td>
<td>(12-46)</td>
</tr>
<tr>
<td>Bilirubin (µmol/l)</td>
<td>272</td>
<td>274</td>
<td>(7-1204)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>624</td>
<td>90</td>
<td>(19-3644)</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>154</td>
<td>273</td>
<td>(4-1668)</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>9.2</td>
<td>13.3</td>
<td>(1-75)</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>128</td>
<td>134</td>
<td>(15-760)</td>
</tr>
</tbody>
</table>

Table 6.2: Patients' preoperative details.
The liver score (Pugh et al 1973) attested to the severity of liver dysfunction and hence of the operative risk. The anaesthetic management varied between patients. Twenty patients received isoflurane in concentrations up to 1.5% while 18 received up to 0.5% trichloroethylene as the volatile agent during anaesthesia. The addition of nitrous oxide to oxygen depended on the preference of the anaesthetist. Fentanyl was employed as required for analgesia and myoneural blockade was provided with atracurium or vecuronium, either as a bolus dose or as a continuous infusion, or with pancuronium administered as a bolus dose.

Monitoring of hepatic, renal and haemopoietic function followed the pattern shown in Table 6.3. Haemoglobin concentration was recorded as part of the blood count, although this did not reflect changes in body production of red cells so much as the use of blood transfusion or venesection. Other results, such as urine output or arterial blood gases, although monitored throughout the period in the ICU, are believed to reflect mainly the quality of care and so are not reported here.
Table 6.3: Monitoring of hepatic, renal and haemopoietic functions following liver transplantation. * Sodium, potassium, urea, creatinine, glucose. ** total proteins, albumin, phosphatase, bilirubin, alkaline phosphate, alanine aminotransferase.
Results

The patients were aged from 3 to 55 years [mean (SD) 35 (16) years], with liver scores between 5 and 14 (mean 9.3), indicating a moderate level of risk. Of the 38 patients, seven died during their stay in the ICU (six during the first week), five from major intra-abdominal bleeding, one from viral infection and one from multiorgan failure.

The mean (SD) duration of stay in the ICU was 7 (9) days; seven patients stayed more than one week. The duration of artificial ventilation was 37 (30) hours, intravenous analgesia was needed for 67 (51) hours and sedation for 42 (36) hours.

Over the first postoperative week, concentrations of albumin were almost constant. Values in the 12 and 24 hour samples were a little higher than preoperative levels but always remained below the normal range, as shown (Figure 6.1).

Following a reduction in the first 24 hours, the bilirubin concentration remained constant until the third day and then started to increase, reaching a value near the preoperative level by the seventh day. This is shown in Figure 6.1.

After operation there was a striking decrease over the
first two days in alkaline phosphatase values, which then remained almost constant for the remainder of the week (Figure 6.1).

By contrast alanine aminotransferase increased during the first day, reaching a level five times greater than the preoperative value (Figure 6.1) and then decreased over the next two days, thereafter remaining constant.

Despite a transient increase followed by a reduction over the first 24 hours, plasma concentrations of urea tended to increase slightly from the preoperative values (Figure 6.2).

Plasma creatinine concentrations increased during the first day following surgery and then decreased again, to reach their preoperative values on the third day, although remaining slightly above normal (Figure 6.2).

The platelet count, also shown in Figure 6.2, decreased until the third day and then increased again up to the end of the second week.

The white cell count remained unchanged for the first 3 days, and then started to increase, reaching a mean value of $17.2 \times 10^9 / l$ at the end of the second postoperative week (Figure 6.2).
Figure 6.1: Serum albumin, bilirubin, alkaline phosphatase and alanine aminotransferase after liver transplantation. Normal laboratory reference ranges: Albumin 30 - 44 g/l, Bilirubin 2 - 17 µmol/l, Alkaline phosphatase (AP) 30 - 135 UI/l, Alanine transaminase (ALT) 7 - 40 UI/l.
Figure 6.2: Changes in the concentration of urea (<7.5 mmol/l) and creatinine (35-125μmol/l) and also platelet (150-300 x 10⁹/l) and white cell count (4-11 x 10⁹/l). Figures in parentheses are the normal range.
Discussion

Albumin infusions are given throughout the early postoperative period to compensate for losses from the wound via the drains and, with a half-life of 14 days, postoperative albumin values tend to reflect the adequacy of replacement therapy rather than synthetic ability. However, during the course of this period the loss via the drains decreased, while at the same time the liver presumably resumed production of albumin, explaining the slight increment observed at the end of the first week.

Bilirubin levels reflect several factors such as hepatic ischaemia (Nunes, Blaisdell and Margaretten 1970), blood transfusion, elimination of excess bilirubin, haematoma reabsorption, and rejection. The trend of bilirubin levels may be divided into three parts; the first immediately follows transplantation, when the elimination of the excess bilirubin occurs (via the large fluid losses and replacement), the second is a plateau representing a balance between production and elimination and the third, beginning on the third day, is when production exceeds the rate of elimination, possibly as a consequence of haemolysis associated with massive blood transfusion. Moreover, this occurs during the period that often sees the first episode of rejection of the transplanted liver, commonly experienced from 5 to 14 days after surgery (Calne 1987b).
Changes in alkaline phosphatase levels demonstrate the metabolic activity of the liver. The steep slope of the first part of the curve is explained by the catabolism of this enzyme, the limited synthetic ability of the liver and the dilutional effect of a large fluid transfusion. The slight increase observed at the end of the first week may also be related to episodes of rejection and cholestasis during this period, although there is a dissociation between the marked increase in bilirubin and the relative stability of the alkaline phosphatase. After transplantation, the liver has to recuperate from a long cold ischaemic period of preservation, inevitably associated with a degree of cytolysis, reflected by the increase in alanine aminotransferase levels during the first postoperative day. In practice, a single measurement of alanine aminotransferase is a relatively insensitive guide to liver function as there is a wide variation in values postoperatively (O’Grady and Williams 1984). Serial measurements provide a comparison from the baseline established in each patient (O’Grady and Williams 1989). Regeneration of destroyed hepatocytes seems to begin within 24 hours of surgery, although on the seventh postoperative day serum concentrations are still greater than preoperative values, which may be due to episodes of rejection. Similarly, early increases in alanine aminotransferase may reflect damage due to ischaemia or handling of the organ during the period of
Renal function is also affected by major liver operations, but plasma urea and creatinine levels depend on hepatic as well as renal function; the slight increase in these levels seen at the end of the operation is a consequence of the haemodynamic perturbations associated with such procedures. Thereafter, the increase in plasma levels of urea may be an expression of increasing production as a normal function of the liver. It can also be affected by the administration of cyclosporin A. Low-dose dopamine infusion, given to protect renal function during and after surgery, is usually stopped on the second day after surgery (Chapter 15), which may contribute to the increase in blood levels by reducing urea clearance. Changes in serum creatinine levels do not parallel those of urea; here again, the increase from the end of the operation to the end of the first postoperative day is possibly explained by the tissue destruction occurring during the procedure. This increase is transient, the levels returning to their preoperative values within 2 days. Cyclosporin A, usually introduced on the third postoperative day, appears to have no major effect on plasma creatinine levels.

Platelet levels are also affected by operation; massive blood transfusion induces thrombocytopenia (Miller

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The presence of the large wound and internal raw areas will account for a considerable consumption, which explains the reduction in the count seen at the end of the procedure. The first hours following the operation may be marked by persistent intra-abdominal bleeding, necessitating the continuation of transfusion. Platelet transfusions are not given unless the count decreases below $50 \times 10^9/l$, or bleeding continues. The mean trend, at first, is therefore downwards. When the bleeding ceases the platelet count increases, reaching normal levels some two weeks later. Numerous factors affect the white cell count, including rejection and infection, which may be an explanation for the tendency of the curve to rise.

It is clear that the changes described in this study are affected by many factors which depend both on the patients and on their preoperative diagnoses. Nevertheless they represent a good model for all patients receiving intensive care following major hepatic operations. Conventional laboratory liver function tests are readily available as reliable automated procedures (bilirubin, alkaline phosphatase and alanine aminotransferase), but they reflect liver damage as well as other aspects of hepatocyte metabolism. The value of the prothrombin time and partial thromboplastin time as liver function tests is limited by the use of fresh frozen plasma given
perioperatively to correct clotting abnormalities. Because of these limitations other tests of liver function have been investigated including the clearance of dyes, pseudocholinesterase activity, antipyrine pharmacokinetic parameters, the $^{14}\text{C}_2$ aminopyrine breath test, oxygen consumption and the measurement of $\alpha_1$-antitrypsin and $\alpha_1$-acid glycoprotein (AAG) desialylation.

The clearance of dyes from the blood, including bromosulphthalein (Rosenthal and White 1925) and indocyanine green (Abdel Salam et al 1976), has been used as an indicator of liver function. The latter test has the advantage of being more rapid than the bromosulphthalein test. These tests are not in routine use clinically, although they may be used in the experimental situation.

Pseudocholinesterase is synthesised by the liver and low levels are found in patients with hepatocellular damage. The association between low plasma cholinesterase and liver disease was first shown by McArdle (1940) in a study of 269 subjects of whom 60 were normal adults and children and acted as the control group. The remaining 210 patients were assigned to several subgroups including patients with definite liver disease, heart failure, uraemia, hepatic jaundice, obstructive jaundice and a miscellaneous group. Some patients appeared in
more than one group. He demonstrated that of the patients assigned to the group with liver disease, except those with obstructive jaundice, 79% were below the lower limit of normal of plasma cholinesterase compared with the control group. In the group with obstructive jaundice it was only low in 12.5% of the patients. Hunt and Lehmann (1960) examined the value of serum albumin and pseudocholinesterase along with the recently developed analytical methods for transaminases in the assessment of liver function before and after venous shunt operations. They concluded that, in the 155 patients they studied, the serum albumin gave an accurate assessment of overall liver function, whilst pseudocholinesterase level was a better trend indicator of day to day liver function. Evans and Lehmann (1971) studied pseudocholinesterase in patients after liver transplantation. In this group of patients, decreased enzyme activity was associated with graft rejection and sepsis, and returned to normal following successful management of these complications. It was proposed that daily estimations of pseudocholinesterase activity and bilirubin may be the most sensitive indices of liver function following transplantation. Pseudocholinesterase is not currently measured because of the technical difficulty, the additional laboratory workload and the more accurate diagnosis obtained by liver biopsy.

The pharmacokinetics of antipyrine have been used to
study the oxidative metabolising capacity of the liver after transplantation. A marked improvement in drug metabolising ability of the donor liver compared with the recipient liver (Mehta et al 1986) was demonstrated. However, the patients were studied between one and two months postoperatively, and this test, which requires a specific assay, may be of limited value in the immediate postoperative period when liver function is assessed on a daily basis. The measurement of $^{14}$CO$_2$ in the expired air following $^{14}$C-aminopyrine administration both orally (Henry et al 1979) and intravenously (Pauwels et al 1982) has been proposed as a fast, sensitive, simple and reliable index of hepatic mixed function oxidases. However, the repeated administration of radio-labelled substances limits the value of this test to the screening and follow-up of patients with chronic liver disease.

In the immediate period following revascularisation of the liver, whole body oxygen consumption can be used to assess return of hepatic function. The liver, being a major organ of metabolism, contributes significantly to oxygen consumption. If the graft fails after revascularisation oxygen consumption will not increase (Svensson et al 1986).

The presence of serum desialylated glycoproteins correlated well with severity of liver disease and has
also been proposed as an index of the severity of hepatic failure (Serbourse-Goguel et al 1983). Surgical trauma, like other forms of injury, induces an acute phase reaction in which the liver decreases its rate of synthesis of albumin and increases its rate of production of a series of acute-phase proteins (Kushner 1982). These changes normally include a particularly rapid increase in the synthesis of C-reactive protein (CRP) and $\alpha_1$-antichymotrypsin (ACT), resulting in increased serum concentrations, while levels of $\alpha_1$-acid glycoprotein (AAG), which is also known as orosomucoid, increase more slowly, reaching lower peak values. Serum concentrations of prealbumin (PA) decrease during an acute phase reaction more rapidly than those of albumin, and can therefore be regarded as a "negative" acute phase reactant. Perioperative plasma concentrations of AAG are of further interest, since AAG is an important drug binding protein in plasma. Alterations in its plasma concentrations may have a significant effect on the pharmacokinetics of highly protein-bound drugs in the perioperative period (Chapters 12 and 13).

The ability of the recently transplanted donor liver to mount a stress response and synthesise acute-phase proteins and their value as indicators of liver function immediately following liver transplantation were therefore assessed. I was assisted with the sample
collection by Dr Alys M Burns (Registrar) and Dr Maire P Shelly (Research Registrar) and with the sample analysis by Dr Sue Walker and Dr Jacqui Calvin from the Department of Clinical Chemistry.

**SERUM ACUTE PHASE PROTEINS AFTER ORTHOTOPIC LIVER TRANSPLANTATION**

*British Journal of Anaesthesia (1990) 65; 418-420*

**Materials and Method**

Seven consecutive patients were studied immediately after liver transplantation. Patients received routine postoperative care as previously described. Serum samples were collected immediately prior to orthotopic liver transplantation and postoperatively on arrival in the Intensive Care Unit, then at four-hourly intervals over a period of twenty-four hours. Two further samples were collected at forty-eight and seventy-two hours. Subsequent analysis for CRP, ACT, AAG and PA was performed using specific immunoassays (Calvin et al 1982; Price et al 1987; Calvin and Price 1986; Calvin et al 1987). Bilirubin, alkaline phosphatase, alanine aminotransferase and albumin were measured in the stored samples over the initial twenty-four hour period using a Technicon SMA 12/60 analyser.
Results

Details of the seven patients are shown in the Table 6.4. The indication for liver transplantation in three patients was sclerosing cholangitis, three further patients had chronic active hepatitis, and one patient had polycystic liver disease. The study was discontinued in one patient owing to continuing postoperative intra-abdominal bleeding, necessitating early re-exploration. This resulted in an incomplete set of data for the first twelve hours.

Figure 6.3 demonstrates the changes in liver function tests over the first twenty-four hours following liver transplantation. Plasma concentrations of albumin increased in the postoperative period from low preoperative values. It should, however, be noted that this increase may have been produced by postoperative infusions of albumin and blood. Bilirubin demonstrated a marked decrease from the high preoperative values, although the postoperative values remained well above the normal range. Alkaline phosphatase showed a similar trend to bilirubin, although the mean postoperative values for the 24 hour sampling period lie within the upper limit of the normal range. In contrast, alanine aminotransferase showed a marked and sustained increase from preoperative values, with all postoperative values greater than the normal range.
<p>| | |</p>
<table>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>37.9 (3.21) years</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>61.7 (3.38) kg</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>3 male / 4 female</td>
</tr>
<tr>
<td><strong>Cold ischaemic period</strong></td>
<td>210 - 389 minutes</td>
</tr>
<tr>
<td><strong>Anhepatic duration</strong></td>
<td>59.4 (8.61) minutes</td>
</tr>
</tbody>
</table>

**Table 6.4.** Details of the patients studied following liver transplantation. Figures shown as mean (SEM), with range for duration of cold ischaemia.
Figure 6.3: Changes in mean (SEM) concentrations of conventional liver function tests over the first twenty four hours following orthotopic liver transplantation in six patients.
Figure 6.4 demonstrates the changes in the acute-phase proteins in the 72 hours following liver transplantation. Plasma concentrations of CRP and ACT showed a marked and sustained increase after surgery. The increase in AAG concentration was less rapid, with the maximal mean values being just above the upper limit of the normal reference range. Plasma levels of PA demonstrated a small increase postoperatively although they remained well below the lower limit of the normal reference range.

Discussion
Stress is a complex series of metabolic, endocrine and physiological processes. The acute-phase response includes the de novo synthesis and secretion of proteins by the liver (Kushner 1982). These proteins include proteinase inhibitors, e.g. ACT, coagulation and complement factors, transport proteins and a miscellaneous group which includes AAG and CRP. The stimuli for the hepatocyte to synthesise these proteins, and the underlying cellular mechanisms, are not fully understood, and the role of the stress response, particularly its prognostic significance, remains unclear. However, the stress response may reduce tissue injury and promote healing in association with enhanced host resistance (Kushner 1982).
Figure 6.4: Changes in the mean (SEM) concentrations of the acute phase proteins C-reactive protein (CRP), $\alpha_1$-antichymotrypsin (ACT), $\alpha_1$-acid glycoprotein (AAG) and prealbumin (PA) in the first seventy-two hours following orthotopic liver transplantation in six patients. Normal ranges: CRP <10 mg/l, ACT 0.35 - 0.63 g/l, AAG 0.5 - 1.0 g/l, PA 150 - 355 mg/l
There is also increased catabolism and turnover so that a number of other proteins show a decrease in concentration and are sometimes referred to as negative acute phase proteins.

The donor liver was able to synthesise acute phase proteins, despite the ischaemic damage sustained prior to transplantation. However, the response was less than that reported previously in association with major tissue injury or bacterial infection. At least a one hundred fold increase may be expected with CRP, and a two to four fold increase with ACT and AAG, although it remains unclear as to whether the degree of the response is important. The moderate increases seen in our patients may reflect dilution of the acute phase proteins, which largely remain within the intravascular space, by transfused blood containing low concentrations of these proteins, or poor donor liver function resulting in a less than maximal response. The levels of acute phase proteins have been studied in various disease states (Morely and Kushner 1982) and in liver disease. Significant increases in CRP concentration were not seen in association with alcoholic hepatitis. However, Chio and Oon (1979) studied AAG levels in patients with liver cirrhosis and demonstrated considerable variation between subjects. Significantly lower levels have been found in patients with severe liver disease (Barre et al 1984). The increase in acute
phase proteins demonstrated in this study following liver transplantation reflects the ability of the donor liver to synthesise these proteins, and may provide an indication of hepatocyte function. Serial values to demonstrate a trend may be of more value in interpreting liver function in the individual, rather than one result taken in isolation.

In this group of patients $\alpha_1$-acid glycoprotein concentrations increased following liver transplantation, although the highest values lay only just above the reference range. Kremer and his colleagues (1988) have demonstrated that patients with hepatic disease may have low levels of AAG. Decreased concentrations of AAG may result in an increased free fraction of those drugs which are strongly bound to AAG, eg erythromycin (Barre et al 1984). Since the free drug is the acute proportion this will result in an enhanced clinical effect (Henry et al 1979). Alteration in dosage regimens postoperatively may be required to achieve a similar therapeutic effect, as greater drug binding may occur with the rising levels of AAG. The pharmacokinetics of alfentanil following liver transplantation have been studied (Chapter 12) and an unpredictably prolonged effect was observed. Alfentanil is strongly bound to AAG but, in contrast to erythromycin, the alterations in AAG levels appeared to have little effect on the pharmacokinetics of this
While conventional liver function tests are a guide to liver damage and its subsequent recovery following liver transplantation, their interpretation remains difficult owing to several complicating factors, including episodes of infarction, infection, rejection and haemolysis. In this group of patients there are only small changes in conventional liver function tests (bilirubin, alkaline phosphatase and alanine aminotransferase) in the first 24 hours and there is normally little value in measuring liver function tests more than once in this period. Exceptionally, a significant increase in ALT over 8 to 12 hours has confirmed a clinical impression of possible hepatic infarction and then has been used as an indicator for immediate biopsy or retransplantation. The increasing use of liver biopsy in the postoperative period to aid interpretation of conventional liver function tests, with particular relevance to the diagnosis of rejection, has proved to be of value (White and Friend 1987). The acute phase proteins demonstrate an immediate response secondary to the operative stress, indicating the ability of the donor liver to synthesise these proteins despite ischaemic damage, and implies a large synthetic reserve in the donor liver. However, interpretation of absolute values is complicated by transfusion requirements, in these patients.
Unfortunately this test is not automated at present and so remains too complex for the daily postoperative assessment of liver function. Abnormalities in hepatocytes secondary to liver disease may affect glycoprotein structures. Measurement of the variation in the carbohydrate component of $\alpha_1$-acid glycoprotein has led to the calculation of a ratio which correlates well with the presence of one or more clinical complications of liver disease (Serbource-Goguel et al 1986). Such a ratio may be used to grade liver damage, but owing to the complexity of the test it again is of little value for routine assessment of liver function in the postoperative period.

