ANAESTHESIA FOR REPAIR OF FRACTURED NECK OF FEMUR

A Comparison of Spinal and General Anaesthesia

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DECLARATION

The thesis was composed by myself and all books and papers were consulted by me personally. The research was conducted while I was a Senior Registrar in the Department of Anaesthesia in the Western Infirmary, Glasgow, between 1977 and 1980. The following publications include work presented in the thesis:

Douglas, I.H.S., McKenzie, P.J., Ledingham, I.McA. & Smith, G. (1978) Effect of halothane on PO_2 electrode (letter). Lancet, ii, 1370-1371.

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British Journal of Anaesthesia, **52**, 49-54.

McKenzie, P.J., Wishart, H.Y. & Smith, G. (1984) Long-term outcome after repair of fractured neck of femur. Comparison of subarachnoid and general anaesthesia.
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I was involved in administration of the anaesthetics along with Dr. Hugh Wishart in almost every case. I or Dr. Wishart took the samples for blood gas analysis, and in almost every instance I was responsible for analysis of results (chapter 2, section I). I collected and analysed all samples in the study presented in chapter 2, section II, except when the ABL1 blood gas analyser was out of action, when anaesthetic laboratory staff kindly performed the analyses. Ian Douglas investigated the calibration error in response to persistent and puzzled complaints about the strange behaviour of the ABL1.

I personally undertook the follow up of all patients (with secretarial help) and analysed all the results.

By the specialist nature of the studies comprising chapters 3 and 4 of the thesis, these were of necessity, collaborative work. As indicated in the acknowledgements, Mr. Ian Gray co-ordinated and arranged venography on patients from my study and these venograms were carried out by the Department of Radiology at the Western Infirmary. Also as indicated, the laboratory work for the viscosity studies was performed by Dr. Maureen Drummond at Glasgow Royal Infirmary. Dr. Alastair Drummond and myself took the blood samples.

PATIENT CONSENT

Where appropriate, consent was sought from patients for blood sampling procedures. In all instances consent was verbal and no written permission was asked. This practice reflected the policy at that time in the Western Infirmary (1977-1980). In the venography study, the matter was left to the discretion of the orthopaedic surgical team who obtained verbal consent, where possible.

More recently, practices regarding consent have become more formal and the author recognises that formal application to a hospital ethical committee would be now be made for all clinical studies and written, informed consent might be considered necessary despite the difficulties in some groups of patients such as the elderly.

ABBREVIATIONS

C	Centigrade
CCF	Congestive Cardiac Failure
CNS	Central Nervous System
CO_2	Carbon Dioxide
CSF	Cerebro-spinal Fluid
CVA	Cerebro-vascular Accident
CVS	Cardio-vascular System
d $litre^{-1}$	per decilitre
DVT	Deep Venous Thrombosis
EDTA	Ethylene diamine tetra-acetic acid
FIO_2	Fractional Inspired Oxygen Concentration
G	Gravitational force
g	grams
GA	General Anaesthesia
Hb	Haemoglobin
IPPV	Intermittent Positive Pressure Ventilation
i.v.	intra-venous
kPa	kilo-Pascals
L	Lumbar Interspace
max	maximum
min	minutes
min^{-1}	per minute
mg	milligram(s)
ml	millilitre(s)
mm Hg	millimetres of Mercury
mmol $litre^{-1}$	millimoles per litre
n	number

op	operative
O_2	Oxygen
p	partial pressure
Pa	Arterial partial pressure
PTE	Pulmonary Thromboembolism
RS	Respiratory System
SAB	Subarachnoid Block
sec^{-1}	Reciprocal seconds
SD	Standard Deviation
T	Thoracic Interspace
y	years

SUMMARY

Patients having repair of fractured neck of femur are one of the highest risk groups commonly presenting for anaesthesia and the incidence of fractured neck of femur is rising almost alarmingly. Patients are generally very elderly and pre-operative medical problems are extremely common. Great demands are placed on health care resources and post-operative morbidity and mortality are high.

The choice of anaesthetic technique lies mainly between conventional general anaesthesia (GA) or some form of regional anaesthesia, of which sub-arachnoid block (SAB), otherwise referred to as "spinal" anaesthesia, is probably the most appropriate. Many anaesthetists feel that spinal anaesthesia is superior to general anaesthesia for the patient with fractured neck of femur and the present thesis attempts to compare and assess objectively some aspects and effects of these anaesthetic techniques in patients having repair of fractured neck of femur.