In the immediate postoperative period the acute phase proteins may complement conventional liver function tests as a guide to the function of the donor liver. However, further studies are necessary to define their exact role.
Following liver transplantation adequate sedation and analgesia are essential. Analgesia is required because there is pain both from the large incision and from the intra-abdominal dissection. Respiratory depression and an antitussive effect are required immediately postoperatively to enable the patient to tolerate artificial ventilation and the tracheal tube. In a noisy and often brightly lit environment there is a further requirement for anxiolysis and the need for sleep. If complications such as bleeding or infection occur then sedation and analgesia may be necessary to enable a more prolonged period of ventilation.

Over the last few years there has been a change in the depth of sedation thought to be necessary for critically ill patients. In 1981 67% of ICUs thought patients should be deeply sedated and detached from the ICU environment (Merriman 1981). The most recent British survey (Bion and Ledingham 1987) has demonstrated a change in attitude, with the current aim in 69% of ICUs being to have the patient asleep but easily rousable. Amnesia for unpleasant events and procedures may also be beneficial, and nocturnal sleep is a further
requirement. Because of this change in emphasis some of the early pharmacokinetic and pharmacodynamic information in this thesis could not now be obtained.

It is difficult to assess whether good sedation and analgesia are achieved in critically ill patients because of their illness, its treatment and the effects of drugs. Two methods are used; members of the medical profession may be able to recount their experiences (Donald 1976; Shovelton 1979) or patients may be interviewed after their discharge. However, accurate recollections of a period of intensive care are often impaired by the severity of illness and some of the drugs, particularly benzodiazepines, interfere with memory. Bion (1988) has reported that 90% of patients who received midazolam during their period of intensive care had impaired memory of events. Asbury (1985) reported that 25% of patients had no memory at all for their period of intensive care and those who did only tended to remember the later part of their intensive care stay. Despite these difficulties, when Bion (1988) interviewed 60 patients after a period of intensive care he found the following incidence of unpleasant memories amongst them:
Physiotherapy 75%
Urinary catheter 75%
Thirst 66%
Face mask 66%
Nasogastric tube 58%
Anxiety 55%
Lack of rest 45%
Pain 40%
Tracheal tube 38%
Nausea 13%
Paralysis 13%

It is of note that thirst was prominent amongst these patients. The particular centre (in common with many others) uses morphine in a high percentage of its patients. White and his colleagues (1989) have recently shown that morphine gives rise to a dry mouth in patients with chronic pain. It is therefore conceivable that this frequent complaint is not only caused by abnormalities in fluid and electrolyte balance but is a feature of the treatment. Wallace, Bion and Ledingham (1988) noted that 33% of patients found their intensive care unit stay a pleasant experience with a further 45% finding it tolerable. Of more concern is the 8% who found it unpleasant and the 3% who were terrified. Interestingly 11% had no opinion whatsoever of it.

Bergbom-Enberg (1989) interviewed by telephone 304

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patients who had received artificial ventilation in Goteborg. She found that in patients less than 60 years old, females remembered more than males but in those patients aged more than 60 years, males remembered more than females. Inability to talk and communicate, tracheal suction and failure to synchronise with the ventilator all aroused feelings of fear and anxiety. Patients were reassured by their own belief in survival, by religious beliefs or by the presence of a nurse they could trust. Some patients felt insecure when cared for by specific nurses.

Chew (1986), working under my direction, interviewed 13 patients who had been treated in this intensive care unit, 3 patients having received liver transplants. The memories of these patients are compared with the other patients in Table 7.1. It is of note that 6 patients recalled pain. Unfortunately the degree and duration of pain were not recorded; in future studies this should be asked. No patient remembered therapeutic paralysis. One patient, who had not had a liver transplant, hallucinated after a change from parenteral to oral morphine and this may have been a reflection of the differing concentrations of metabolites seen after oral compared with intravenous administration (Park, Chew and Shelly 1985).
### Table 7.1: Patients' recall of intensive care following liver transplantation and after other causes of critical illness.

<table>
<thead>
<tr>
<th></th>
<th>Liver Transplants (n = 3)</th>
<th>Other Patients (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days in ICU (mean)</td>
<td>3</td>
<td>7.8</td>
</tr>
<tr>
<td>(range)</td>
<td>(3-4)</td>
<td>(1-34)</td>
</tr>
<tr>
<td>Days of ventilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean)</td>
<td>0.7</td>
<td>4.4</td>
</tr>
<tr>
<td>(range)</td>
<td>(0.5-1)</td>
<td>(0-28)</td>
</tr>
<tr>
<td>Recall: Ventilation</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Explanations</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Equipment</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Night/day</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Pain (includes discomfort)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Relatives</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disturbance</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dreams</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
This small study suggests that patients with uncomplicated liver transplants stay for a shorter period of time in the ICU and have a better recollection of events than other patients.

THE PATIENTS AND THEIR ENVIRONMENT

Certain features of patient care should be considered before pharmacological methods of relieving discomfort are discussed.

Patient’s Personality
The response to pain, unpleasant situations and discomfort will be modified by the patient’s prior experiences, fear, knowledge and personality. Stoics and deniers may do better than complainers; however, if deniers are given too full an explanation then their advantage disappears (Peck 1986). The liver transplant programme is international and has provided a unique insight into the differing expectations and personalities of many nationalities.

Preoperative Visit
Lazarus and Hagens (1978) demonstrated that the incidence of psychological stress is reduced by a preoperative visit by the anaesthetist and explanation of the postoperative period. A further study (Egbert et al 1964) demonstrated that a detailed explanation, from
the anaesthetist, about postoperative pain and methods of relaxation to reduce it decreased opiate requirements by half. Involvement of the family in this preoperative visit and in the subsequent postoperative course can be invaluable. When children are transplanted their need for sedation and analgesia decreases when they have the reassuring presence of their parents at the bedside.

The Environment
Some patients recalling their experiences in the ICU remember the frightening atmosphere, the unusual sounds and the feeling of being restrained by the various wires and monitoring lines etc. The importance of windows in an intensive care unit and of being able to recognise day and night have been emphasized (Keep, James and Inman (1980). When patients are close together in a cramped environment an increased need for sedative and analgesic drugs has been reported (Merriman 1981). In February 1989 the new John Farman Intensive Care Unit was opened. This has approximately three times the floor space of the previous ICU for only a 50% increase in bed complement. It remains to be shown whether this has led to a reduction in sedative requirements. The need to have clocks in view of the patients, so that they can remain orientated in time, has been suggested (Wallace, Bion and Ledingham 1988). However, not all patients like being able to see clocks; some feel it makes the day pass by very slowly.
Sleep

The importance of a good nights' sleep in the prevention of psychiatric morbidity has been emphasised (Kornfield, Zimberg and Malm 1965; Lazarus and Hagens 1968). Gross disturbances of both the type and duration of sleep have been described in critically ill patients. Immediately following major noncardiac surgery patients may only sleep for 2 hours each night with almost complete suppression of REM sleep (Aurell and Elmqvist 1985). Adams and Oswald (1983; 1984) have highlighted the metabolic necessity for a good nights' sleep. Growth hormone, essential for protein anabolism, is only released during sleep. At this time catabolic hormone secretion (particularly catecholamines and corticosteroids) is inhibited. Cell division and protein synthesis have been shown in many tissues to be highest when animals sleep. In humans, bone growth (in boys) is greatest and skin mitosis at its peak during sleep.

Psychiatric Problems in the Critically Ill

Depression is a major cause of morbidity, occurring in one-third to one-quarter of all medically ill patients (Brock Utne, Cheetham and Goodwin 1976; Bronheim et al 1985). It is particularly a problem when patients have been critically ill for many days and as a result may be sleep-deprived (Kornfield, Zimberg and Malm 1965). Some patients may become psychotic, which can be a severe manifestation of sleep deprivation or an
unwanted effect of immunosuppression with corticosteroids.

Suicidal thoughts and the wish to die are particularly common amongst liver transplant patients who have a long and complicated postoperative course. The majority of these patients are in renal failure, although it is difficult to know if this is a contributory cause or a manifestation of their severe illness. Initially they have all responded to low doses of imipramine, although the response has taken longer than that reported by others who used a larger and more frequent dose (Brock Utne, Cheetham and Goodwin 1976; Bronheim et al 1985).

Staffing Levels
The better staffed an intensive care unit is, the more time the patients' attendants will be able to spend reassuring the patient and on procedures such as sedation. Shortage of medical staff results in difficulties in providing adequate analgesia and sedation (Merriman 1981). However, if medical staff levels are high then reassessment of sedative regimens and regional anaesthetic techniques will be undertaken more frequently. Early on in the liver transplant programme both nursing and medical staffing levels were low, with at times less than one nurse per patient and, at night, no junior medical staff with sole responsibility to the Intensive Care Unit. Over recent
years these staffing levels have improved so that there is always at least one nurse per patient and one medical trainee in the Intensive Care Unit.

Equipment
The use of more sophisticated intensive care equipment will change the amount of sedation required by patients. In the initial stages of the liver transplant programme simple volume-cycled ventilators were available. They had no sophisticated weaning patterns such as intermittent mandatory ventilation (IMV) or synchronised IMV (SIMV) found on the current generation of ventilators. The use of these weaning modes has been shown to reduce the amount of sedation, but not analgesia, necessary following cardiac surgery (Sladen and Jenkins 1978). Since we adopted these weaning modes for patients following liver transplantation, the time spent receiving artificial ventilation has been reduced. In the initial period artificial ventilation was necessary for 2-3 days, whilst at the moment, following an uncomplicated transplant, the patient will only require assisted ventilation for 8-12 hours. The use of other special equipment, particularly air or bead beds, probably results in less need for sedation, although there is no evidence to support this.

The Stress Response
Kehlet (1982) has suggested that prevention of the
stress response may, by reducing catabolism and postoperative demands, decrease morbidity. However, it is not clear whether modifying the normal physiological response of stress is beneficial to critically ill patients; certainly extremes are undesirable. In highly stressed patients large amounts of catecholamines may be secreted leading to hypertension and cardiac arrhythmias; in addition, high levels of corticosteroids inhibit wound healing and lead to excessive catabolism. However, hypothyroidism is associated with a poor prognosis in the critically ill and excessive beta blockade obtunds the normal physiological response to hypovolaemia, which may result in sudden catastrophic haemodynamic instability. Hypoadrenalism occurring either as part of the disease process or following the administration of etomidate (Ledingham and Watt 1983) is also associated with a high mortality.

Pain itself may not be the sole initiating mechanism for the stress response and the release from damaged tissue of interleukin 1 (and probably other mediators) may be part of the response. To diminish the stress response during surgery is difficult. High dose opioids have been studied in an attempt to decrease the stress response. Morphine (1-4 mg/kg) or fentanyl (50 μg/kg) given before cardiac surgery both decrease the metabolic and endocrine response until the time cardiopulmonary bypass starts (Hall 1985). If epidural anaesthesia is used
to obtund the responses from pelvic surgery, then the dermatomes T4-S5 need to be blocked (Kehlet 1982), more than is necessary for analgesia. To be effective at abolishing the stress response both epidural analgesia and high dose opioids need to be started before surgery. Although it would be possible to start these techniques preoperatively in liver transplant patients both would be too dangerous in the postoperative period, particularly since no proven benefit has as yet been shown from ablating the stress response (Editorial 1985).

Thermal stress can be reduced by nursing on a fluidized bed at 32°C, instead of an ordinary hospital bed. This has been shown to reduce nitrogen loss in patients following aorto-bifemoral surgery (Ryan 1985; Jones et al 1985). In addition, the use of such beds may also reduce stress caused by pain, since patients in these beds do not have to be moved to the same extent as those on ordinary beds.

PHARMACOLOGICAL METHODS

Little is known about pharmacokinetics of many of the drugs commonly used in critically ill patients (Penfold and Park 1990). Studies are made difficult by not only the differences between patient groups but also the enormous differences between patients in the same group.
Furthermore, the pharmacokinetics and pharmacodynamics in a individual patients may change rapidly as their condition improves or deteriorates (Chapters 8 and 12).

A plethora of analgesics, hypnotics, sedatives, tranquillisers, neuroleptics and muscle relaxants has been used for patients requiring analgesia and sedation during intensive care. The range of drugs available suggests that the ideal treatment regimen does not yet exist.

Undersedation and inadequate analgesia in critically ill patients will have adverse pathophysiological effects. These may include autonomic disturbances, such as hypertension and tachycardia resulting in damage to an ischaemic myocardium. The inadequately sedated patient may disconnect or dislodge some of the equipment essential to his well-being and failure to synchronise with the ventilator may result in hypoxia and hypercarbia. Without adequate analgesia patients, particularly children, who are breathing spontaneously may fail to cough and expectorate their sputum effectively which, combined with underventilation, will result in atelectasis, lobar collapse, and an increase in pulmonary shunting of blood. They may progress to respiratory failure. Nurses (who usually decide when and how much sedation a patient receives) have a preference towards oversedation rather than undersedation. However, whilst
undersedation is obviously dangerous, oversedation is not without hazards and these are not so immediately apparent as those of undersedation.

The risks of oversedation include:

**Respiratory Depression**

This is a well-recognised hazard of excessive opiate analgesia. Direct depression of the brain stem pontine and bulbar respiratory centres occurs with all agonist opiates, and patients may have to rely on their hypoxic drive, rather than use of hypercarbia, to maintain ventilation. The increased use of hypoxic drive to maintain ventilation after morphine administration has been illustrated in a case report of a patient who became apnoeic after 6 mg of morphine following bilateral carotid endarterectomy. The same dose given preoperatively had produced no untoward effects (Lee et al 1981).

Catling and his colleagues (1980) demonstrated irregular breathing patterns in a group of patients following cholecystectomy. Apnoeic episodes of up to 40 seconds were seen in four of seven patients given a papaveretum infusion, whilst this pattern was seen in only one of seven patients given IM papaveretum. The infusion group also had a significantly greater decrease in PaO₂ than the IM group. Further studies,
at the same institution (Catley et al 1985) compared 16 patients who received regional analgesia (intercostal nerve blocks and epidural analgesia) with an identical group in whom a continuous intravenous infusion of morphine was used for analgesia. Serious abnormalities in respiratory pattern were seen in the morphine group, 10 of whom had 456 episodes of arterial desaturation (<80%), which always occurred whilst the patient was asleep. In the group receiving regional anaesthesia, $\text{SaO}_2$ never decreased below 87% and obstructive episodes were less common.

Both of these studies demonstrated disturbing changes in the immediate postoperative period and these can be expected to be even more profound following a more complex operation such as liver transplantation. Furthermore, since the liver is particularly sensitive to hypoxia, and the recently transplanted liver even more so, hypoxaemia is extremely detrimental to these patients.

In sensitive patients the administration of morphine may precipitate bronchospasm by releasing histamine.

Regional analgesia may avoid some of these problems by being less sedative and providing better analgesia. However, some authors have suggested a small amount of pain is an effective antagonist to the respiratory depressant effects of morphine (Duthie and Nimmo 1987).
When nerve blocks are performed in patients with chronic pain who have been receiving long term therapy with opiates, then respiratory depression may occur (Wells, Lipton and Lahuerta 1984; Hanks, Twycross and Lloyd 1981). This is a feature that has been noted in patients after liver transplantation. In the immediate postoperative period, whilst the patient requires artificial ventilation, morphine and midazolam are administered to keep the patient rousable but comfortable. The antitussive effect (Jaffe and Martin 1985), respiratory depression, euphoria and drowsiness produced by morphine are used to advantage in this situation. However, once the trachea is extubated these can be unwanted effects. To avoid these problems, when the patient is ready for weaning from ventilation, bilateral intercostal nerve blocks are performed. After these are performed and the trachea is extubated the patient may become bradypnoeic for a short period until the effects of the morphine and midazolam have worn off, since nearly all of the pain from the incision is removed by the nerve block.

All benzodiazepines depress the respiratory centre. Some 2-3 minutes after an IV bolus of benzodiazepines apnoea may be seen, with a small but prolonged increase in $E_\text{T}CO_2$. These effects can be completely reversed with flumazenil. There appears to be no effect on peripheral ventilatory responses (Reves 1986). Patients with chronic airflow...
limitation appear more sensitive than normal volunteers to the respiratory depressant effects of midazolam (Gross et al 1983).

Haemodynamic Effects

The administration of opiates commonly results in a decrease in systemic blood pressure and if the patient is hypovolaemic this may be significant. Pain causes the release of catecholamines and adequate analgesia leads to a reduction in these hormones with a consequent decrease in cardiac output (CO) and systemic vascular resistance (SVR). Morphine has additional haemodynamic effects, Hsu, Hickey and Forbes (1979) studied patients during heart surgery when they were on cardiopulmonary bypass in order to obviate any effects due to myocardial or respiratory depression. They observed that 0.5 mg/kg or 0.1 mg/kg of morphine produced a 46% decrease in SVR. This was associated with a later and more prolonged increase in vascular capacitance. The decrease in SVR could be attenuated (but not prevented) by the prior administration of promethazine (a H₁ blocker), the remaining decrease in SVR being attributed to either H₂ effects or a neurohumoral response. The decrease in SVR was not blocked by the administration of naloxone, excluding centrally mediated effects. Morphine is also thought to have a vagal stimulating effect. In patients following myocardial infarction, inappropriately slow heart rates in the presence of hypotension have been
observed and attributed to this effect (Semenkovich and Jaffe 1985).

Fentanyl is said to have fewer haemodynamic effects than morphine. In dogs, Liu and his colleagues (1976) demonstrated that high doses of fentanyl decreased heart rate, CO, SVR and MAP, whilst stroke volume increased. A similar decrease in heart rate was also observed when smaller doses (5 and 10 \( \mu \)g/kg) of fentanyl were administered to dogs. When these dogs were restudied, after cervical vagotomy, the decrease in heart rate was 10% of the previous study, confirming that vagal stimulation was responsible. Mean arterial pressure also decreased but since CO was not measured no conclusion about this observation could be made (Reitan et al 1978).

Sedative agents also have significant cardiovascular effects. Midazolam results in a decrease in blood pressure in both normal volunteers and patients with ischaemic heart disease. Three principal mechanisms are involved; there is a reduction in systemic vascular resistance by 15-33\%, a decrease in venous return and a small degree of myocardial depression. Compensatory baroreceptor reflexes result in an increase in heart rate by 18\%, which maintains cardiac index (Reves et al 1985; Reves 1986). Diazepam in equipotent sedative doses lowers the blood pressure less than midazolam (Reves 1986). Ketamine is unique as a sedative agent in that it may
increase blood pressure, through release of endogenous catecholamines (Park et al 1987a).

**Postoperative Ileus**

The reflex ileus that follows abdominal surgery is mediated through two neurogenic mechanisms; vagal fibres which cause relaxation of the stomach, and sympathetic fibres which have an inhibitory effect on the whole of the gastrointestinal tract. The dual innervation of the stomach may explain why gastric stasis can occur (with the resulting large nasogastric aspirates) in the presence of normal small bowel function (which is influenced little by abdominal surgery). In cats, epidural fentanyl could almost completely abolish the sympathetically induced ileus whilst fentanyl administered parenterally enhanced it (Lisander and Stenqvist 1985). Furthermore, opiates may also aggravate the postoperative ileus by inhibiting gastric emptying, delaying gastrointestinal transit and constricting smooth muscle (Nimmo et al 1975).

Prolonged postoperative ileus increases the duration of time parenteral nutrition may be necessary. In conscious patients opiates may cause nausea and vomiting.

**Gastrointestinal Blood Flow**

The clinical significance of changes in gastrointestinal
blood flow in patients following liver transplantation is difficult to determine. Leaman and his colleagues (1978) measured splanchnic blood flow, using indocyanine green, in 13 patients given 0.2 mg/kg morphine. Blood flow increased by 19% and splanchnic vascular resistance decreased by 16%. When fentanyl (10, 20 and 50 mg/kg IV) was administered to anaesthetised dogs with an isolated intestinal loop, a decrease in both oxygen uptake and vascular resistance and an increase in arteriovenous shunting were observed. After morphine 1 mg/kg was given to the same preparation no significant change in blood flow or vascular resistance was observed, but nutritive blood flow increased. At a higher dose of morphine (5 mg/kg) vasoconstriction was seen, which was abolished by alpha adrenoreceptor blockade (Tverskoy et al 1985). Although increasing arteriovenous shunting in the intestinal circulation may appear deleterious, it will result in an increased oxygen delivery to the liver, which may be beneficial immediately following liver transplantation.

The effects of benzodiazepines on hepatic arterial and portal flow have also been studied in dogs following induction of anaesthesia with midazolam (Gelman, Reves and Harris 1983). At this time heart rate and portal blood flow increased whilst cardiac index and hepatic arterial flow (HABF) decreased. Later, portal blood flow (PBF) also decreased. The biphasic response was thought
to be due to mobilisation of blood from the spleen and intestinal circulation. Since the ratio HABF/HABF + PBF did not change, the authors concluded that hepatic ischaemia should not occur. Whether this can occur in jaundiced patients who may not be able to mobilise blood in the splanchnic reservoir is unknown.

**Hepatotoxicity**

Shinju and his colleagues (1983) showed that in rats breathing a hypoxic nitrogen/oxygen mixture ($F_{\text{O}_2} 0.1$) isoflurane, halothane, enflurane and fentanyl are mildly hepatotoxic. Since this damage was seen with concentrations as low as 5-10% of MAC, they postulated that the agents induced further intracellular hypoxia. Baden and his colleagues (1985) have also shown a small amount of hepatocellular dysfunction in rats, who were not hypoxic, and given the same anaesthetic agents. These observations further support the need to avoid arterial hypoxaemia and to maintain hepatic blood flow in patients following liver transplantation.

**Muscle Tone**

Although muscle rigidity can be a problem when high dose opiates are used as part of an anaesthetic technique, it is rarely seen in the critically ill patients. This probably reflects the concomitant use of benzodiazepines which act as muscle relaxants. A generalised decrease in muscle tone with prolonged benzodiazepine
administration has not been observed.

Cerebral Function
Cerebral function is depressed with all of these drugs. If the duration of action of these drugs is prolonged and unrecognised then depression may be confused with cerebral damage, resulting in inappropriate major management decisions. Falsely abnormal neurological signs attributable to the drugs, such as upgoing plantar responses, may further confuse the picture and result in unnecessary investigations such as cranial computerised tomography being performed.

Immune System
Infection remains a major cause of mortality and morbidity in the critically ill and the contribution of sedation to this was described and recognised 35 years ago (Lassen et al 1954; 1956). Large doses of morphine (50 mg/kg) given to mice subcutaneously twice a day for five consecutive days have been shown to inhibit phagocytosis and the killing properties of polymorphonuclear leucocytes (Tubaro et al 1983). A dose-dependent inhibition of phagocytic activity is also seen in leucocytes, when exposed to therapeutic concentrations of morphine (Moudgill 1981). This is seen not only with morphine but also with diazepam, local anaesthetic agents (except bupivacaine) and intravenous induction agents. When these effects were studied in patients undergoing
inguinal herniorraphy, similar decreases in the migratory component of neutrophil function were found in the groups having repairs performed under general anaesthesia (spontaneous ventilation with halothane vs artificial ventilation with neuromuscular paralysis and N₂O, morphine for anaesthesia). In the group receiving epidural anaesthesia no decrease in neutrophil function was seen (Edwards et al 1984). Thus, unnecessary or excessive sedation may predispose the patient to infection, a problem exacerbated following liver transplantation because of the additional need for immunosuppression.

Renal Function

Codeine, which can be manufactured within the body from morphine and is present in papaveretum, has been implicated in the cause of renal failure (Shelly, Quinn and Park 1989). In 1957 Papper and his colleagues noted an antidiuresis when morphine, in normal therapeutic doses, was given to 16 normal subjects on 22 occasions. The decrease in urine output was not associated with an increase in osmolality and so could not have been due to stimulation of antidiuretic hormone. Creatinine clearance decreased during the same period. The decrease in urine output was due to a decrease in glomerular filtration rate. No adverse effects on renal function have been demonstrated with induction doses of midazolam in man (Lebowitz et al 1983).
Nitrogen Loss

Immobility caused by unnecessarily prolonged sedation will result in increased muscle wasting and nitrogen loss (Allison 1986).

In the light of these difficulties, and the high probability of others, deep sedation is now reserved only for patients who have head injuries (in whom cerebral protection may be necessary) or tetanus (when the aim is to prevent cardiovascular instability through sympathetic stimulation), or as a temporary measure during some painful procedure.

**DRUG UTILISATION IN INTENSIVE CARE**

Studies have demonstrated that opiates, in combination with a benzodiazepine, are the most frequently used method of sedation. In 1978 Buchanan and Cane studied 200 critically ill patients of whom 30% received diazepam and 35% morphine. Similarly, Campos and his colleagues (1980) noted that in excess of 50% of his patients received diazepam. A multicentre study published in 1981, involving 15 ICUs and 648 patients, showed that sedatives and analgesics were prescribed in more than 40% of patients, the majority receiving diazepam (Farina, Levati and Tognoni 1981). In the same year Merriman (1981) reported the results of visiting 34
British intensive care units to enquire about sedation and noted the wide variety of aims, techniques and drugs used. Phenoperidine was the commonest opiate in frequent use (21/34) (although many ICUs used more than one opiate). Diazepam was used in 22 units with the remainder using althesin or chlormethiazole for sedation. Interestingly, six of the ICUs used N₂O for periods in excess of 24 hours despite recognition of its adverse effects (Lassen et al 1956). Pancuronium was used in 91% of the ICUs. Merriman also suggested the advantages of the administration of drugs by constant infusion. Six years later a postal survey, in the United Kingdom, found that 60% of ICUs were using opiates and benzodiazepines together. Of these, 55% were using a continuous intravenous infusion with intermittent boluses, 10% mainly infusion regimens and the remainder were mostly using bolus administration of these drugs. Phenoperidine, morphine and papaveretum were the commonest analgesics. Since the introduction of midazolam in 1983, the use of diazepam has been steadily decreasing (Bion and Ledingham 1987). The change from diazepam to midazolam reflects ease of administration of midazolam (being water soluble) and its shorter duration of action. Even when the half-life of midazolam is prolonged it is still shorter than diazepam (Gamble, Dundee and Gray 1976). The influence of propofol on sedative practice remains to be elucidated.
Although some opiates do possess sedative effects, the criteria for an ideal drug producing sedation and analgesia would include the following:

- rapid onset of analgesic and sedative effect.
- rapid reversibility to allow assessment of cerebral function.
- no accumulation following prolonged administration.
- safe and reliable elimination even with impaired hepatic or renal function.
- lack of acute or chronic toxicity, enzyme induction and tachyphylaxis.
- reliable pharmacodynamics; affected as little as possible in shock, hypoproteinaemia, water, electrolyte or acid-base imbalance and organ failure.
- a pharmacokinetic profile suitable for use by infusion allowing easy dose adjustment.
- predictable dose-dependent depression of respiration.
- cardiovascular stability.
- no adverse endocrinological effects.
- no increase in muscle tone.
- minimum immunological or metabolic effects.
- no venous irritation.
- high therapeutic ratio.
- absence of active metabolites.
- simple administration, not requiring complex or
expensive equipment.
- no psychic or physical withdrawal symptoms on discontinuation of treatment.
- no absorption on toplastic or glass.
- no interactions with other drugs.
- water soluble so that the effects of solvents can be ignored.
- stable in solution and on exposure to light.
- low cost.

Sedation and the Severity of Illness

Bion and his colleagues (1986) demonstrated that the higher the sickness score, the lower the blood morphine level necessary to produce sedation. They did not measure morphine-6-glucuronide, an active metabolite of morphine, which has attracted comment (Park et al 1987b). However, in some extremely ill patients increasing amounts of sedation may be necessary to diminish respiratory drive and allow adequate ventilatory support. Young patients who have limited systemic illness may require large amounts of sedative and analgesic drugs. The differing requirements of patient groups may reflect alterations in the elimination of drugs in the more seriously ill patient or a change in the receptors (Hasselgren 1986). Other factors may alter the pharmacokinetics and pharmacodynamics of the drug. Changes in the carrier protein (usually albumin) concentration may alter the
volume of distribution and free drug concentrations. Blood pH will affect the affinity of the drug for the carrier protein and its binding sites. Changes in regional blood flow may also alter the disposition of drugs; for example, hypercarbia in dogs produces an increase in the plasma and cerebral cortex half life of morphine (Fink et al 1977). These changes were attributed to alterations in cerebral flow and a decrease in binding to albumin.

Changing Dose Requirements
Rapid adaptation of the central nervous system to many agents has been demonstrated, including thiopentone (Dundee, Price and Dripps 1956), nitrous oxide (Whitwam et al 1976) and opiates (McQuay, Bullingham and Moore 1981). A group in Glasgow (Marshall et al 1985) studied two groups of patients following elective cholecystectomy. The first group received an infusion of morphine for the first 24 hours and the second group a placebo infusion of saline. Both groups were allowed to demand intermittent intramuscular morphine as necessary. The group that received the morphine infusion required the same amount of intramuscular morphine as the control group in the first 24 hours. In the subsequent 24 hours they required more morphine than the control group. Over the total study (48 hours) the infusion group required considerably more than the control group. Although pain control in both groups was
identical, and although pain is decreasing naturally during this time, the increase in dose requirement of morphine in these patients indicates that pain will result if the dose is not increased. In critically ill patients, however, the increasing dose requirements can be of great significance. There may be several operations in a short period of time and the need for respiratory depression and the antitussive effect of narcotics may increase if the patient becomes unwell.

SEDATIVE AGENTS

Benzodiazepines
Many different benzodiazepines are available. The most commonly used ones in critically ill patients are lorazepam, diazepam and midazolam.

Figure 7.1 shows the differing pharmacokinetic parameters and metabolic pathways of some of the benzodiazepines in common use.

Lorazepam
Dundee, Johnston and Gray (1976) described the intermittent IV administration of this long-acting benzodiazepine every 4-6 hours for 25 patients requiring intensive care, of whom 22 required artificial ventilation.
Figure 7.1: Metabolic pathways and pharmacokinetic parameters of the commonly used benzodiazepines. Reproduced by permission of Roche Products Ltd.
Haemodynamic studies with large IV doses of lorazepam (8 mg) demonstrated a 25% decrease in cardiac output, which was not accompanied by a fall in blood pressure. Although satisfactory sedation was achieved, the technique did not achieve popularity. When this method was compared with a continuous intravenous midazolam infusion it proved difficult to use and this arm of the study was subsequently abandoned. This may have been an unfair comparison since we were comparing not only two drugs but two different methods of administration.

Diazepam
This is available in two preparations: either as diazepam, in propylene glycol, or as diazemuls, when the diazepam is dissolved in soya bean extract. In critically ill patients, the metabolism of the drug and its elimination may be markedly reduced and its active metabolite, desmethyldiazepam, has an even longer half-life (Lowry et al 1985).

Midazolam
Midazolam is a water-soluble benzodiazepine with a rapid onset and short duration of action in normal subjects (Dundee et al 1980). Its main metabolite, \( \alpha \)-hydroxymidazolam, is pharmacologically active but has a shorter elimination half-life than midazolam (Crevoiser et al 1983). Midazolam has been used for sedation for minor procedures (Whitwam, Al-Khudhairi, McCloy 1983),
induction of anaesthesia (Gamble et al. 1981) and sedating critically patients.

**Flumazenil**

Flumazenil is a specific benzodiazepine antagonist which acts on the GABA receptors (Amrein et al. 1987; Klotz and Kanto 1988). Several authors have described its role in reversing prolonged sedation, due to benzodiazepines, in critically ill patients (Bodenham et al. 1988; Pepperman 1989). Its use for this indication is discussed in greater depth in Chapter 9.

**Methohexitone**

This is a short-acting oxybarbiturate with a half-life of approximately two hours. Barbiturates have not achieved popularity because of prolonged elimination and slow recovery. However, this agent has occasionally been found to be useful, particularly if tolerance is developing to other agents. It might be expected to have a lower convulsive threshold if the patient is receiving cyclosporin A, although this has not been reported.

**Chlormethiazole**

This agent is structurally similar to thiamin (Vitamin B₁). It has been widely used in pre-eclampsia and status epilepticus and during regional analgesia. It is only available as a 0.8% solution and large volumes may be
needed to sedate patients; because of this, it has not found widespread acceptance in the management of the critically ill. New methods of renal support may overcome this difficulty (Chapter 10).

**Phenothiazines**

These have been widely used in the past as sedative agents and continue to be used as antiemetics. Chlorpromazine is the most widely used in the critically ill. It is an alpha adrenergic blocking agent and so can produce hypotension. In liver transplant patients it is avoided because it can cause a cholestatic jaundice which may confuse the clinical picture. In some studies of ICU drug utilisation they have been found to be widely used (Farina et al 1981).

**Butyrophenones**

This group of drugs comprising principally droperidol and haloperidol, is not widely used. Their use may result in hepatic dysfunction and dystonic reactions. Compared with other agents they are less sedating and are amongst the most powerful antiemetics known. Haloperidol has occasionally been useful in managing psychoses caused by the corticosteroids given for immunosuppression.

**Propofol**

Di-isopropylphenol in soya bean emulsion is a short-
acting anaesthetic agent. When used as an induction agent during anaesthesia it is associated with rapid recovery. Its use for sedation has been investigated by several authors (Grounds et al 1987; Beller et al 1988; Aitkenhead et al 1989). A detailed description of this agent is given in Chapter 10.

Ketamine

This agent is not widely used for sedating critically ill patients. It produces bronchodilation, does not depress the respiratory centre, maintains cardiac output and does not cause vasodilation. These last two actions are mediated by central stimulation and the release of catecholamines. It may be useful in hypotensive patients, particularly if they have bronchospasm (Park et al 1987a).

Etomidate

Etomidate, a water-soluble imidazole derivative, formulated in propylene glycol, was introduced as an anaesthetic induction agent and was found to be very cardiostable. It was soon introduced into intensive care practice (Edbrooke et al 1982) where it rapidly gained popularity. The Glasgow group (Ledingham and Watt 1983, Watt and Ledingham 1984) noted an increased mortality rate amongst patients following major trauma who had been sedated with this agent. Simultaneously and in the same unit, others had noted low
plasma cortisols and a decrease in mortality after the administration of cortisol to these patients (Findlay and McKee 1982; McKee and Finlay 1983). It is now known that etomidate inhibits the synthesis of cortisol in the adrenals at the 11\beta and 17\beta hydroxylase stage.

Although etomidate was given to patients after liver transplantation, all patients had fortunately received corticosteroids as part of their immunosuppression and did not suffer from adverse effects due to etomidate. Since these adverse effects were recognised it is no longer recommended for sedation of critically ill patients.

Althesin

This agent was also introduced as an intravenous induction agent in anaesthesia. It is a mixture of 2 steroids, alphaxolone and alphadalone, and since it is insoluble in water it was formulated in 20% polyoxyethylated castor oil (cremophor EL). Two groups (Ramsey et al 1974; Miller-Jones and Williams 1980) have described its use for sedation of patients requiring ventilatory support. Although it was a satisfactory agent for this purpose, the high incidence of anaphylactoid reactions and decreases in plasma albumin following infusions led to its withdrawal (Knell, Turner and Chalmers 1983; Lawler, McHutchon and Bamber 1983). Both of these adverse effects can be attributed to the...
solvent. The anaphylactoid reactions were independent of dosage but prolonged administration of althesin led to 50 - 100 g per day of solvent being administered which could then not be eliminated and resulted in hypoalbuminaemia (Morgon and Dawson 1984).

INHALATIONAL AGENTS

Nitrous Oxide
Nitrous oxide has been widely used to provide analgesia and sedation in the critically ill (Lassen et al 1954; Parbrook 1972; Merriman 1981). Concerns about bone marrow depression led to discontinuation of its use for this purpose (See Chapter 5).

Isoflurane
Kong, Willatts and Prys-Roberts (1989) have evaluated isoflurane for sedation of critically ill patients. They found it a satisfactory agent, although their studies were only for 24 hours, and its role for prolonged sedation needs to be investigated further. It would be particularly attractive in patients with liver disease because of its low biotransformation and excretion via the pulmonary system. It does however have the disadvantage of the necessity to duct the expired gases away from the ventilator if pollution is to be avoided. Although it is only minimally
metabolised some fluoride is released. In hepatic and renal failure, fluoride concentrations may increase. One such case, in a patient after liver transplantation, has been reported. Dr Alys Burns was my co-author with this report.

SERUM FLUORIDE AFTER ISOFLURANE SEDATION

British Medical Journal (1989) 298; 1642

A 21-year-old girl required sedation following a combined liver and renal transplant which was complicated by acute tubular necrosis (managed with continuous haemofiltration and dialysis), recurrent sepsis and life-threatening gastrointestinal haemorrhage. She remained agitated and distressed whilst receiving a midazolam infusion at up to 15mg/hour and bolus doses of morphine. Effective sedation was finally achieved using a combination of 0.5-2% isoflurane and a continuous intravenous infusion of, initially, midazolam (10mg/hour) and, subsequently, alfentanil (8mg/hour). Because of concern about nephrotoxicity of fluoride released from the breakdown of isoflurane and the potential failure to eliminate it in this patient, a serum fluoride was measured after 6 days of treatment and found to be elevated at 18μmol/l (normal range 5.3-10.5μmol/l). Although this is not at the toxic level of 50μmol/l, it is greater than that previously reported with isoflurane (Mazze, Cousins and Barr 1974;
Since this report the Bristol group has published the results of a study measuring the plasma concentrations of fluoride in 26 patients sedated with isoflurane for 24 hours. An increase in the plasma concentration of fluoride was noted, reaching its maximum (13.57μmol/l) 12 hours after discontinuation of the isoflurane (Kong et al 1990). There remains the possibility that even higher concentrations may be achieved in critically ill patients who receive isoflurane for longer periods or if renal impairment is present. Furthermore, the toxic concentration of fluoride may be lower than previously reported, particularly in patients after liver transplantation who are receiving concomitant treatment with other nephrotoxic drugs such as cyclosporin.