Sub-arachnoid spinal anaesthesia was compared with conventional general anaesthesia in respect of effects on respiratory function in the immediate peri-operative period, incidence of post-operative deep venous thrombosis and peri-operative changes in blood viscosity and its determinants. Comparative results are presented of mortality and outcome over the year following operation. 148 patients presenting for "pin and plate" repair of fractured neck of femur were randomly allocated to receive general (GA) or spinal (SAB) anaesthesia.

Anaesthetic Techniques

GA group

Anaesthesia was induced with althesin (Glaxo) 1-3ml i.v. Tracheal intubation was facilitated by suxamethonium 50mg and patients breathed 0.5%-1% halothane in 66% nitrous oxide in oxygen.

SAB group

1.3-1.5ml of "heavy" nupercaine was injected into the sub-arachnoid space. If sedation was necessary small doses of intra-venous diazepam were given.

Blood Gas Studies

Arterial blood gas analysis was performed in 100 patients, immediately before induction of anaesthesia, one hour after induction and one hour after the end of surgery. Pre-operative pO_2 values were low (mean 9.04 kPa) and remained unchanged during and after anaesthesia in the SAB group. However, in the GA group there was a significant fall in mean PaO_2 of 0.68 kPa by one hour after the end of anaesthesia.

The changes in PaO_2 in the GA group were further investigated in detail, by multiple sampling over the first hour after anaesthesia in 10 patients, who breathed room air. This revealed a highly significant fall in PaO_2, greatest in the first 10 minutes after disconnection from the anaesthetic gases, and a gradual recovery from a mean of 6.65 kPa at worst to 8.5 kPa at the end of the hour. Some patients had pO_2 values repeatedly less than 4 kPa.

Incidence of Deep Venous Thrombosis

Deep venous thrombosis (DVT) occurs in up to 80%, or more, of patients with fractured neck of femur, and pulmonary thrombo-embolism is a major cause of the high mortality associated with the condition. An accurate objective assessment of the incidence of DVT is obtained by ascending venography. Twenty patients in each anaesthetic group received venography between the 7th and 10th days after surgery. The incidence of DVT in the SAB group (40%) was significantly lower than that in the GA group (75%). An assessment of possible mechanisms of effects of anaesthesia concludes that general anaesthesia may precipitate DVT while spinal anaesthesia may be protective in this respect.

Peri-operative Changes in Blood Viscosity

Blood viscosity is determined by three main variables; haematocrit, plasma protein concentrations (particularly fibrinogen), and the deformability of red cells. Viscosity can affect the incidence of DVT formation and is important in determining perfusion of vital organs.

Whole blood viscosity was measured along with its major determinants, before, during and 2 hours after surgery. Mean viscosity was significantly reduced from pre-operative values in the SAB group both intra-operatively and post-operatively. Values were unchanged in the GA group. Mean haematocrit was significantly lower in the SAB group both during and after anaesthesia compared with the GA group. Fibrinogen levels did not change in either group but red cell deformability was significantly increased from pre-operative values in the SAB group intra-operatively, but had returned to baseline by the time of the post-operative sample. In the GA group deformability was significantly reduced from pre-operative values both during and after anaesthesia.

The viscosity changes may offer part of the explanation for the difference in incidence of DVT between the anaesthetic groups.

Mortality and Long Term Outcome

148 patients were followed up for the first year after repair of fractured neck of femur. By the end of the year there were no significant differences between the groups. Overall, 34% had died, 50% had gone home, 12% were in hospital or institutional care and 4% were lost to follow up.

Length of hospital stay did not appear to be affected by anaesthetic technique. The mean length of stay in the acute hospitals was 42.9 days for the GA group and 38.8 days for the SAB group. Mean hospital stay including convalescence was 84.4 days overall.

Although long term mortality was essentially identical there was a significantly lower early cumulative mortality in the SAB group by 14 days after surgery. A clustering of deaths was seen in the GA group between the 6th and 16th post-operative days. This difference in distribution of timing of deaths could be attributable to a difference in incidence of thrombo-embolic events, a hypothesis supported by the DVT and viscosity results.

An analysis of the relative merits of the two anaesthetic techniques is attempted and the influence of practical as well as theoretical factors assessed. The dangers of drawing conclusions from short term follow up is clearly demonstrated. The author considers that, contrary to the opinion currently held by many anaesthetists and despite the specific advantages of spinal anaesthesia demonstrated in this thesis, general anaesthesia is the preferable method of anaesthesia for repair of fractured neck of femur. Spinal anaesthesia should continue to be taught and reserved for those patients for whom it should offer particular benefits.