The question of cost must also be considered. The ventilator used for this patient was an open-circuit ventilator necessitating large fresh gas flows and the estimated cost of isoflurane for our patient was £1200 over the six day period (the cost of the midazolam at 10mg/hour was £19.20/24 hours and of alfentanil at 8mg/hour was £107/24 hours).

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The choice of opiate chosen by many ICUs is based on perceived advantages that often are not scientifically proven. Phenoperidine has been thought to be more predictable than other opiates (Merriman 1980), although others have shown this not to be so (Miller-Jones and Williams 1980). Similarly, papaveretum is commonly chosen because it is said to be more sedative and produce less emesis; this remains to be proven. All opiates, particularly morphine (Dodson 1982), show an immense variation in requirements.

**Morphine**

Morphine is commonly used either alone or as papaveretum, to provide analgesia to patients receiving intensive care. It is often given by continuous intravenous infusion. Its metabolism is discussed in Chapter 11.

**Papaveretum**

This narcotic is a mixture of alkaloids of opium and includes codeine (2.5-5%), morphine (47.5-52.5%), noscapine (16-22%) and papaverine (2.5-7%). Its use is restricted almost entirely to Europe and Australia. It has no significant advantages over morphine apart from containing more opiate than most clinicians imagine.
Pethidine

Pethidine is a narcotic which has been used to provide postoperative analgesia in the critically ill (Yate et al 1986), although it is infrequently used for this purpose. Its pharmacokinetics in critically ill patients have not been fully evaluated. The clearance of pethidine is decreased in patients with impaired liver function, although the volume of distribution and degree of protein binding are unchanged. This pattern has been observed in patients with cirrhosis and in those with viral hepatitis (Klotz et al 1974) when a collateral circulation does not develop. Because of this, the prolonged half-life of pethidine in these patients has been attributed to an impaired metabolic function of the liver. In patients with impaired renal function receiving repeated doses of pethidine, accumulation of the major metabolite of pethidine, norpethidine, will occur (Szeto et al 1977). This metabolite has a central excitatory action which can lead to fits and other CNS excitatory phenomena (Kaiko et al 1983).

Phenoperidine

This opiate has been used as an analgesic for critically ill patients, particularly those following head injury. It has a half-life of approximately 60 minutes and its main metabolites are pethidine and norpethidine. In patients with liver disease phenoperidine has a prolonged elimination half-life and a reduced clearance.
(Isherwood et al 1984). This appears to be due to reduced hepatic metabolism, since the proportion of the administered dose excreted as pethidine and norpethidine is decreased, while that excreted as phenoperidine is increased. The pharmacokinetics of phenoperidine in renal failure are not known and accumulation of norpethidine might occur.

**Fentanyl**

This is a synthetic opiate which has been used to provide analgesia to critically ill patients and is usually administered by continuous intravenous infusion. In the critically ill, fentanyl appears to have a prolonged terminal half-life with an enlarged volume of distribution; the clearance and degree of protein binding remained the same (Alazia et al 1987; Shafer et al 1983). This altered pattern was thought to be due to interactions with other drugs administered concomitantly, leading to an increased penetration of fentanyl into preferentially perfused tissues (Alazia et al 1987).

The pharmacokinetics of fentanyl are not altered significantly in the presence of hepatic cirrhosis (Haberer et al 1982). Fentanyl is a drug with a high extraction ratio but because of its large volume of distribution it has been suggested that its terminal half-life probably reflects its slow release from
tissue depots rather than hepatic elimination (McClain and Hug 1980). Fentanyl clearance appears to be normal in renal failure (Coral, Moore and Strunin 1980), although detailed studies are lacking.

Tolerance to fentanyl may develop during prolonged infusions, with patients being awake and responsive at serum fentanyl levels normally associated with anaesthesia (Shafer et al 1983; McQuay et al 1981).

Alfentanil
This new short-acting opiate is currently being promoted as an analgesic for use by infusion in artificially ventilated patients. Pharmacokinetic studies in intensive care patients have shown decreased clearances comparable with those seen in anaesthetised surgical patients (Yate et al 1986; Sear et al 1987). A normal clearance in renal failure has been demonstrated (Van Peer et al 1986), suggesting that alfentanil is a suitable opioid for use in this situation. An investigation of its pharmacokinetics following liver transplantation is described in Chapter 12.

Naloxone
Naloxone is a specific opiate antagonist acting at the $\mu$ receptors. Its use in sedation and analgesia is limited to assessment of patients who may have prolonged sedation. If used to facilitate weaning it can produce
arrhythmias and sudden hypertension when analgesia is reversed along with respiratory depression unless an additional method of pain relief is provided. Should respiratory depression be evident in a liver transplant patient it is usual to leave them receiving SIMV until the problem has resolved.

MUSCLE RELAXANTS

These do not provide sedation or analgesia but are included in this chapter because they may be needed to supplement sedative and analgesia techniques following liver transplantation. They do however reduce the requirements for halothane and possibly other analgesic agents by preventing movement (Green 1980). They may also reduce analgesic requirements by causing cortical deafferentation by decreasing the input of the muscle spindles into the reticular activating system. Alternatively, but less likely, they may decrease synaptic transmission centrally (Forbes, Cohen and Eger 1979). However, a major concern with their use is that patients may be paralysed and awake (Miller-Jones and Williams 1980; Shovelton 1979). Their use is therefore restricted to certain well-defined indications, including the prevention of a rise in intracranial pressure, reduction of pulmonary barotrauma and, in situations where critical oxygenation exists, a reduction in oxygen consumption.
Park and Manara 1988a). There has been a significant reduction in their use with improvements in both sedative techniques and changes in ventilator technology. Merriman (1980) reported their use in 91% of patients, whereas by 1987 they were in use in 16% (Bion and Ledingham 1987).

REGIONAL ANALGESIA

When patients are breathing spontaneously and their trachea has been extubated, there is no longer any need for sedation, but there may still be a continuing need for analgesia. This need may be even greater at this time because underventilation, particularly if combined with a failure to expectorate, will result in areas of collapse, an increase in pulmonary shunting and the risk of infection and respiratory failure. Opiates can be used but their antitussive and respiratory depressant effects limit their use in this situation, so regional analgesia is superior (Engberg 1975). Suitable techniques to provide postoperative analgesia for patients following liver transplantation include epidural analgesia, paravertebral blocks, subarachnoid analgesia, intrapleural catheters, wound perfusion and intercostal nerve blockade. The last two methods are discussed in depth in the chapter dealing with this subject. Spinal analgesia using local anaesthetic
agents has too short a duration of action to be useful, and the intrathecal opiates are unpredictable, although the use of midazolam by this route may warrant investigation in the future (Goodchild and Noble 1987; Cripps and Goodchild 1988). Paravertebral nerve blockade and epidural analgesia can both be used with a catheter to provide continuous analgesia. However, they require the use of large needles to insert catheters and in patients with liver disease the coexisting coagulopathy makes this hazardous. Furthermore, both techniques also interfere with the thoracic sympathetic outflow and this, combined with the abnormal splanchnic circulation, following liver transplantation, and the inability of jaundiced patients to mobilise blood from this area, can result in profound hypotension. Because of these hazards these techniques are not used.

Opiates administered into the epidural space (Yaksh and Ready 1976) may be effective and not produce cardiovascular instability (Reiz and Westberg 1980), but late respiratory depression (Scott and McClure 1979) limits their usefulness, particularly since the analgesia is mediated by cephalad spread to an area where receptors may be abnormal in liver disease.

BACK PAIN

This is common in patients following liver
transplantation who have been chronically unwell for some time. It is usually an accompaniment of osteoporosis and vertebral body collapse. Treatment can be difficult, and, although mobilisation usually resolves the problem this particular group is often unwell postoperatively, making this impracticable. Since the response to morphine is poor, other analgesics are tried with varying degrees of success, including paracetamol and buprenorphine. Aspirin is not used because of its adverse effects on platelet function. Transcutaneous nerve stimulation on occasions has been useful.

ASSESSING SEDATION AND ANALGESIA IN THE CRITICALLY ILL

Regular monitoring of conscious level is a valuable clinical observation and is essential to pharmacodynamic studies. The routine recording of conscious level in patients receiving intensive care allows assessment of the level and duration of sedation and therefore more rational use and investigation of sedative agents. This is an advantage, not only in clinical trials of sedative agents but also where comparison of different sedative regimens may be necessary in a patient difficult to sedate. Regular monitoring of sedation also facilitates description of the level of sedation of a patient between members of the medical and nursing staff and avoids ambiguous descriptions such as 'light' and 'heavy' sedation. In addition, it may facilitate teaching by
illustrating the differences between different agents.

In the light of our current lack of knowledge of pharmacokinetics greater reliance must be placed on pharmacodynamics. Great effort is expended in accurately measuring cardiovascular changes after giving cardioactive drugs; similar efforts should be made for the pharmacodynamics of other drugs. In the case of sedatives and analgesics the introduction of sedation scores, regularly assessing analgesia and avoiding fixed dose regimens should avoid many of the problems of drug accumulation.

No simple system exists to standardise the regular recording of the level of sedation in patients receiving intensive care. An indirect assessment of the depth of sedation may be made by measurement of some variable influenced by conscious level. Tests of performance, such as the peg board test (Dundee et al 1980), the p deletion test (Kennedy and Ogg 1985) and reaction times (Crevoisier et al 1983) have been used to indirectly assess sedation. In healthy patients or volunteers, tests of performance may provide an index of sedation if motor function is not impaired; however, these tests require a high degree of patient cooperation and are, therefore, inappropriate for use on patients receiving sedation on an intensive care unit. In patients requiring intensive care, other indirect observations
such as haemodynamic parameters may be taken to indicate the level of sedation. However, these may be unreliable in critically ill patients where haemodynamic instability may result from disease or concomitant drug treatment and be unrelated to sedation. The direct assessment of sedation relies on monitoring conscious level in some way. A variety of systems have been described to assess conscious level, however, not all are appropriate to the critically ill patient. A subjective score of how sedated the patient feels, although useful in well patients and volunteers (Crevoisier et al 1983), cannot usually be completed by a critically ill patient because of illness or the concomitant drug administration.

The system most commonly used to measure sedation in a clinical situation is the Glasgow Coma Score (Teasdale and Jennett 1974). This relies on eliciting an appropriate response to voice and pain and is primarily a measure of neurological function. As such, it is a valuable system and has been incorporated into the APACHE II scoring system to assess disease severity (Knaus et al 1985). While it does evaluate conscious level, the Glasgow coma score is not designed as a simple assessment of sedation; it is time consuming for the nurse to perform and disturbing for the patient. Linear analogue scores are accurate and reproducible (Revill et al 1976) and have been used by observers to
assess the depth of sedation of a patient. There is marked interindividual variation in the completion of linear analogue scores, and one person must, therefore, complete the entire assessment in order to reduce bias. This is time consuming, and, while such a system may provide an accurate record of the level of sedation, it is impractical for long term use in an intensive care unit.

Point scoring systems for the recording of sedation by an observer have been described previously but have been designed primarily as experimental tools. A scoring system based on numbered points may be insensitive (Huskinson 1974), but one based on clinically identifiable end points is more accurate and identifiable. A scoring system has been described by Ramsey and his colleagues (1974) using six points, three with the patient awake and three with the patient asleep. It was designed as a system to assess sedation frequently during a clinical trial, a use for which it has become widely used (Kong, Willatts and Prys-Roberts 1989; Aitkenhead et al 1989), but it has not been widely adopted for routine clinical measurement.

An objective assessment of sedation may be obtained by monitoring cerebral function directly (Sebel et al 1983). Different drugs alter electroencephalographic and cerebral function tracings in different ways and

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these, together with the measurement of evoked potentials, may be useful in establishing the depth of anaesthesia (Jones and Konieckzo 1986). The effect of liver disease on cerebral function in critically ill patients is not known. Lower oesophageal motility has been useful during anaesthesia to determine depth and has been reported as useful in a case report in a patient with renal failure (Sinclair and Suter 1988). Because the oesophagus is so friable it is unlikely to be of use in liver transplant patients. Further developments are necessary in this field if these techniques are to be useful in the assessment of sedation in a patient receiving intensive care.

A simple scoring system for sedation, developed for routine use on this Intensive Care Unit, is shown in Table 7.2 (Shelly, Dodds and Park 1986).

This system uses six identifiable clinical end points, 'paralysed' or 'asleep' being written in a space by the nurse as appropriate. The use of neuromuscular blocking agents is, therefore, noted since assessment of sedation is difficult in their presence. For the purposes of quantification or statistical analysis, sleep is assumed to be roused by voice and recording it as such avoids waking the patient to assess sedation.
1. Fully Alert
2. Roused by voice
3. Roused by pain
4. Unrousable
   Paralysed/Asleep

Figure 7.2: The First Addenbrooke’s Sedation Score
This early scoring system proved not to be sufficiently sensitive and in particular did not allow for agitation or confusion in the original design. In addition, the painful stimulus was not standardised.

The recognition of these deficiencies led to a modified score which is shown in Table 7.3. No blank boxes were left on this score since previous experience had shown them to be filled in with words such as "sedated".

The first line represents unsatisfactory sedation. The next two categories represent currently perceived satisfactory levels of sedation, whilst the next two are excessive sedation. The painful response was standardised as tracheal suction, which avoided the need to inflict further pain on patients for the purpose of assessment. As in the previous score the final two categories mean that sedation was not assessed. This scoring system has now been used in approximately 500 patients and found to be a marked improvement on the previous score (O'Sullivan and Park 1990).
1. Agitated
2. Awake
3. Roused by voice
4. Roused by tracheal suction
5. Unrousable
6. Paralysed
7. Asleep

Figure 7.3: The revised Addenbrooke’s sedation score.
Midazolam is a water-soluble benzodiazepine with a rapid onset and short duration of action in normal subjects (Dundee et al 1980). It has been used to provide sedation for minor procedures (Whitwam, Al-Khudhairi, McCloy 1983), induction of anaesthesia (Gamble et al 1981) and for anxiolysis in critically ill patients requiring intensive care.

Midazolam is metabolised by hydroxylation and subsequent conjugation with glucuronic acid (Figure 7.1) before excretion in the urine (Allonen, 1981). The cytochrome P450 system is thought to be involved in its biotransformation and because of the extensive first pass metabolism of midazolam following oral administration, the liver has been proposed as the site of metabolism (Allonen, 1981; Dundee et al, 1986). The principle metabolite is α-hydroxymidazolam which is pharmacologically active but has a shorter elimination half life than midazolam (Crevoiser et al 1983).

This chapter aims to demonstrate how problems identified in the general population of the intensive care unit were resolved using studies in patients undergoing liver transplantation. The first part therefore reports...
general studies performed in patients who have not necessarily undergone liver transplantation, to enable the later parts of this chapter to be placed in context.

INITIAL STUDIES WITH MIDAZOLAM IN CRITICALLY ILL PATIENTS

The first study with this drug, performed in 1984/5, was a retrospective review of 40 patients who required a midazolam infusion as part of their intensive care. Twenty-four of the patients were surgical and, of these, seven had received a liver transplant. The remaining 16 patients had medical problems necessitating intensive care. All of the patients were adults and their age varied from 13-84 [mean (SD) 45.0 (21.6)] years. The duration [mean (SD) <range>] of the midazolam infusion was 4.8 (3.7) <1-13> days and the rate of infusion was 3.8 (2.0) <1-11> mg/hr.

This technique provided adequate sedation for 93% of the patients reviewed; in only 3 patients was supplementary sedation required. The mortality rate in this study was 40%, greater than expected but this was probably a reflection of the severity of illness. Severity of illness scoring was not practised at this time but it is of note that sixteen of the patients were in renal failure. Interestingly, no patient was observed
to have any difficulty with recovery from the midazolam.

Following the retrospective study a prospective study was undertaken with Dr Maire Shelly and Dr A Bodenham, who assisted with the data collection, and Dr M Sultan, who assisted with the data tabulation.

MIDAZOLAM INFUSIONS IN CRITICALLY ILL PATIENTS

Method
Information was collected prospectively on a further 50 consecutive patients who required sedation during their period of intensive care. These patients received a continuous intravenous infusion of midazolam as a 1mg/ml solution in 5% dextrose. The rate of midazolam infusion was under the control of the nursing staff (subject to prescribed limits). This enabled titration of the dosage according to individual requirements. Pain was controlled by concurrent administration of analgesic agents.

The rate of infusion of midazolam was recorded hourly. Sedation was assessed using the five point score described in Chapter 7. Awakening was defined as an increased conscious level of two points on the sedation score. Each day at 1700 hours the nurse caring for the patient was also asked to rate patient cooperation,
tolerance of ventilation and comfort on a four point scale (1 = poor, 2 = fair, 3 = good, 4 = excellent).

The severity of the patient’s illness was assessed by recording the sepsis score (Elbute and Stoner 1983) daily and an APACHE II score (Knaus et al 1985) on admission, each week and on cessation of the infusion. Heart rate, blood pressure, central venous pressure, urine output and respiratory rate were recorded hourly in all patients until they were in the convalescent phase of their illness when observations may have been recorded two hourly. Daily full blood counts and estimations of urea and electrolyte concentrations were made. In addition, liver function tests were performed three times each week and a short synacthen test was performed at least once each week unless corticosteroids were being administered concurrently.

Statistical analysis was performed using Student’s paired and unpaired t test and the Wilcoxon rank sum test where appropriate.

Results
The patient diagnostic groups are shown in Table 8.1 and information about the patients’ age, weight and their infusion of midazolam is shown in Table 8.2. Of particular note is the high percentage of liver transplant patients in the surgical group of patients.
Table 8.1: The diagnosis on admission of the patients who received a continuous intravenous infusion of midazolam. During treatment 20 patients developed renal failure. ARDS = adult respiratory distress syndrome.
<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>51.1</td>
<td>19.0</td>
<td>2.0-75.0</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>63.0</td>
<td>15.6</td>
<td>11.5-82.0</td>
</tr>
<tr>
<td>Duration of stay (days)</td>
<td>14.3</td>
<td>14.8</td>
<td>1.0-81.0</td>
</tr>
<tr>
<td>Duration of artificial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ventilation (days)</td>
<td>11.4</td>
<td>12.6</td>
<td>1.0-81.0</td>
</tr>
<tr>
<td>Duration of midazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infusion (days)</td>
<td>4.4</td>
<td>1.9</td>
<td>1.8-9.5</td>
</tr>
<tr>
<td>Rate of infusion of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>midazolam mg/hr</td>
<td>4.7</td>
<td>1.9</td>
<td>1.8-9.5</td>
</tr>
<tr>
<td>APACHE II on admission</td>
<td>16.5</td>
<td>8.6</td>
<td>2.0-32.0</td>
</tr>
<tr>
<td>Sepsis score on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>admission</td>
<td>7.0</td>
<td>8.0</td>
<td>0 -27.0</td>
</tr>
</tbody>
</table>

Table 8.2: Details of the patients receiving a continuous intravenous infusion of midazolam and of the dose of midazolam received.
Sedation was satisfactory in the majority of patients. Thirteen patients received a bolus dose of midazolam to achieve sedation as the infusion was started. Five patients required additional sedative agents, two received lorazepam, two bolus doses of etomidate and one haloperidol to achieve satisfactory sedation. Narcotic analgesia was required by 27 patients; 23 received morphine and the others received papaveretum, pethidine, fentanyl and phenoperidine. The principal method of administration and the daily range of opioid analgesia are shown in Table 8.3. As might be expected, all the surgical patients required opioid analgesia; however, eight of the medical patients did not require opioids, reflecting the need for anxiolysis rather than analgesia in this group.

The mean (SD) score for cooperation in all patients was 2.76 (0.71), for tolerance of ventilation 3.17 (0.56) and for comfort was 2.99 (0.52). The number of dose changes/day was 1.5 (1.2). The mean sedation score and the daily dose of midazolam in all 50 patients are shown in Figure 8.1.

The sedation score was unchanged but the mean daily dose of midazolam increased each day. As the condition of the patients improved, sedation was withdrawn; Figure 8.1 therefore has a variable number of patients at each time point.
Medical (34)

Continuous Intravenous Infusion (11)
  morphine 24-108 mg/24h
Intermittent Intravenous Injection (14)
  morphine 2.5-40 mg/24h
  alfentanil 0-10 mg/24h
No opioid (8)
No Information (1)

Surgical (16)

Continuous Intravenous Infusion (8)
  morphine 12-120 mg/24h
Intermittent Intravenous Injection (14)
  morphine 2.5-30 mg/24h
  phenoperidine 0-6 mg/24h

Table 8.3: Principal method of administration and opioid requirements (daily dose range) of medical and surgical patients.
Figure 8.1: Mean daily dose of midazolam together with sedation score for all patients receiving a continuous infusion of midazolam. The numbers of patients considered at each time point is indicated.
However, the same phenomenon is demonstrated by a subgroup of 15 patients who received midazolam continuously for more than seven days. Figure 8.2 shows the rate of infusion and sedation scores from these 15 patients. The mean daily dose of midazolam for all 15 patients on day 8 was significantly greater than that on day 1 (P<0.001).

The APACHE II score on admission was 16.45 (8.58), mean (SD), with a range of 2-32. After one week, the score had decreased to 14 (5.42), but it remained unchanged thereafter. There was no significant difference in the midazolam requirements of patients with an APACHE II score of more than 20 compared with those with a score of less than 20. In addition, the increase in the daily dose of midazolam to maintain the same degree of sedation was seen in both groups. There was no correlation between the dose of midazolam administered and the sepsis score.

The mortality rate of patients in this study was 44%, similar to the previous study. The admission APACHE II score for survivors was 13.9 (7.8) and for non-survivors was 20.1 (8.5), a significant difference (p<0.05). Ten patients died without discontinuing the midazolam infusion and in 3 patients follow up was incomplete.
Figure 8.2: Mean daily dose of midazolam together with sedation score for 15 patients who received a continuous infusion of midazolam for 7 days or more.
In the remaining 37 patients the time to awakening following cessation of the midazolam infusion was 27.77 (37.2) hours. Of these 37 patients 24 did not have renal or hepatic insufficiency and awoke 13.6 (16.4) hours after discontinuation of the infusion. Nine patients had renal failure and they had significantly delayed awakening, taking 44.6 (42.5) hours to recover. The longest times to awaken were in two patients with hepatorenal failure, both of whom had received liver transplants, whose recovery times were 124 and 140 hours.

No significant cardiovascular changes attributable to the midazolam were observed but detailed statistical analysis of the large quantity of data collected proved impossible. There were no significant haematological changes or changes in electrolyte concentrations attributable to the midazolam. Furthermore, the only change in liver function noted was a decrease in alanine amino transferase from 172.25 (340) on day 1 to 163 (239) on day 8. The patients' response to the short synacthen test was unchanged by midazolam.

Discussion
A continuous intravenous infusion of midazolam provided satisfactory sedation in most of the patients receiving intensive care. A number of patients received other drugs in addition, the most common being an opioid
analgesic. Both sedation and analgesia may be necessary to achieve patient comfort and the combined use of an opioid and a benzodiazepine is popular (Yate et al 1986).

Morphine was most frequently used because of its effectiveness and safety in the critically ill and because of familiarity with its use and the desire to keep other factors unchanged. Agents with shorter half-lives in healthy volunteers, such as fentanyl and alfentanil, may not behave in the same way in critically ill patients (Bodenham and Park 1988). In some patients adequate comfort could not be achieved using large doses of midazolam (approximately 15mg/hr). In such instances, an alternative agent was introduced; one such patient has been described in detail (Park et al 1987a). This phenomenon may represent a point where a further increase in midazolam dose is beyond the maximal enhancement of the GABAergic inhibitory system and so has no clinical effect.

The increasing dose requirement of midazolam to achieve the same degree of sedation suggests either the
development of tolerance to its effects or an increased ability of the patient to metabolise the drug. An improvement in the patients’ condition may decrease sedation requirements; conversely, a deterioration may increase sedation requirements owing to the development of agitation or hyperventilation in response to metabolic disturbances. In this study, however, the dose of midazolam appeared to be unrelated to the APACHE II scores of the patients.

After long term administration of benzodiazepines tolerance is well described (Haefely 1986; Owen and Tyrer 1983) but there are few reports of an acute increase in dose requirements. Animal studies have shown the development of an acute, dose related tolerance to both the sedative and respiratory depressant effects of benzodiazepines (Al-Khudiari, Askitopoulou and Whitwam 1982; Rosenberg and Chiu 1985). Children sedated with midazolam following cardiac surgery awoke with plasma concentrations of midazolam normally associated with sedation (Lloyd-Thomas and Booker 1986). Acute tolerance has also been reported in patients who have self-administered an overdose of benzodiazepines (Greenblatt et al 1977). It is of note that Michalk and his colleagues (1988) in a smaller study of 13 critically ill patients failed to demonstrate any evidence of accumulation. However, the inclusion criteria for their study were far more stringent than in this study.
Patients who had any abnormalities in their liver function (manifest as an increase of prothrombin time of <50% normal and/or a plasma albumin of <25 g/litre) or renal dysfunction (urine output <60 ml/min) or clinical signs of cardiac failure or persistent hypovolaemia were excluded; a markedly different population to those described in this study. The mechanism underlying the development of tolerance, should it exist, is unclear; benzodiazepines have little effect on liver enzyme activity and are unlikely to induce their own metabolism (Greenblatt and Shader 1986).

A possible implication of benzodiazepine tolerance in the critically ill is that withdrawal phenomena may be seen after prolonged midazolam administration (Pertusson and Lader 1981). No withdrawal phenomena were observed in these patients but they were not specifically sought. The incidence of benzodiazepine withdrawal states in the critically ill is unknown and the influence of other drugs is not clear; even the effect of the benzodiazepine antagonist, flumazenil, is disputed (Lukas and Griffiths 1982; File and Baldwin 1987; Nutt and Costello 1987).

The high overall mortality rate in this study (44%) correlates with the admission APACHE II scores of the patients and must, therefore, reflect the severity of illness in this group of patients (Knaus et al 1985).
Delayed awakening following administration of midazolam occurred in some of our patients and this phenomenon has been reported previously (Bryne, Yeoman and Mace 1984; Byatt et al 1984). There is a considerable variation in the response of healthy individuals to sedative drugs. A pharmacogenetic abnormality is thought to occur in 6-10% of the normal population (Dundee et al 1986) resulting in decreased metabolism of midazolam. In addition, clearance of midazolam decreases with increasing age (Harper et al 1985); while sepsis and other pathological processes may be associated with a type of encephalopathy (Hasselgren and Fischer 1986). Midazolam is thought to undergo predominantly hepatic metabolism (Allonen, Zeigler and Klotz 1981) and the clearance of midazolam is reduced in patients with cirrhosis (Chauvin et al 1987) but not those in renal failure (Vinik et al 1983). The patients who took the longest period of time to recover were the liver transplant patients, indicating the importance of adequate liver function. Whether liver function is important in the elimination of this drug or in the response of the receptors to it is unknown.

The metabolites of midazolam are pharmacologically active but accumulation of these in disease states is unproven. However, accumulation of the active metabolites of morphine may have contributed to the prolonged sedation seen in some of these patients with
renal failure.

As a further part of this study, 6 of the 50 patients were studied pharmacokinetically at the same time as the pharmacodynamic evaluation, to see if the mechanism of prolonged awakening could be established. Dr Maire Shelly and Dr L Mendel assisted with the plasma sampling. The plasma analysis was performed by Dr J Dixon (Royal Bath Hospital, Harrogate) and the pharmacokinetic calculations by Ms S Malcolm (Roche Products Ltd).

**FAILURE OF CRITICALLY ILL PATIENTS TO METABOLISE MIDAZOLAM**

*Anaesthesia (1987) 42; 619-626*

**Patients and Methods**

Informed consent was obtained from three of the patients themselves but the remaining three were unable to consent personally and informed assent for the study was obtained from their relatives. Blood samples were withdrawn from an indwelling arterial line and placed in tubes containing oxalate as anticoagulant, before the infusion was commenced and one hour after starting the infusion; thereafter daily blood samples were taken to ascertain when steady state had been reached. Further blood samples were taken immediately before cessation of the infusion and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8
hours afterwards and continued until the patient was awake. The blood was centrifuged and the supernatant plasma separated and stored at -20°C for analysis by gas liquid chromatography with electron capture detection (Heizmann, Von Alten 1981).

Results
The details of the six patients in whom plasma concentrations were measured are shown in Table 8.4. One patient failed to complete the protocol and a further patient was studied on two occasions. Patient E received an infusion of midazolam for 16 days to facilitate controlled ventilation. No sample was taken during the period after cessation of the infusion but his results are included because of the duration of the infusion. In patient F the infusion was discontinued on the fifth day to assess the patient’s conscious level but was restarted to control agitation. The infusion was finally stopped 3 days later to attempt weaning from controlled ventilation. Blood samples were taken on each occasion the infusion was stopped.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Weight (Kg)</th>
<th>APACHE II Score *</th>
<th>Sepsis Score *</th>
<th>Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>76</td>
<td>M</td>
<td>78</td>
<td>14</td>
<td>2</td>
<td>prolonged postoperative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>neuromuscular blockade</td>
</tr>
<tr>
<td>B</td>
<td>68</td>
<td>M</td>
<td>66</td>
<td>20</td>
<td>6</td>
<td>post cardiac arrest</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>54</td>
<td>F</td>
<td>60</td>
<td>8</td>
<td>0</td>
<td>multiple trauma</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>62</td>
<td>M</td>
<td>70</td>
<td>16</td>
<td>12</td>
<td>re-exploration of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>femoro-popliteal graft</td>
</tr>
<tr>
<td>E</td>
<td>60</td>
<td>M</td>
<td>60</td>
<td>30</td>
<td>20</td>
<td>Chronic myeloid</td>
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<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>leukaemia, septic shock</td>
</tr>
<tr>
<td>F</td>
<td>76</td>
<td>M</td>
<td>60</td>
<td>26</td>
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<td></td>
<td></td>
<td></td>
<td>septic shock</td>
</tr>
</tbody>
</table>

Table 8.4: Details of the six patients studied. * (i) = on admission (ii) = on the day of cessation of midazolam infusion, except for patient E, day 4 scores (iii) = patient E: scores on day 14; patient F: scores on the second occasion when the midazolam infusion was stopped.
All patients except patients E and F survived to be discharged to the wards. Patient E died on his 20th day of intensive care, 5 days after his last dose of midazolam and patient F died on his 82nd day of intensive care, 75 days after his infusion ended; both died of multisystem failure. APACHE II and sepsis scores are shown for patient E on day 4 of his midazolam infusion, when he suffered from septic shock, and on day 14 when clinical improvement was evident. The same scores are shown for patient F on both days his sedation was discontinued. The dose and duration of the infusion are shown in Table 8.5 together with other sedative and analgesic agents. None of the patients received other benzodiazepines or neuromuscular blocking agents during the study period. Concomitant drugs were administered including antibiotics, steroids, heparin and diuretics. All patients received ranitidine and morphine, which was administered by intravenous bolus dose or by continuous intravenous infusion. Low dose dopamine was given by continuous intravenous infusion to all but patient A.

Patients A and C had normal renal function and patient B and D had impaired renal function, whilst patients E and F were in renal failure. Only patients E and F had impaired liver function and reduced serum albumin concentrations.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean dose (ng/hour)</th>
<th>Infusion duration (hours)</th>
<th>Analgesia</th>
<th>Vasoactive agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2.7</td>
<td>10</td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>6.4</td>
<td>26</td>
<td>Morphine</td>
<td>Dopamine, Lignocaine, Digoxin</td>
</tr>
<tr>
<td>C</td>
<td>3.4</td>
<td>143</td>
<td>Morphine</td>
<td>Dopamine</td>
</tr>
<tr>
<td>D</td>
<td>3.8</td>
<td>39</td>
<td>Morphine</td>
<td>Dopamine</td>
</tr>
<tr>
<td>E</td>
<td>7.0</td>
<td>369</td>
<td>Morphine</td>
<td>Dopamine, Dobutamine, Methoxamine, Alfentanil, Phenylephrine, Digoxin, Adrenaline, Pentamyl, Verapamil</td>
</tr>
<tr>
<td>F</td>
<td>4.6</td>
<td>159</td>
<td>Morphine</td>
<td>Dopamine, Dobutamine, Methoxamine, Alfentanil, Adrenaline, Digoxin</td>
</tr>
</tbody>
</table>

**Table 8.5:** The mean dose of midazolam, the duration of infusion and other sedative, analgesic and vasoactive drugs administered to each patient.
The derived pharmacokinetic parameters are shown in Table 8.6, together with the normal values. One patient (C) had normal pharmacokinetic parameters and in another (A) the data were incomplete but appeared normal. The remaining patients had prolonged elimination half lives as a result of reduced clearance of midazolam. In 2 cases (patients B and D), plasma concentrations of \( \alpha \)-hydroxymidazolam were normal and the increased half life was due partly to an increased volume of distribution.

Two patients (E and F) initially had a reduced clearance of midazolam with increasing plasma concentrations of midazolam during the period of their infusion and low or absent plasma concentrations of \( \alpha \)-hydroxymidazolam. As their condition improved plasma concentrations of midazolam decreased and those of \( \alpha \)-hydroxymidazolam increased, which indicates that clearance was returning towards normal. The plasma concentrations of midazolam and \( \alpha \)-hydroxymidazolam for patient E throughout the period of his infusion are shown in Figure 8.3. Plasma concentrations of midazolam increased rapidly after the start of the infusion and reached a peak on day 4. Plasma concentrations of \( \alpha \)-hydroxymidazolam were low or absent during this time. On day 5, which coincided with the patient’s first period of haemodialysis, the plasma concentrations of midazolam decreased but that of \( \alpha \)-hydroxymidazolam increased.

Page 270
<table>
<thead>
<tr>
<th>Patient</th>
<th>Clearance (l/kg/hr)</th>
<th>Half-Life (hr)</th>
<th>Volume of Distribution (l/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.24–0.71</td>
<td>0.84–5.4</td>
<td>0.86–1.86</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>*</td>
<td>2.5</td>
<td>*</td>
</tr>
<tr>
<td>B</td>
<td>0.11</td>
<td>13.9</td>
<td>2.23</td>
</tr>
<tr>
<td>C</td>
<td>0.42</td>
<td>2.5</td>
<td>1.51</td>
</tr>
<tr>
<td>D</td>
<td>0.06</td>
<td>18</td>
<td>High**</td>
</tr>
<tr>
<td>E (i)</td>
<td>0.04</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>(ii) 0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (i)</td>
<td>0.03</td>
<td>21</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>(ii) 0.08</td>
<td>7.8</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Table 8.6: Pharmacokinetic parameters for midazolam in each patient  * = No values  Patient A – not at steady state when infusion discontinued, Patient E – no samples during decay from plateau level.  ** = Clearance at steady state probably reduced due to interfering peak in predose sample. (i) = patient E – day 4, patient F – first cessation of midazolam infusion. (ii) = patient E – day 14, patient F – second cessation of midazolam infusion
Figure 8.3: Plasma midazolam and α-hydroxymidazolam concentrations for patient E throughout the period of study.

- plasma midazolam concentration
- plasma α-hydroxymidazolam concentration
Following this the plasma concentrations of midazolam and α-hydroxymidazolam decreased to a steady state level which was maintained until the infusion was discontinued. The phase immediately following discontinuation was not studied in this patient but, 24 hours after the cessation of the infusion, no midazolam or α-hydroxymidazolam was detectable in the plasma.

The plasma concentrations of midazolam and α-hydroxymidazolam for patient F during his entire study period are shown in Figure 8.4. Plasma concentrations of midazolam again increased rapidly to high levels by day 4 but, following the first cessation of the infusion, the levels remained high. No α-hydroxymidazolam was detected in the plasma during this period. After the infusion was restarted plasma midazolam concentrations declined slightly until the infusion was finally stopped on day 8. Following this, the plasma concentration decreased to therapeutic levels within 24 hours.

Table 8.7 shows the time taken for the patients to wake and the plasma concentrations of midazolam and α-hydroxymidazolam at this time.
Figure 8.4: Plasma midazolam and α-hydroxymidazolam concentration for patient F during the study period, including both occasions the midazolam infusion was discontinued.

--- plasma midazolam concentration

--- plasma α-hydroxymidazolam concentration
<table>
<thead>
<tr>
<th>Patient</th>
<th>Time to Wake (hours)</th>
<th>Plasma Midazolam (ng/hr)</th>
<th>Plasma α-hydroxy midazolam (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>117</td>
<td>25</td>
</tr>
<tr>
<td>B</td>
<td>11</td>
<td>365</td>
<td>43</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>97</td>
<td>40</td>
</tr>
<tr>
<td>D</td>
<td>12</td>
<td>519</td>
<td>32</td>
</tr>
<tr>
<td>E</td>
<td>*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F (i)</td>
<td>**</td>
<td>2582</td>
<td>0</td>
</tr>
<tr>
<td>(ii)</td>
<td>24</td>
<td>166</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 8.7: The time taken for the patients to wake following cessation of the midazolam infusion and the plasma midazolam and α-hydroxymidazolam concentrations at this time. * = remained unrousable ** = infusion restarted because of agitation
Discussion

The prolonged sedation seen in critically ill patients following intravenous bolus doses or intravenous infusions of midazolam may represent a spectrum of response and reflect alterations in the hepatic blood flow (Byatt et al 1984) or impaired hepatic metabolic capacity (Harper et al 1985).

The patients reported here show 3 different pharmacokinetic and pharmacodynamic patterns, which appear to be related to the severity of the patient's disease.

The 2 patients (A and C) with the lowest APACHE II and sepsis scores have normal pharmacokinetic parameters. In both of these patients plasma concentrations of midazolam and α-hydroxymidazolam decreased rapidly when the infusion was discontinued and both awoke soon after the infusion was discontinued. At the time of awakening plasma concentrations of midazolam were approximately 100 ng/ml and concentrations of α-hydroxymidazolam were approximately 30 ng/ml.

All the remaining patients had low plasma clearances and a prolonged elimination half life of midazolam. Two of these patients (B and D) had intermediate APACHE II and sepsis scores. The prolonged elimination of midazolam in these patients was associated with a large volume of
distribution and normal plasma concentrations of α-hydroxymidazolam. These patients remained sedated for approximately 12 hours after cessation of the infusion and were awake, with plasma concentrations of midazolam normally associated with sedation. Plasma concentrations of α-hydroxymidazolam were again approximately 30 ng/ml. Patients who undergo major surgery and patients with chronic renal failure have an altered volume of distribution of midazolam (Harper et al 1985; Vinik et al 1983). This change has been attributed to reduced protein binding of the drug which leads to a higher free drug fraction. A similar mechanism may be responsible for the large volume of distribution of midazolam in these patients, both of whom had impaired renal function. Their concentrations of serum albumin were normal but its ability to bind midazolam may have been altered by disease or other drugs administered concomitantly (Halliday et al 1985).