CHAPTER 1

INTRODUCTION AND BACKGROUND

SECTION I Fractured Neck of Femur

[1.1] The Problem of Fractured Neck of Femur

The acute and long term care of patients who have sustained a fracture of the femoral neck is a great burden on the resources of the National Health Service. As the condition occurs mainly in the elderly, a section of the population steadily increasing in number, the need for hospital and after-care facilities is certain to increase in the future. This elderly population frequently suffers from a wide variety of concurrent disease processes, forming a particularly difficult and high risk group for anaesthesia and surgery.

The studies presented in this thesis attempt to examine the effects of two different anaesthetic techniques on a variety of physiological parameters in patients having surgical repair of fractured neck of femur, and also to examine effects of anaesthetic management on outcome, both in the short and long term. It is important, firstly, however, to put the problem of fractured neck of femur into perspective, both in terms of the great demands on health care resources, and the considerable morbidity and mortality associated with the condition.

[1.2] Incidence of Fractured Neck of Femur

There seems little doubt that the incidence of femoral neck fracture is rising at an almost alarming rate and substantially faster than may be explained by the increasing proportion of elderly in the population. In 1968, 3,855 patients were admitted to hospital in Scotland with the diagnosis of fractured neck of femur but by 1978, the comparable figure was 6,160 (Scottish Hospital Inpatient Statistics, 1968 and 1978). This rise may be due partly to the rise in the proportion of elderly in the population, but discharges from hospital after fractured neck of femur expressed per million Scottish population, have risen from 739 in 1968, to 1,193 in 1978 and the majority of patients are women with a ratio in excess of 3 to 1.

Although the Scottish Hospital Inpatient Statistics do not give a detailed breakdown of incidence in each age range on admission, they do quote discharge rates for various age groups. For example, in 1968, in females of 75 years of age and over, the discharge rate was 13.1 per 1000 population. By 1978, this had increased to 18.1 per 1000.

Other studies confirm the rise in incidence of femoral neck fracture both in this country and elsewhere. In Sweden, Zetterberg and Andersson (1982) reported a highly significant increase in incidence in both sexes over the period from 1965 to 1979. In England and Wales, annual admissions for fractured neck of femur increased threefold over the period 1959 to 1977 (Lewis, 1981). Lewis calculated that 81% of the increase for males and 68% of that for females was independant of the change in age structure of the population. However, that study used

"Hospital Activity Analysis" data and Rees (1982) cautioned that such methods may be an unreliable guide to true incidence. Knowelden, Buhr and Dunbar (1964) reported an annual incidence of about 3 fractures of the neck of femur per 1000 population in women over 75 years of age. Wallace (1983) found the comparable incidence to be 8 per 1000 in 1971 rising to 16 per 1000 in 1981. Femoral neck fracture may comprise one sixth of all fractures (Keith, 1973).

The incidence rises sharply with age, from 0.42 per 1000 per year in those under 60 years of age, to 5.11 per 1000 per year from ages 70-79 and 27.11 per 1000 in those aged 90-94 years (Gallannaugh, Martin and Millard, 1976). Thus, it is salutary to consider that approximately 2% of women and 1% of men over the age of 85, fracture their femoral necks each year (Gallannaugh et al, 1976).

The reasons for changes in incidence are not clearly understood and do not fall within the scope of the present thesis.

[1.3] Hospital Bed Occupancy

The elderly patient with a fractured hip tends to have a very long duration of stay in hospital. The mean duration of stay has, however, decreased from 45 days in 1968 to 35.3 days in 1978, but the total "bed days" increased from 172,094 in 1968 to 218,258 in 1978 (Scottish Hospital Inpatient Statistics, 1968 and 1978).

In a regional survey of 2,619 patients with fractured neck of femur, Gallannaugh et al (1976) found the average length of hospital stay to vary with age from less than 24 days in patients under 60 years to over 35 days in patients over 75 years. The authors of that study calculated that patients with hip fracture occupied the equivalent of a 250 bed hospital in the South West Thames region.

[1.4] Mortality

The condition carries a very considerable mortality. The majority of deaths occur in the first few weeks after the fracture and after 6 months the mortality rate approaches that of the general population (Alffram, 1964). The mortality rate in that study appeared to be unrelated to the sex of the patient or the type of fracture, but rose steeply with age.

Barnes, Brown, Garden et al (1976), in a multi-centre prospective review of 1503 patients with subcapital fractures of the femur found the overall mortality at one month after operation to be 7.4% in females and 13.3% in males. In patients under 65 years of age, only 1.6% of females and no males died within one month of operation, while the comparable mortality rates in patients aged over 84 years was 20.7% of women and 37% of men. By 6 months after the fracture, 24% of males and 16% of females had died. Only a few further deaths occurred over the next 6 months. The mortality rates at 6 and 12 months may be an underestimate as a considerable number of patients (about 16%) were lost to follow up.