The remaining 2 patients (E and F) both initially suffered from septic shock and had high APACHE II and sepsis scores; both patients received inotropic support. These 2 patients initially had a reduced clearance associated with a low or absent plasma concentrations of α-hydroxymidazolam. The plasma concentrations of midazolam in these patients reached high levels (3000 ng/ml) on the 4th and 5th days of their infusions, but no adverse haemodynamic or biochemical effects of these
high concentrations were noted. Both patients subsequently showed clinical evidence of improvement confirmed by a decrease in their APACHE II and sepsis scores. This improvement was associated with the appearance of α-hydroxymidazolam in their plasma and an increase in midazolam clearance towards normal. In patient E, this change coincided with his first period of haemodialysis. This did not initiate his improvement but is a reflection of it, since haemodialysis could not be undertaken in the presence of haemodynamic instability. Furthermore, similar changes in plasma concentrations of midazolam and α-hydroxymidazolam were not seen when haemodialysis was repeated.

The high plasma concentrations of midazolam and the absence of metabolite suggest that impaired metabolism resulted in its accumulation. A reduction in metabolism may result from reduced liver perfusion or an enzyme defect (Dundee et al 1986). The increase in midazolam clearance as the patients' condition improved, however, suggests a reversible impairment rather than an inherited reduction in midazolam metabolism. Because midazolam has a high hepatic extraction, the rate of its metabolism is thought to be dependent upon hepatic blood flow and any reduction in liver perfusion could reduce the rate of its metabolism. Acute hypovolaemia in dogs lowered the clearance of midazolam without changes in volume of distribution or in protein
binding (Gelman, Reeves and Harris 1983). Midazolam itself has been shown to affect splanchnic blood flow. Following bolus administration hepatic arterial flow decreases and portal venous flow, after an initial rise, also falls (Gelman, Reeves and Harris 1983). The haemodynamic stability that follows administration of midazolam is thought to be due to compensatory mechanisms which lead to redistribution of blood within the splanchnic bed; this may also occur in man (Kawar et al 1985).

Overall there appeared to be no correlation between plasma midazolam concentrations and the time at which the patients woke following the infusion. There does, however, appear to be an association between waking and plasma concentration of α-hydroxymidazolam, patients waking with concentrations between 20 and 40 ng/ml.

Plasma concentrations of α-hydroxymidazolam were lower than those of the parent drug with a wide range. Although the metabolite α-hydroxymidazolam only demonstrates 10% of the activity of midazolam (Ziegler et al 1983) in volunteers, little is known about the relationship of the plasma concentrations to receptor concentration in the critically ill (Bodenham et al 1988). It may be that the action of midazolam is influenced by its metabolites in the same way as the effects of morphine appear to be dependent upon its
metabolites.

This study appeared to implicate a decrease in either hepatic blood flow or the metabolic ability of the liver due to an acute deterioration in the patients' condition, as a cause for the prolonged elimination and duration of effect of midazolam. Studies in patients with chronic liver disease have given conflicting results about the effects of midazolam (Hamdy et al 1986; Rinetti et al 1985; MacGilchrist et al 1986). The extrapolation of results, such as these, derived from patients with chronic liver disease to patients who have suffered acute liver injury may not be valid. Acute hepatic dysfunction is more commonly seen in patients receiving intensive care as a secondary event after illness or surgery. Studies in patients during and after liver transplantation were therefore performed to obtain further information about the importance of acute alterations in liver function on the metabolism of midazolam.

STUDIES IN PATIENTS IN THE PERIOPERATIVE PERIOD OF LIVER TRANSPLANTATION

In the first study I was assisted with the specimen collection by Dr Maire P Shelly, with the specimen analysis by Dr J S Dixon and with pharmacokinetic advice by Ms S Malcolm and Dr J G Allen (Roche Products Ltd).
Patients and Methods

Seven subjects were studied in the immediate postoperative period, after arrival in the intensive care unit, when haemodynamic stability had been achieved. A baseline blood sample was taken and midazolam hydrochloride (10 mg) was diluted to 10ml with 0.9% saline and injected over 2 minutes through a centrally placed venous catheter. Arterial blood was sampled at 2, 5, 10, 15, 30, 45, 60 min and 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 6, 12, 18, 24h after the injection of drug. At each sampling point, 10ml of blood was removed, placed in a tube containing an oxalate anticoagulant and mixed. The tubes were centrifuged at 3,000 rpm and the supernatant plasma removed and stored at -20°C until subsequent analysis by gas liquid chromatography (Heizmann, von Alten, 1981). Drug and metabolite concentrations were determined relative to standard curves containing 50-1000ng/ml midazolam and 25-375ng/ml α-hydroxymidazolam. Mean precisions for the standards were ±8.4% and ±7.4% respectively and virtually identical values were found for quality assurance samples (n=20) containing 250ng/ml and 125ng/ml of midazolam and α-hydroxymidazolam. These
were prepared and included in every analysis and mean accuracies of the quality assurance samples were within 5% of the prepared values.

Sedation and analgesia during this period were provided by intermittent bolus doses of diazepam and morphine as required.

Pharmacokinetic parameters were calculated by model independent analysis. Plasma concentrations immediately after dosing \((Co)\) were determined by back extrapolation of the log-linear line for samples collected during the first 10-15 min after dosing. The initial volume of distribution \((V_1)\) was then calculated from \(\text{Dose}/Co\). Values for elimination half-lives \((t_{1/2})\) were estimated from the log-linear decline of the last four or five measurable plasma concentrations. Areas under the plasma concentration - time curves (AUC) were calculated by linear trapezoidal analysis between all samples that contained measurable midazolam concentrations. Values for the initial and terminal portions of the curve were then determined by addition of \((\text{Co}+C_2)/60\) and \(C_t \times t_{1/2}/0.693\) respectively, where \(C_t\) was the last determined concentration. Clearance \((Cl)\) was calculated from \(\text{Dose}/\text{AUC}\).

Results
Analysis of the plasma from three of the patients
revealed interference with the assay, probably from temazepam used as premedication. This rendered pharmacokinetic interpretation impossible and these patients have, therefore, been excluded from further consideration. The details of the remaining four patients including their postoperative liver function tests are shown in Table 8.8. All had impaired liver function in the postoperative period. The unusually low alanine transferase of patient 3 subsequently rose rapidly and may represent a spurious result. No delayed awakening was seen in the patients studied; all patients required further sedation at a mean time of 2h (range 0.5–5h).

The derived pharmacokinetic parameters for midazolam and α-hydroxymidazolam are shown in Table 8.9 together with normal values (Allonen et al 1981; Heizmann et al 1983). It was only possible to calculate approximate values for the distribution and elimination of midazolam in these patients owing to the biphasic decline and the relatively small number of data points obtained. The pharmacokinetic parameters found for midazolam were similar to those obtained from healthy volunteers, however, the plasma concentrations of α-hydroxymidazolam were higher than expected following intravenous administration of a 10mg bolus.
<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42</td>
<td>40</td>
<td>49</td>
<td>18</td>
</tr>
<tr>
<td>(yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Weight</td>
<td>53.3</td>
<td>75.0</td>
<td>50.0</td>
<td>66.0</td>
</tr>
<tr>
<td>(kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Chronic</td>
<td>Chronic</td>
<td>Polycystic</td>
<td>Chronic</td>
</tr>
<tr>
<td></td>
<td>Acute</td>
<td>Rejection</td>
<td>Disease</td>
<td>Rejection</td>
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<tr>
<td>Hepatitis</td>
<td>(RT)</td>
<td>(RT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>52</td>
<td>484</td>
<td>145</td>
<td>220</td>
</tr>
<tr>
<td>(μmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>840</td>
<td>&gt;1200</td>
<td>20</td>
<td>500</td>
</tr>
<tr>
<td>(U/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP</td>
<td>62</td>
<td>231</td>
<td>43</td>
<td>652</td>
</tr>
<tr>
<td>(U/l)</td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

Table 8.8: Details of the patients studied.

RT = Retransplantation
<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
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<th>3</th>
<th>4</th>
<th>Normal Values</th>
</tr>
</thead>
</table>

### Midazolam

<table>
<thead>
<tr>
<th>Co (ng/ml)</th>
<th>950</th>
<th>800</th>
<th>600</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$ (l)</td>
<td>10.5</td>
<td>12.5</td>
<td>16.7</td>
<td>- 21(7)</td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>80</td>
<td>30</td>
<td>55</td>
<td>105</td>
</tr>
<tr>
<td>Cl (l/h)</td>
<td>20.0</td>
<td>38.1</td>
<td>31.6</td>
<td>17.5</td>
</tr>
</tbody>
</table>

### $\alpha$-hydroxymidazolam

<table>
<thead>
<tr>
<th>Cmax (ng/ml)</th>
<th>62</th>
<th>124</th>
<th>219</th>
<th>123</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng.h/ml)</td>
<td>66</td>
<td>122</td>
<td>120</td>
<td>103</td>
<td>42</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.17</td>
<td>0.17</td>
<td>0.08</td>
<td>0.50</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Table 8.9: The pharmacokinetic parameters for midazolam and $\alpha$-hydroxymidazolam for the individual patients. The normal values are from Allonen et al (1981) and Heizmann et al (1983). - = Not calculated.
In healthy volunteers, the mean maximum plasma concentration (mean Cmax) of α-hydroxymidazolam is approximately 7.6% (Heizmann et al 1983) of the mean Cmax of midazolam, following intravenous administration of midazolam; in our patients, the ratio using the same method of calculation was 18%. Half lives for the metabolite could not be determined due to the triphasic nature of the plasma concentration - time curve.

Discussion

Prolonged awakening and slow elimination of midazolam have been attributed to impaired hepatic metabolism resulting in slow clearance of the parent drug. The explanations offered for the impaired metabolism of midazolam include a congenital impairment of cytochrome P450 function (Dundee et al 1986), or as demonstrated previously, it may follow reduced organ perfusion secondary to sepsis.

Studies of the pharmacokinetics and pharmacodynamics of other benzodiazepines in patients with liver disease suggest that those benzodiazepines undergoing predominantly phase I metabolism, such as diazepam, tend to be profoundly affected by liver disease (Reeves 1981; Klotz et al 1975) whilst those undergoing mainly conjugation reactions, such as temazepam, are relatively spared (Ghabrail et al 1986; Ochs et al 1986). In addition, the clearance of benzodiazepines undergoing
phase I reactions is decreased by the concomitant administration of cimetidine, which is thought to act as an enzyme inhibitor; benzodiazepines metabolised by phase II reactions are unaffected by cimetidine (Klotz and Reimann 1980a,b).

Midazolam does not fit into this pattern. It undergoes predominantly phase I metabolism and therefore its pharmacokinetics would be expected to be affected profoundly by liver impairment. The pharmacokinetic profile of oral midazolam in patients with compensated cirrhosis is similar to that in healthy volunteers (Rinetti et al 1985). Only in patients with severe cirrhosis are the pharmacokinetics and pharmacodynamics of midazolam affected (Hamdy et al 1986; Rinetti et al 1985; McGilchrist et al 1986). In addition the pharmacokinetics of midazolam are not influenced by cimetidine enzyme inhibition as are those of diazepam (Greenblatt et al 1986). Since patients with liver impairment retain considerable metabolic capacity for midazolam, it suggests that the metabolism of midazolam differs in some way from the phase I metabolism of other benzodiazepines. It may be that the enzymes responsible for the metabolism of midazolam are particularly resistant to damage or that they occur in extrahepatic sites; extrahepatic metabolism of lorazepam in dogs has been postulated (Gerkens et al 1981).
Liver transplantation can be considered as a severe, acute hepatic injury and these patients demonstrated normal pharmacokinetics of midazolam but with a higher than normal plasma concentration of \( \alpha \)-hydroxymidazolam, the primary metabolite. The increased plasma concentrations of \( \alpha \)-hydroxymidazolam may be due either to an increased rate of formation of the metabolite or to a reduced rate of conjugation to the glucuronide. Since the pharmacokinetics of midazolam appeared normal, the latter is more likely. This could have been confirmed by measuring the plasma concentrations of the secondary metabolite \( \alpha \)-hydroxymidazolam glucuronide but this assay was not available at the time of study. The amount of pharmacokinetic data obtained from this study was limited because of the small numbers of patients and data points. However, the fact that the initial metabolism of midazolam to \( \alpha \)-hydroxymidazolam was not substantially impaired suggests that, following liver transplantation, patients retain considerable metabolic capacity for midazolam either within the newly transplanted liver or at extrahepatic sites.

To determine the significance of extra-hepatic sites for the metabolism of midazolam, a further study during the anhepatic period of liver transplantation was performed. I was assisted with the plasma sampling by Dr A R Manara (Registrar), the plasma analysis by Dr S Dawling (Guys Hospital, London), the pharmacokinetic analysis by Dr P
E O Williams and Ms S L Malcolm who arranged some of the analysis by mass spectroscopy.

EXTRA-HEPATIC METABOLISM OF MIDAZOLAM

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(1989) 27; 633-634

Method:
In the previous study premedication with temazepam resulted in subsequent interference with the midazolam assay. For this study premedication with a benzodiazepine was specifically avoided and a narcotic and antismialagogue substituted. In other respects anaesthesia was conducted as previously described.

Immediately before vascular isolation and removal of the diseased liver a baseline blood sample was taken. As soon as haemodynamic stability was achieved after vascular isolation and removal of the diseased liver (approximately 2 minutes), 10 mg of midazolam hydrochloride was injected into a central vein and flushed with 10 ml 0.9% sodium chloride. Blood was removed at 2, 5, 10, 15, 20, 30, 40 minutes or the end of the anhepatic period and immediately before revascularisation of the new liver. Following revascularisation, the sampling protocol was repeated. After removal, blood was placed into tubes containing oxalate anticoagulant, mixed, centrifuged at 3,000 rpm,
the supernatant plasma separated and frozen at -20°C until subsequent analysis by gas chromatography with electron capture (GC/ECD) (Heizman and Von Alten 1981) for midazolam, α-hydroxymidazolam and α-hydroxymidazolam glucuronide. The lower limits for using this method for the detection of midazolam and its metabolites are: midazolam 3μg/l, α-hydroxymidazolam 2μg/l and α-hydroxymidazolam glucuronide 2μg/l. Further analysis of 4 samples, with sufficient remaining plasma, by gas chromatography with mass spectroscopy (GC/MS) for midazolam and α-hydroxymidazolam levels were undertaken to obtain additional information to that obtained with GC/ECD.

Pharmacokinetic parameters were calculated for midazolam during the anhepatic period and assumed a mono exponential decline.

Results:
Patient information, details of the anhepatic phase and preoperative liver function tests are shown in Table 8.10. Liver function had been deteriorating for many years in patients 2, 3, 4 and 5 whereas patient 1 had a one month history of deteriorating liver function following administration of an antidepressant and liver function was normal in patient 6.
<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>34</td>
<td>46</td>
<td>53</td>
<td>54</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65</td>
<td>61</td>
<td>52</td>
<td>48</td>
<td>60</td>
<td>74</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>SAHN</td>
<td>PBC</td>
<td>PBC</td>
<td>PBC</td>
<td>SC</td>
<td>HEP</td>
</tr>
<tr>
<td>Anhepatic Period (mins)</td>
<td>32</td>
<td>42</td>
<td>43</td>
<td>50</td>
<td>52</td>
<td>86</td>
</tr>
<tr>
<td>Blood Loss (mls)</td>
<td>200</td>
<td>970</td>
<td>180</td>
<td>130</td>
<td>768</td>
<td>174</td>
</tr>
<tr>
<td>Bilirubin (μmol/l)</td>
<td>868</td>
<td>428</td>
<td>112</td>
<td>134</td>
<td>309</td>
<td>12</td>
</tr>
<tr>
<td>Alanine Aminotransferase (U/l)</td>
<td>1124</td>
<td>188</td>
<td>138</td>
<td>111</td>
<td>99</td>
<td>32</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>167</td>
<td>1022</td>
<td>780</td>
<td>1968</td>
<td>344</td>
<td>127</td>
</tr>
<tr>
<td>Prothrombin ratio</td>
<td>9.9</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 8.10: Patient information, details of the anhepatic period and preoperative liver function tests. SAHN = subacute hepatic necrosis, PBC = primary biliary cirrhosis, SC = sclerosing cholangitis, HEP = hepatoma.
The plasma concentrations of midazolam, α-hydroxymidazolam and α-hydroxymidazolam glucuronide for patients 2, 3, 4, 5 and 6 during the anhepatic period and following reperfusion are shown in Figure 8.5. Metabolites of midazolam were detected during the first 15 minutes of the anhepatic period at significant but low plasma concentrations in these patients using GC-ECD.

Patient 1 did not at any time have detectable plasma concentrations of α-hydroxymidazolam using GC-ECD and the results for this patient are shown in Figure 8.6. Calculated pharmacokinetic parameters [mean(SD)] for midazolam during the anhepatic period were: half life 0.52 (0.23) hour, volume of distribution 12.4 (1.96) l and clearance 12.6 (1.96) l/h.

When analysed by GC-MS the low plasma concentrations of α-hydroxymidazolam prevented full spectral data being obtained. Instead, the two typical mass fragments of α-hydroxymidazolam were scanned for and found at the same retention time and ratio as standard material. The α-hydroxymidazolam/midazolam ratios obtained by GC-MS and GC-ECD for four specimens are shown in Table 8.11.
Figure 8.5: Plasma concentrations [mean (SEM)] of midazolam (□), α-hydroxymidazolam (Δ) and α-hydroxy-midazolam glucuronide (■) in five patients following 10 mg of midazolam intravenously at the start of the anhepatic period of liver transplantation.
Figure 8.6: Plasma concentrations [mean(SEM)] of midazolam (□), α-hydroxymidazolam (▲) and α-hydroxy-midazolam glucuronide (■) in patient 1 following 10mg of midazolam intravenously at the start of the anhepatic period of liver transplantation.
<table>
<thead>
<tr>
<th>Time of Samples (mins)</th>
<th>α-hydroxymidazolam/midazolam ratio</th>
<th>GC-MS</th>
<th>GC-ECD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (A)</td>
<td>0.002</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>30 (A)</td>
<td>0.012</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>40 (A)</td>
<td>0.103</td>
<td>0.08</td>
<td></td>
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<tr>
<td>40 (R)</td>
<td>0.43</td>
<td>0.54</td>
<td></td>
</tr>
</tbody>
</table>

Table 8.11: α-hydroxymidazolam/midazolam ratios determined by gas chromatography with electron capture detection (GC-ECD) and mass spectroscopy (GS-MS). A = anhepatic period. R = period following revascularisation.
All of the samples are similar apart from the specimen from patient 1 taken 30 mins into the anhepatic period. The concentration of α-hydroxymidazolam in this sample is below the limit of detection by GC-ECD but was detectable by GC-MS. The results obtained by GC-MS confirm the validity of those obtained by GC-ECD and also determine that a small amount of α-hydroxymidazolam was made by patient 1.