Gallannaugh et al (1976) found the overall hospital mortality in 2,619 patients with hip fracture, to be 21.6% of males and 19.6% of females. That study also found that hospital mortality rose steeply with age from 14% in the 69 to 74 age group to 36.9% in the 90 to 94 year old group. Allen and

Metcalf (1965) found a lower overall hospital mortality of 8.7% in a study of 343 patients of 60 years and over, reaching 13.9% in the 80 to 89 years group. One third of deaths occurred in the first 3 days after operation, a further third between the 3rd and the 12th day after operation and the remainder of the deaths over a further period of 45 days.

By comparison, the official Scottish statistics quote an overall mortality rate, in 1978, of 10.2%. In the 65-74 age group the mortality rates were 7% for males and 5.2% for females. In those of 75 years and over, 20.6% of males and 13.2% of females died (Scottish Hospital Inpatient Statistics, 1978).

The major causes of death after fractured neck of femur are pulmonary thromboembolism, pneumonia, cardiac failure, myocardial infarction and cerebrovascular accident (Allen and Metcalf, 1965; Honkonen, Tarkkanen and Julkunen, 1971).

[1.5] Morbidity

The elderly patient with a hip fracture suffers considerable morbidity as a result of the injury, surgery and anaesthesia (if performed) and post-operative immobilisation. In many cases medical problems present before the injury are exascerbated. Honkonen et al (1971) quote the incidence of pneumonia post-operatively as 25%, pulmonary thromboembolism, 5% and myocardial infarction, 4.5%. Deep venous thrombosis is a very common complication, with an incidence of up to 75% (Field, Kakkar and Nicolaides, 1972).

About 25% of subcapital fractures fail to unite and of those that do unite, between 15 and 24% suffer late segmental collapse of the femoral head (Barnes et al, 1976). Confusional states and incontinence contribute greatly to the major problem of nursing this group of patients.

An editorial entitled "Fractures near the hip" in the British Medical Journal (1976) stated, "the management of the fracture, though controversial is a relatively minor problem in comparison with the management of the patient as a whole. The prognosis of this fracture is bad... Clearly management of these patients and their subsequent rehabilitation are likely to present growing problems if we are to prevent our hospitals being filled with aged, immobile patients."

SECTION II <u>Background of Studies</u>

[1.6] Aims of Studies Comprising the Thesis

To enable the surgical correction of the fracture to be carried out, some form of anaesthesia is essential. In recent years, in the United Kingdom, general anaesthesia has been the usual method. However, there has been a relatively recent resurgence of interest in local anaesthetic techniques which, as will be seen, is reflected in the anaesthetic literature. For example, Scott and Thorburn (1975) considered that spinal anaesthesia was the best method for lower limb surgery in patients with impaired respiratory performance. The present thesis examines and compares the effects of subarachnoid spinal anaesthesia and conventional general anaesthesia in patients receiving surgical repair of hip fractures.

[1.7] Spinal Anaesthesia

Spinal anaesthesia consists of the injection of a small dose of local anaesthetic agent into the subarachnoid space and produces blockade of sensory, autonomic and some motor fibres below certain dermatome levels. These levels are determined by various factors including volume and speed of injection, dose, concentration, and type of local anaesthetic drug chosen, the positioning of the patient, the specific gravity of the solution, and the size and age of the patient (Mackintosh and Lee, 1973; Bryce-Smith, 1976).

The studies that are described were initiated to confirm or deny the commonly held clinical impression that spinal anaesthesia may be the method of choice for patients requiring surgical correction of fractured neck of femur. To this end, the studies compare the effects of spinal anaesthesia with conventional general anaesthesia in their effects on several physiological parameters, and on short and long term clinical outcome.

[1.8] History of Spinal Anaesthesia

Spinal anaesthesia has an unusually chequered history, and it would seem important to place the technique in its historical context.

The first recorded attempt to place a local anaesthetic agent to affect the spinal cord was by Corning (1885). In two experiments he injected cocaine between two vertebral processes. In the first experiment, 20 minims of cocaine was injected between the spinous processes of two of the lower thoracic vertebrae of a dog. The hind legs became completely insensitive to painful stimuli and there was some inco-ordination, but the front legs were unaffected. The dog returned to normal in about 4 hours. The second experiment was performed on a man and cocaine was injected between the spinous processes of the 11th and 12th thoracic vertebrae. After some 15 to 20 minutes there was complete anaesthesia of the lower limbs, the lumbar region, genitalia and urethra. There was complete recovery of sensation when the patient returned for examination the following morning. Impressive though these attempts appear, they were based on the misconception that cocaine injected between two spinous processes would enter into the circulation and be "transported by the blood to the substance of the cord and give rise to anaesthesia of the sensory and perhaps also the motor tracts of the same".