Discussion:
Five of the six patients clearly demonstrated metabolism of midazolam during the anhepatic period of liver transplantation with significant concentrations of both α-hydroxymidazolam and α-hydroxymidazolam glucuronide being detected, confirming the presence of extrahepatic sites of benzodiazepine metabolism. The remaining patient (patient 1) only had low plasma concentrations of α-hydroxymidazolam glucuronide at the final two time points of the anhepatic period when measured by GC-ECD. The α-hydroxymidazolam metabolite was identified in the 30 minute sample from this patient when measured by GC-MS but the plasma concentration was extremely low. The reason for the difference between patient 1 and the other patients is unclear. The acute nature of this patient's liver disease may not have allowed sufficient time for the development of extrahepatic sites of metabolism or venous anastomotic channels. Venous anastomotic channels would develop in chronic liver
disease secondary to portal hypertension and were found in four of the patients. These would allow free communication of any extrahepatic site of metabolism (such as the kidney or gut) distal to the infrahepatic inferior vena caval clamp to communicate with the upper part of the body (above the inferior vena caval clamps) and allow the detection of metabolites in arterial blood. However, patient 6 had normal liver function with no apparent disturbance of hepatic haemodynamics and still had detectable levels of metabolites. Six percent of the population have a pharmacogenetic abnormality and are slow metabolisers of midazolam. The first pharmacokinetic study in this chapter demonstrated a reversible inhibition of its metabolism in critically ill patients related to the development of sepsis. Patient 1, who was critically ill preoperatively and subsequently died of an overwhelming viral infection, may have had either of these two abnormalities affecting her liver. Whatever the cause it also affected the extrahepatic metabolic sites. Revascularisation of the donor liver appeared to correct whichever of these abnormalities was present. If it was a pharmacogenetic abnormality this, in common with other enzyme defects, would be permanently resolved. If revascularisation of the donor liver corrected the metabolic defect seen in critically ill patients it might represent only a temporary improvement before it too became affected by the patient’s illness.
Revascularisation of the liver was followed in all patients by a large increase in the plasma concentrations of metabolites. Patient 1 showed a similar increase in plasma concentrations of metabolites to the other patients although the concentrations were always lower. This would be consistent with the transplanted liver containing the normal amount or type of enzyme responsible for the metabolism of midazolam. There are two possible reasons for the concentrations being lower in the revascularisation period in patient 1 than in the other patients. Firstly there was a lower concentration to start with at revascularisation following the minimal metabolism of midazolam during the anhepatic period. Secondly, if the liver enzyme deficiency had been corrected the peripheral sites were unchanged; their contribution to the metabolism of midazolam would continue to be minimal and therefore the plasma concentrations of metabolites would be correspondingly lower.

The exact sites where extrahepatic metabolism of midazolam is occurring are unknown. The possible sites include the gut which has been shown to metabolise flurazepam in man (Mahon et al 1977), the kidney (which has been implicated in the metabolism of morphine (Moore et al 1986)) and the lung (Heizman et al 1983). Further studies are necessary to determine the exact site in the human and may be important to our
understanding of the metabolic fate of this and other drugs in critically ill patients.

Although the number of time points are too few to make definite conclusions, the pharmacokinetics of midazolam in these patients appear to show a shorter elimination half life and a smaller volume of distribution than is seen in healthy volunteers (Brown et al 1979; Dundee et al 1980; Greenblatt et al 1981). The duration of the anhepatic period is necessarily short, and the calculated half life may therefore represent a distribution rather than an elimination half life. The decreased volume of distribution may also be due to the short period of sampling, with inadequate time being available for the distribution of the drug. Alternatively, midazolam may concentrate in the liver, thus in the anhepatic period distribution would be reduced. The first of these explanations appears the most likely considering the similar distribution half-life described by Heizmann, Eckert and Ziegler (1983), with the distribution phase lasting for two hours after dosing. The pharmacokinetic parameters calculated for midazolam in patient 1 did not differ from the other patients.

The initial pharmacodynamic studies described in this chapter also indicate that further abnormalities may occur in these patients when renal failure supervenes. Some of the pharmacokinetic abnormalities were investigated
further in one such patient who developed renal failure after liver transplantation. I was assisted with the sample analysis by Dr Dixon for this part of my thesis.

**THE INFLUENCE OF RENAL FAILURE AND ITS TREATMENT ON MIDAZOLAM PHARMACOKINETICS IN ONE PATIENT FOLLOWING LIVER TRANSPLANTATION**

The patient was a 49-year-old female who underwent combined liver and renal transplantation for polycystic disease. Postoperatively she required controlled ventilation and a 10mg bolus of midazolam was administered for sedation. Samples of blood and urine from both her original diseased kidneys and the transplanted kidney were collected and analysed for midazolam and \( \alpha \)-hydroxymidazolam using GC-ECD.

The plasma midazolam and \( \alpha \)-hydroxymidazolam concentrations for this patient are shown in Figure 8.7. Plasma concentrations decreased rapidly, the elimination half life for midazolam being 0.5hr, and negligible quantities of midazolam and \( \alpha \)-hydroxymidazolam were detected three hours after administration. Insignificant quantities of midazolam were found in urine from both her original and transplanted kidneys. The urine volumes and the urine concentration of \( \alpha \)-hydroxymidazolam from both the recipient and donor kidneys are shown in Table 8.12.
Further sedation was required 5 hours following administration of midazolam.

Renal transplantation has little effect on the pharmacokinetic profile of midazolam, as illustrated by this patient. Plasma midazolam concentrations were within normal limits. Insignificant quantities of midazolam were detected in the urine samples from the original and transplanted kidneys but little unchanged midazolam is normally excreted (Allonen, Ziegler and Klotz 1981). Both donor and recipient kidneys excreted α-hydroxymidazolam.
Figure 8.7: Plasma concentrations of midazolam and \( \alpha \)-hydroxymidazolam after renal transplantation.

\[ \text{--- = Midazolam} \quad \text{---- = \( \alpha \)-hydroxymidazolam} \]
<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Recipient kidney</th>
<th>Donor kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>α-hydroxy midazolam volume (ng/ml)</td>
<td>α-hydroxy midazolam volume (ng/ml)</td>
</tr>
<tr>
<td>0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
<td>1.13</td>
</tr>
<tr>
<td>3</td>
<td>0.47</td>
<td>0.94</td>
</tr>
<tr>
<td>4</td>
<td>0.38</td>
<td>1.16</td>
</tr>
<tr>
<td>5</td>
<td>0.58</td>
<td>2.75</td>
</tr>
<tr>
<td>6</td>
<td>0.89</td>
<td>2.14</td>
</tr>
<tr>
<td>8</td>
<td>1.35</td>
<td>1.56</td>
</tr>
</tbody>
</table>

Table 8.12: Urine volumes and concentrations of α-hydroxymidazolam from the donor and recipient kidneys of Patient 3. ND = None detectable. NA = Not assayed.
Midazolam given in small intravenous increments is the routine method of sedation in patients after liver transplantation. Despite its short duration of action in healthy patients, prolonged sedation is recognised in the critically ill (Chapter 8). In addition, 6% of the population have a pharmacogenetic abnormality which results in slow metabolism of midazolam (Dundee et al 1986). Both of these may lead to accumulation and result in excessive and prolonged sedation in some patients. The many difficulties caused by this problem are discussed in Chapter 7. Benzodiazepine sedation is reversible using the benzodiazepine antagonist flumazenil (Ro 15-1788) which has been commercially available for some time in Europe and recently in the United Kingdom. Clinical trials have demonstrated its efficacy in reversing the effects of benzodiazepine overdose (Geller et al 1985), single dose therapeutic administration of benzodiazepines (Darragh et al 1981) and after the longer term use of benzodiazepines for intensive care sedation (Kleiberger et al 1985; Pepperman 1989). Few adverse effects have been seen in these trials except for nausea and vomiting. In particular, flumazenil has been shown to lack significant cardiovascular effects (Geller et al 1986).
Flumazenil was assessed in patients after liver transplantation who remained undesirably sedated and who had received multiple doses or infusions of midazolam. Two prospective studies were therefore performed in this group; the first an open study in five patients, the second a randomised, placebo controlled study in eight patients.

REVERSAL OF PROLONGED SEDATION IN PATIENTS AFTER LIVER TRANSPLANTATION USING FLUMAZENIL

STUDY 1 (OPEN)
Part of Anaesthesia (1989) 44, 603-605

Patients and Methods
Five patients were studied who were known to have received significant amounts of midazolam during their treatment and who remained apparently excessively sedated after it was discontinued. Patients with known hypertension or ischaemic heart disease were excluded because of the theoretical risk of inducing acute hypertension or myocardial ischaemia which may follow rapid awakening. If a tracheal tube was in place an isoflurane vaporiser was connected to the ventilator circuit, to allow rapid resedation should cardiorespiratory instability develop on reawakening. In all patients blood pressure was measured continuously using intra-arterial pressure monitoring and pulse rate...
and cardiac rhythm were displayed on an electrocardiogram.

Opiates may cause similar prolonged sedation in these patients, particularly if there is renal dysfunction (Chapter 11). Therefore patients who were thought to have opiate-related sedation were given naloxone in 0.1mg increments intravenously to a maximum of 0.4mg or reversal of sedation. Since the administration of naloxone would reverse analgesia this was provided with intercostal nerve blocks (Chapter 13). If no significant improvement with naloxone had occurred flumazenil was given in 0.1mg increments until satisfactory awakening occurred or a total of 1mg was given. The APACHE II score (Knaus et al 1985) without the Glasgow coma scale (GCS) component was recorded prior to the administration of naloxone and flumazenil. The GCS component of the APACHE II score may be an entirely reversible element if it is due to excessive sedation and so may increase the score inappropriately.

Sedation was assessed before and after administration of naloxone and flumazenil using a score modified from that described by Ramsay and his colleagues (1974) (Table 9.1). An improvement in conscious level was taken as a rise of greater than three points on the scale.
1. Alert, writing coherent messages
2. Alert, writing meaningless but legible letters
3. Alert, writing unintelligible scrawl
4. Alert, unable to write
5. Awake, but confused
6. Awake, agitated
7. Awakens with soft spoken voice
8. Awakens with loud voice
9. Awakens with gentle shaking
10. Awakens with glabella tap
11. Responds to fingernail pressure in a purposeful way
12. Responds to fingernail pressure in a unpurposeful way
13. Does not respond to fingernail pressure

Table 9.1: Sedation score used to assess change in conscious level of critically ill patients following the administration of flumazenil. A significant response was defined as a rise of three points or more.
Results

Information about the five patients is shown in Table 9.2. After the administration of flumazenil 3 (60%) of the patients showed an improvement of more than 3 points on the scale. The short duration of action of flumazenil did not cause difficulties in this group and resedation requiring a continuous intravenous infusion of flumazenil did not occur. One patient required resedation with isoflurane when she bit her tracheal tube resulting in airway obstruction.

The success of flumazenil appeared to be related to the total dose of midazolam; only those patients who had received more than 100 mg responded. Awakening was not related in a consistent way to age, sex, APACHE II score, duration of sedation or the time after stopping the drug. There were no unwanted effects such as nausea and vomiting due to the flumazenil in any of these patients. Blood pressure and pulse rate did not increase more than 20mmHg and 12-25 beats/min respectively.

Four patients received significant quantities of opiates during the sedation period. These patients received naloxone to evaluate if opiate-related sedation was present. Two had an improvement in conscious level of 3 points following naloxone but showed no further improvement with flumazenil.
Sex 3 male/2 female
Age (years) 40.6 (12.8)
Score change (3 patients) 5, 8, 9
Total dose morphine (mg)
(4 patients) 45 (31)
Total dose midazolam (mg) 139.2 (115.6)
APACHE II (without
Glasgow Coma Scale) 11.2 (3.4)
Duration of sedation (days) 4.8 (6.7)
Time of last midazolam
administration (hours) 24.4 (27.5)

Table 19.2: Details of the 5 patients who received flumazenil to reverse midazolam [mean (SD)]
Patients and Methods

Eight patients were studied in a similar way to the previous study except following the naloxone the contents of an ampoule containing either flumazenil (0.1 mg/ml) or 0.9% saline were administered. All of the ampoules were identical and identified only by number. The nature of the contents was unknown to the investigator or the patient.

Sedation, heart rate, mean arterial blood pressure and respiratory rate were recorded immediately before the naloxone (baseline), 2 minutes after the naloxone, then 5, 30, 60, 120, 180 and 240 minutes after the administration of naloxone. A significant change in respiratory rate was defined as an increase or decrease of 10 breaths/minute. Similarly cardiovascular changes were defined as an increase or decrease in mean arterial blood pressure of 15mmHg and heart rate of 20 beats/minute. The total dose and duration of administration of midazolam and opioid were recorded. In addition, liver function tests and the plasma concentration of morphine, M3G and M6G were measured using HPLC (Svensson et al 1982). In all other respects the study was performed in an identical way to the previous study.
Results

Patient information is shown in Table 9.3. Liver function tests (Table 9.4) were deranged in all patients. Five patients had their tracheas intubated throughout the study and two did not. The remaining patient’s trachea was extubated as her conscious level improved. The total dose of all drugs and the duration of administration are shown in Table 9.5. The amount of midazolam and opioid varied widely between patients. Naloxone was administered to all patients but flumazenil to only three, the remaining five receiving placebo. After naloxone a significant improvement was seen in four patients (2, 3, 6 and 7) (Table 9.6).

One of two patients who received flumazenil, after naloxone, had a further improvement of conscious level, indicative of mixed drug accumulation as a cause for her unconsciousness. This patient is also the only one of the three who received flumazenil in whom an improvement in conscious level was seen with its administration. Patient number 4 had a significant improvement in conscious level after administration of the placebo. Improvement from either naloxone or flumazenil tended to last for only 60 minutes. At this time conscious level returned towards the baseline value, although it was always 2-3 points higher up the scale.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>Diagnosis</th>
<th>APII-GCS</th>
<th>Sepsis score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>27</td>
<td>1.6</td>
<td>70</td>
<td>CAH</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>66</td>
<td>1.85</td>
<td>60</td>
<td>VH</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>59</td>
<td>1.6</td>
<td>65</td>
<td>CC</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>27</td>
<td>1.6</td>
<td>55</td>
<td>CC</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>44</td>
<td>1.7</td>
<td>68</td>
<td>Car</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>53</td>
<td>1.8</td>
<td>80</td>
<td>Hep</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>55</td>
<td></td>
<td>55</td>
<td>PBC</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>44</td>
<td>1.7</td>
<td>68</td>
<td>Car</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 9.3: Patient information. CAH = chronic active hepatitis, VH = viral hepatitis, CC = cryptogenic cirrhosis, Car = carcinoid tumour, Hep = hepatoma. Patients 6 and 8 are the same patient studied on separate occasions.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Bilirubin (μmol/l)</th>
<th>ALT (U/l)</th>
<th>AP (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>260</td>
<td>204</td>
<td>102</td>
</tr>
<tr>
<td>2</td>
<td>292</td>
<td>516</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>420</td>
<td>49</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>351</td>
<td>1560</td>
<td>160</td>
</tr>
<tr>
<td>5</td>
<td>265</td>
<td>716</td>
<td>200</td>
</tr>
<tr>
<td>6</td>
<td>984</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>249</td>
<td>674</td>
<td>965</td>
</tr>
<tr>
<td>8</td>
<td>214</td>
<td>1270</td>
<td>229</td>
</tr>
</tbody>
</table>

Table 9.4: Liver function tests at the time of the study.
<table>
<thead>
<tr>
<th>Total dose of midazolam (mg)</th>
<th>Duration of midazolam administration (days)</th>
<th>Flumazenil dose (mg)</th>
<th>Total dose of fentanyl (f)(μg) (days)</th>
<th>Duration of morphine <a href="mg">m</a> opioid administration (days)</th>
<th>Total dose of naloxone (mg)</th>
<th>Duration of morphine [m] opioid administration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>241</td>
<td>12</td>
<td>1</td>
<td>m 183</td>
<td>9</td>
<td>0.4</td>
<td>0.35</td>
</tr>
<tr>
<td>115</td>
<td>4</td>
<td>0.3</td>
<td>m 67.5 f 300</td>
<td>5</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>17.5</td>
<td>2</td>
<td>1</td>
<td>m 22.5 f 700</td>
<td>3</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>341</td>
<td>9</td>
<td>0</td>
<td>m 205 f 700</td>
<td>10</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>62.5</td>
<td>2</td>
<td>0</td>
<td>m 80</td>
<td>2</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>135</td>
<td>4</td>
<td>0</td>
<td>m 145</td>
<td>4</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>0</td>
<td>m 10</td>
<td>2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>62.5</td>
<td>2</td>
<td>0</td>
<td>m 80</td>
<td>2</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 9.5: Total dose and duration of midazolam and opioid required by eight patients after liver transplantation.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline</th>
<th>Post</th>
<th>Time after test drug (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Naloxone 5 30 60 120 180 240</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>13</td>
<td>13 13 13 13 13 13 13</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>7*</td>
<td>3* 7* 7 7 7 5 7</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>7*</td>
<td>8 8 8 11* 7 8 8</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>7</td>
<td>4* 1* 5* 5 5 5 5</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>9</td>
<td>9 11 11 11 11 11 11</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>1*</td>
<td>1 1 7* 1* 5* 5 5</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>7*</td>
<td>7 10* 10 10 10 7*</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>12</td>
<td>11 11 12 12 12 12 12</td>
</tr>
</tbody>
</table>

Table 9.6: Sedation scores after naloxone and flumazenil (patients 1-3) or placebo (4-8). * = significant change in conscious level.
Cardiorespiratory changes were associated with reversal of sedation and analgesia. Patient 2 increased her respiratory rate by 10 breaths/minute after the flumazenil. Patient 3 also increased his respiratory rate by 13 breaths/minute after the naloxone. Both respiratory rate (14 breaths/minute) and blood pressure (17 mmHg) increased after naloxone in patient 4. No cardiorespiratory changes were seen in patients 6 and 7 after arousal with naloxone or with the placebo effect seen in patient 4, although heart rate decreased 30 minutes after the placebo by 30 beats/minute. Significant changes were seen on single occasions in two other patients. At 120 minutes after flumazenil heart rate and mean arterial pressure increased in patient 1 and were probably related to external stimulation. Heart rate increased by 25 beats/minute when the patient developed bigeminy 5 minutes after administration of the placebo.

Unfortunately, plasma concentrations of morphine and its metabolites could only be measured in four of the patients. These are shown in Table 9.7 along with the sedation scores for these patients before and after naloxone. No correlation between the plasma concentration of morphine, M3G or M6G and the effects of naloxone is apparent.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sedation scores:</th>
<th>Morphine (ng/ml)</th>
<th>M6G (ng/ml)</th>
<th>M3G (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre Naloxone</td>
<td>Post Naloxone</td>
<td>Pre Naloxone</td>
<td>Post Naloxone</td>
<td>Pre Naloxone</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>7</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>7</td>
<td>16</td>
<td>23</td>
</tr>
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<td>6</td>
<td>7</td>
<td>1</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>12</td>
<td>1</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 9.7: Sedation scores before and after naloxone in four patients who had plasma concentrations of morphine measured. os = off scale.
Discussion

The prolonged sedation attributable to midazolam in these patients may be explained by drug accumulation due to the delayed elimination seen in the critically ill, particularly with sepsis (Chapter 8). Flumazenil (RO 15-1788) is a specific benzodiazepine receptor antagonist. It has been shown to be a safe agent for the reversal of short term benzodiazepine sedation in patients requiring intensive care (Kleiberger et al 1985). The only adverse effects that have been reported in critically ill patients have been nausea and vomiting. Fear and anxiety have also been described if large doses (greater than 10mg) of flumazenil are given rapidly, but these may represent rapid awakening of the patient in a seemingly hostile environment. The apparent safety of flumazenil does not obviate the need for careful dose titration. Cardiovascular instability has not been reported in studies reversing sedation after coronary angiography (Geller et al 1986) but these patients had neither a tracheal tube in place nor a painful surgical incision. Adverse cardiovascular responses may be seen if patients are suddenly awakened with a tracheal tube in place, although hazardous increases were not seen in either study. Cardiorespiratory changes after naloxone administration (Smith and Pinnock 1985) were greater than those seen with flumazenil.

Flumazenil has been shown to have an elimination half
life of about one hour in normal volunteers (Klotz, Ziegler and Reimann 1984; Roncari, Ziegler and Guentert 1986). The clearance of the drug is thought to be hepatic although, in common with other benzodiazepines, extrahepatic metabolism may occur. The duration of action is approximately one hour, similar to naloxone. Since both were given with only a short time interval between them this may explain why conscious level decreased after initial arousal, by either agent, at 60 minutes. No patient resedated sufficiently, at 60 minutes or any other time, to require an infusion of either drug. It is noteworthy that in the second study none of the patients who responded to flumazenil or naloxone returned to their baseline level of consciousness. The reasons for this are not known and several explanations are possible. The effects of the agonist may have been waning at the time of the study and the level of consciousness seen at 60 minutes would have been reached at this time without the agonist. This is unlikely because of the long time interval between last administration of the drug and the start of the study. Alternatively, the antagonists resulted in an increase in blood flow (perhaps secondarily to an increase in cardiac output resulting from general arousal) to the organs metabolising midazolam. Finally, the antagonists may have altered the receptors in some way for a longer period. Anecdotal reports have suggested that flumazenil may reverse some features of
hepatic encephalopathy, mediated via the GABA system (Mullen et al 1988), although further studies are necessary to evaluate its value in this condition. If resedation was a problem then large bolus doses or infusions may increase the duration of effect (Pepperman 1989), but neither was necessary in this study.

All of the patients, in both studies, who responded to flumazenil had required doses of midazolam in excess of 100mg. This may be a useful observation when evaluating coma in this group. Patients who have required less midazolam for sedation and are comatose may have causes, other than benzodiazepine intoxication, for their unconsciousness. However, it should be noted that some patients who received doses in excess of 100mg did not respond to flumazenil.

In the second study four patients responded to naloxone; plasma concentrations of morphine and its metabolites were available for two of these patients and a further two who did not respond. No correlation was seen between plasma concentrations and effect of naloxone. This illustrates how unreliable the measurement of plasma concentrations can be in the critically ill when sampled some time after discontinuing the drug; concentrations of the drug and its metabolites measured in easily accessible body fluids fail to correspond to concentrations at the receptor. This feature has
been clinically documented previously with midazolam and flumazenil (Bodenham et al 1988).

Those patients who did not show an improvement in conscious level following flumazenil are thought to have had other causes for their depressed conscious level including electrolyte abnormalities, tissue hypoxia, cerebral oedema, hepatic and septic encephalopathy (Hasselgren and Fischer 1986), since neurological recovery eventually occurred.

When flumazenil is used in patients who have a tracheal tube in place sudden awakening may occur and result in sudden discomfort. In one of the patients in the first study this produced airway obstruction when the tracheal tube was bitten. The addition of isoflurane to the inspired gas rapidly resolved the situation. Not all ventilators have the facility for the addition of vapours to the inspired gas. In such circumstances, when a patient whose trachea is intubated is to receive flumazenil, it may be prudent to have ready a suitable dose of a short acting intravenous anaesthetic agent, such as thiopentone. The short action of flumazenil makes it unlikely to be a problem of any duration.

In conclusion, flumazenil appears to be a useful agent for reversal of unexpectedly prolonged benzodiazepine sedation in patients after liver transplantation who
have received large doses (> 100mg) of midazolam. If flumazenil does not reverse sedation then other recoverable causes of depression of conscious level must be considered.
This chapter describes how the anhepatic period was used to investigate the extrahepatic metabolism of propofol, which is increasingly being used for sedation in the critically ill. It also describes two patients who developed a complication of hepatic transplantation, renal failure, in whom a new method of renal support allowed an older sedative drug, chlormethiazole, to be used.

PROPOFOL

Propofol (di-isopropyl phenol) is an intravenous anaesthetic agent suitable for induction and maintenance of anaesthesia. It has a short duration of action with a blood elimination half life of 34 – 64 minutes. Its major metabolite is propofol glucuronide, which is thought to be produced principally in the liver, with less than 0.3% of an administered dose excreted unchanged in the urine. Clearance values of propofol are in the range 1.3 – 2.2 l/min (Cockshott 1985, Simonds et al 1985, Simons et al 1988) which are in excess of generally accepted values of hepatic blood flow (1.5 l/min). Since clearance is greater than can be expected from hepatic metabolism alone, extrahepatic sites of
metabolism may also contribute to the elimination of propofol. Studies have suggested that the parent compound of propofol, phenol, undergoes substantial extrahepatic metabolism in rats (Powell et al 1974; Cassidy and Houston 1980; Cassidy and Houston 1984). Others have also suggested that extrahepatic metabolism of propofol occurs in sheep (Mather et al 1989) and humans (Dogra et al 1989). The lungs and the gastrointestinal tract have been suggested as possible sites (Cassidy and Houston 1980; Cassidy and Houston 1984; Hook 1982; Dogra et al 1989, Mather et al 1989).

The absence of the large hepatic component of propofol metabolism, during the anhepatic period, was used in this study not only to demonstrate extrahepatic drug metabolism but also to determine the contribution of the lungs to any extrahepatic metabolism of propofol. I was assisted during the study with the sample collection by Dr P A Gray and with the sample analysis by Dr E J Douglas and Dr I D Cockshott (ICI Pharmaceuticals Ltd).

EXTRAHEPATIC PROPOFOL METABOLISM IN MAN DURING THE ANHEPATIC PHASE OF ORTHOTOPIC LIVER TRANSPLANTATION


Patients and Methods

The trial was an open study in six adult patients undergoing orthotopic liver transplantation, who were thought likely to have an uncomplicated intraoperative
course. Anaesthesia and surgery were conducted as previously described.

It was necessary to use $^{14}$C labelled propofol to allow quantification of metabolites. The total amount of radiolabelled substance, representing both propofol and its metabolites, was measured using thin layer chromatography, and propofol was measured using HPLC. The difference between the two was an estimate of the amount of metabolite present (Simonds et al 1988). The $^{14}$C radiolabelled propofol had a specific activity of approximately 1.0 $\mu$Ci/mg. Authorisation to administer radiolabelled propofol was obtained from the Administration of Radioactive Substances Advisory Committee of the Department of Health and Social Security.

Five minutes after the start of the anhepatic period a single intravenous dose of $^{14}$C radiolabelled propofol (0.5 mg/kg) was administered over a period of 30 seconds through a peripherally sited venous cannula and flushed with 10 ml 0.9% saline. Blood was sampled simultaneously from a previously sited radial arterial line and central venous line at 2 and 30 minutes after drug administration during the anhepatic and at the same time during the reperfusion period to investigate the uptake and metabolism of propofol by the lungs. It is not the practice, at this centre, to insert routinely...
pulmonary artery flotation catheters into all patients undergoing this operation which precluded obtaining true mixed venous blood from the pulmonary artery (Chapter 4).

Two samples of arterial blood were collected at each time point. The first samples of 5ml were mixed with potassium oxalate and stored at 4°C until analysed for propofol content and total radioactivity. Venous blood was also treated in the same way. A second sample of 10ml of arterial blood was mixed with potassium oxalate, rapidly centrifuged, the plasma then removed and stored at -20°C until analysed for total radioactivity and the concentrations of circulating metabolites.

Results
The demographic information for the six patients is summarised in Table 10.1. Patient 1 suffered excessive haemorrhage postoperatively and died shortly after reaching the intensive care unit. For this reason he has been excluded from the data analysis. Figure 10.1 shows the mean (SEM) arterial concentrations of propofol and total $^{14}$C during the anhepatic and reperfusion periods. The mean (SEM) arterial and venous propofol concentrations are shown in Figure 10.2, whilst Figure 10.3 shows the mean (SEM) arterial and venous total $^{14}$C concentrations for the anhepatic and reperfusion periods.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>21</td>
<td>Cryptogenic cirrhosis</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>21</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>52</td>
<td>Hepatoma</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>31</td>
<td>Chronic active hepatitis</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>53</td>
<td>Haemochromatosis</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>50</td>
<td>Primary biliary cirrhosis</td>
</tr>
</tbody>
</table>

Table 10.1: Demographic information for the six transplant patients
Figure 10.1: Mean (SEM) arterial concentrations of propofol and total $^{14}$C during the anhepatic and reperfusion periods.
Figure 10.2 Mean (SEM) arterial and venous propofol concentrations for the anhepatic and reperfusion periods.
Figure 10.3: Mean (SEM) arterial and venous total $^{14}$C concentrations for the anhepatic and reperfusion periods.
Two and 30 minutes after the dose, both arterial and venous concentrations of propofol are lower than total $^{14}$C concentration, and this divergence increases in the reperfusion period. Venous concentrations of propofol and total $^{14}$C are less than, or comparable with the arterial concentrations during both the anhepatic and reperfusion periods.

**Discussion**

Extrahepatic metabolism of propofol is evident from the divergence between the concentrations of total $^{14}$C and propofol in the anhepatic period. However at 30 minutes the percentage of total $^{14}$C as metabolites was less than that seen in volunteers receiving a similar dose of propofol. Arterial concentrations of propofol were higher at 2 and 30 minutes than was observed in volunteers receiving similar doses. Samples taken after revascularisation quickly approached the values found in volunteers (Simons et al 1988). This indicates that although extrahepatic metabolic sites for propofol exist they do not have a metabolic capability equivalent to that of the liver.

Venous concentrations of both propofol and total $^{14}$C were shown to be lower than or equivalent to simultaneously measured arterial concentrations. If pulmonary extraction of propofol had been significant, venous
concentrations of propofol would have been expected to be higher than those in arterial blood, since they would be measured before passing through the lungs. There is, therefore, no evidence from this study to suggest that the lung eliminates propofol. The higher arterial concentration two minutes after administration of the propofol may indicate a distribution effect within the central compartment.

The exact site of extrahepatic metabolism is unknown. Studies in rats, of the parent compound phenol (Cassidy and Houston 1980; Cassidy and Houston 1984), and of propofol in sheep (Mather et al 1989) and in humans (Dogra et al 1989) have all suggested that pulmonary metabolism may be important. All of these studies were performed in animals or humans in whom the liver was still present and infer their conclusions from results based on blood sampling at various points in the systemic and pulmonary circulation. This study was performed when no effective liver was present and demonstrates that in humans pulmonary metabolism is not significant. The gastrointestinal tract is known to metabolise actively many substances (Hartiala 1974). Metabolic activity is thought to be concentrated in the mucosal cells. Although they are ideally placed to metabolise orally administered substances, it is not known whether parenterally administered substances can obtain access to these cells from the bloodstream for subsequent
metabolism (Ilett and Davies 1982). The studies by Cassidy and Houston (1980; 1984), in rats, also suggested that phenol was metabolised by the gastrointestinal tract but when Powell and her colleagues (1974) studied rats in which both their livers and their gastrointestinal tracts had been removed, metabolism of phenol still occurred. Since metabolism of phenol occurs without the gut being present and it is unlikely that drugs gain access to the mucosal cells, the gastrointestinal tract is probably not a major site of propofol metabolism. At the time of preparation of this thesis, results of other data from this study are awaited. Early indications are that the kidneys may be implicated in the elimination of propofol. Indeed, Mather and his colleagues (1989) have demonstrated renal production of propofol, probably from one of its own metabolites, in a sheep model.

Extrahepatic metabolism of propofol does occur. This study demonstrated that the lungs are not the primary site, and that it is unlikely to be the gastrointestinal tract. The kidneys, however, may play a significant role in propofol elimination.
Infusions of chlormethiazole are well established in the management of alcohol withdrawal, status epilepticus, pre-eclampsia and anaesthesia. It has also been used for prolonged infusion in critically ill patients (Scott et al 1980) where it can produce effective sedation, allowing artificial ventilation whilst preserving cardiovascular stability. Modig (1988) has suggested that chlormethiazole may also have a protective effect in endotoxic shock, minimising the cardiovascular and pulmonary instability, which could be advantageous in the patient after liver transplantation, sepsis having remained a major cause of mortality in this group over the last 20 years (Chapter 17).

When administered intravenously by bolus doses or by short infusions chlormethiazole produces effective sedation with rapid onset and recovery due to redistribution into a large volume of distribution. It is eliminated mainly by hepatic metabolism, with less than 1% of unchanged drug excreted in the urine (Moore et al 1975). During long term infusions saturation of redistribution sites may occur leaving its effect to be terminated by metabolism alone (Robson et al 1984). This problem may be exacerbated in the elderly (Nation et al 1976), the critically ill and where hepatic function is chronically impaired (Pentikainen et al 1978). Workers
in Edinburgh (Scott et al 1980) have suggested that in the critically ill, the decrease in metabolism may be due to a reduction in hepatic blood flow. Recovery from long term infusions, those lasting more than 24-48 hours, may therefore be significantly prolonged in some patients.

Chlormethiazole, for intravenous use, is formulated as a 0.8% solution in 4% glucose buffered with approximately 30 mmol sodium hydroxide to achieve a pH in the normal range. It is not available in a more concentrated form because the incidence of venous thrombophlebitis is unacceptably high and it may produce haemolysis if concentrations of 5% or greater are used (Runciman et al 1981). A large fluid load may therefore need to be given if chlormethiazole is used for prolonged sedation. This feature has limited its usefulness, particularly in patients with renal failure and others with fluid and electrolyte problems. The advent of new techniques of renal support has led to both advantages and disadvantages. Haemofiltration (Kramer, Wigger and Reiger 1977) removes fluid and small molecular weight substances (approximate molecular weight <20,000) and can remove large volumes of fluid. If arterial and venous lines are inserted, the patient's own blood pressure can be used to drive the blood around the circuit (continuous arterio-venous haemofiltration (CAVH)). Alternatively, two venous lines with a blood pump
can be used to circulate the blood. (continuous veno-venous haemofiltration (CVVH)). Large volumes of haemofiltrate may be removed and replaced with a suitable solution. Continuous arteriovenous haemofiltration with dialysis (CAVHD) combines low volume arteriovenous haemofiltration with continuous perfusion of the filter using a haemodialysis solution (Brown and Kox 1988). Continuous veno-venous haemofiltration with dialysis (CVVHD), like CVVH, uses two venous lines and a blood pump, and provides a high and consistent flow through the membrane. These latter two techniques allow slow, gentle, continuous haemodialysis as well as control of fluid balance.

**CHLORMETHIAZOLE SEDATION FOR CRITICALLY ILL PATIENTS IN RENAL FAILURE**

*Anaesthesia (1989) 44: 913-915*

Two patients are described who developed renal failure after liver transplantation. This complication was treated with CVVHD, which allowed the use of chlormethiazole for night sedation.

**Patients**

The first patient, a 49-year-old male, had undergone orthotopic liver transplantation for cirrhosis due to $\alpha_1$-antitrypsin deficiency. This had been complicated by the development of both acute lung injury and renal
failure 12 days postoperatively.

The second patient, a 44-year-old female, required orthotopic liver transplantation for primary biliary cirrhosis. The patient had deteriorating renal function preoperatively, due to the hepatorenal syndrome, and developed acute renal failure on the second postoperative day. Both patients required respiratory support (CMV or SIMV) as well as CVVHD. Liver function deteriorated in patient 1 and was predominantly obstructive in nature. Patient 2 also had abnormal liver function which was primarily hepatocellular in nature and which improved during the period of chlormethiazole infusions (see Table 10.2).

Each night chlormethiazole infusions were given to the patients to facilitate sleep. Patient 1 received his from the 21st to the 39th day and patient 2 from the 10th to the 19th day in the ICU. Prior to this, sedation had been with bolus doses of morphine and midazolam given when required, but this proved difficult to control. Propofol infusions were not used since this method of sedation, in deeply jaundiced patients may result in bradyarrhythmias.
<table>
<thead>
<tr>
<th>Test</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (\mu\text{mol/l})</td>
<td>240-466</td>
<td>45-97</td>
</tr>
<tr>
<td>Alkaline Phosphatase (\text{U/l})</td>
<td>88-460</td>
<td>158-224</td>
</tr>
<tr>
<td>Alanine Aminotransferase (\text{U/l})</td>
<td>28-51</td>
<td>33-203</td>
</tr>
</tbody>
</table>

Table 10.2: Range of liver function tests during the period of chlormethiazole infusion for the two patients.
The rate of the chlormethiazole infusions was controlled by the nursing staff within prescribed dose limits. The infusions were discontinued during the day to encourage a normal circadian rhythm and prevent drug accumulation. Sedation was assessed by the nursing staff each hour using the sedation score described in Chapter 8. For each infusion the following information was recorded:

1. The infusion rate.
2. The total dose of chlormethiazole given.
3. The average sedation score during the infusion.
4. The time taken for the patient to reach maximum awakening after termination of the infusion.

Figures 10.4 and 10.5 show these data for the patients. Adequate night sedation was judged to be 2 to 3 on the scale. On only two occasions was this objective not achieved in the total of 42 nightly infusions. However, excessive sedation (score greater than 3) occurred on six occasions and three times patient 1 had not recovered noticeably before the infusion was inadvertently recommenced (marked with * in Figure 10.4). On three occasions it was necessary to withhold sedation for patient 1 because of oversedation.

In the two patients, recovery time increased rapidly in the first six nights and only improved on reduction of
drug dose (usually achieved by a decrease in the duration of the infusion to approximately 3 to 4 hours, rather than a change in the rate of infusion). Towards the end of the period of chlormethiazole infusions recovery times decreased as experience was gained in administering the appropriate dose of chlormethiazole. This dose was noticeably reduced from that used in the first few days.

Large changes in heart rate or blood pressure were not seen. The maximum decreases in systolic blood pressure were 20-25% of the values recorded before the chlormethiazole infusion and probably not much greater than that seen during natural sleep. Chlormethiazole is known to cause rises in heart rate of about 20-40 beats per minute (Scott et al 1980), but we did not observe this.

No problems in fluid or electrolyte balance were encountered that were not easily controlled by CVVHD.
Figure 10.4. Patient 1. Drug dose (mg) ■; recovery time (hours) □; and sedation score ▽ for 19 nightly chlormethiazole infusions. * marks the three occasions when patient 1 had not recovered noticeably before the infusion was inadvertently recommenced.
Figure 10.5. Patient 2, Drug dose (mg) □; recovery time (hours) □ and sedation score □ for 10 nightly chlormethiazole infusions.
Discussion

Chlormethiazole provides good sedation with cardiovascular stability but one of its major drawbacks has been the large fluid load associated with its administration. CAVH and more recently CVVHD and CAVHD are being used increasingly in critically ill patients with renal failure, and these can be used to solve the fluid balance problems.

In these patients during the first 4-6 days relatively large doses of chlormethiazole were needed and these were associated with a rapid recovery time. This represents cessation of clinical effect by redistribution. However, as the redistribution sites become saturated, the recovery times dramatically increase as termination of effect becomes dependent on metabolism. The dose has to be reduced to match this change if acceptable recovery times are to be achieved.

Later in the study period recovery time decreased. This may represent the development of tolerance like that described with morphine (Marshall et al 1985) and fentanyl (Schafer et al 1985). Alternatively, clearance may have been reduced due to poor liver function and as the patients' condition improved so elimination of chlormethiazole increased, in a similar way to midazolam (Chapter 8). Once experience was gained with chlormethiazole, particularly in downtitration of the dose to avoid
accumulation, it was found to be an effective and safe technique providing smooth and consistent sedation. Furthermore, there is animal evidence that chlormethiazole might attenuate the cardiovascular and pulmonary instability of septic shock (Modig 1988). Sepsis remains a major cause of morbidity and mortality in patients after liver transplantation, particularly in those with renal failure (Chapter 17), and perhaps the use of this agent may reduce it.