It was thus not surprising that the experiments could not be reproduced. Whether the reported success of the two experiments was due to injection of the cocaine into the subarachnoid or the extra-dural space is debatable (Mackintosh and Lee, 1973). However, Corning made a statement at the end of the report (Corning, 1885) which subsequently gave him incorrect credit for the introduction of subarachnoid anaesthesia: "Whether the method will ever find an application as a substitute for etherisation in genito-urinary or other branches of surgery, further experience alone can show."

The description of the technique of lumbar puncture by Quincke (1891) led the way to the development of a repeatable and reliable technique of subarachnoid anaesthesia by August Bier in Kiel, Germany in 1898. In 1899 he published his technique of "cocainization" of the spinal cord (Bier, 1899). His technique was to perform lumbar puncture with the patient in the lateral position using a needle with stilet and to inject cocaine into the cerebro-spinal fluid. This technique was used in six patients having various fairly major operations on the lower limbs and sacrum. Anaesthesia was adequate in all the patients but side effects were prominent. Four of the patients suffered headaches, some of which were severe. Other problems were vomiting and excitement. As Bier considered these problems to "equal those of general anaesthesia", he had a spinal anaesthetic performed on himself by his colleague, Dr. Hildebrandt. Unfortunately the syringe did not fit the needle tightly and cocaine solution and cerebro-spinal fluid were lost on the floor and the procedure was abandoned. However, a successful spinal anaesthetic was then performed by Bier on his assistant. He was able to determine that touch and temperature sensation were preserved, while perception of pain was abolished. Both men had dinner, wine and cigars following the experiments but Bier was then confined to bed for 9 days because of headache and dizziness. His colleague had severe headaches and vomiting. Bier's symptoms were probably due to loss of cerebro-spinal fluid, a problem which is still associated with lumbar puncture and spinal anaesthesia. However, considering the toxicity of cocaine, the lack of sterility and the use of tap water to dissolve the crystals, the occurrence of such morbidity is not surprising.

Tuffier (1901) improved the technique by attention to asepsis, altering the level of puncture and changing the position of the patient after injection. He used the technique for surgery of the kidney, stomach and even of the breast. 40% of the patients had headache but follow-up of 60 patients for 6 to 13 months revealed no other complications attributable to the anaesthetic.

In 1904, stovaine, a new local anaesthetic agent was introduced (Fourneau, 1904). Fourneau found it to be less toxic than cocaine and it also had the advantage of being able to be sterilised.

In Britain, A.E. Barker, Professor of Surgery at University College Hospital, London, published his experiences of 300 spinal anaesthetics using stovaine (Barker, 1907, 1908a, 1908b). In these excellent, detailed papers he described how he had demonstrated, with a "glass spine", the spread of local anaesthetic agent, and he stressed the importance of the solution being isotonic with blood and thus hypertonic and "heavy" with respect to cerebro-spinal fluid. This property enabled positioning and gravity to cause the drug to flow to act on the required nerve roots. No serious complications attributable to the technique were found and he concluded that in comparison with general anaesthesia, conditions were not worse and might be better for the surgeon (Barker, 1908b).

As early as 1907, Dean discussed the relative value of "inhalation and injection methods" of anaesthesia (Dean, 1907). He considered subarachnoid block to be better for lower abdominal and lower limb orthopaedic procedures in severely ill patients. Ryall (1911) considered that "the probation period of spinal anaesthesia is now over...For old and weak people it has an undoubted advantage over general anaesthesia, for, as a rule they bear it surprisingly well and seldom suffer from after-effects."

By 1911, large numbers of spinal anaesthetics were being administered in Germany. The German Surgical Society reported 9 deaths in 71,000 patients having procedures under spinal anaesthesia, in comparison with 21 deaths in 71,000 patients having general anaesthesia (Brownlee, 1911). However, Brownlee considered that the results of general anaesthesia could be incomparably better if administered by those of equal calibre to Bier, Tuffier and Barker.

It was many years before any further significant developments occurred, despite various fashions including the use of additives to the local anaesthetic solution such as adrenaline, strychnine, and caffeine (Labat, 1921). Labat described high blocks with "barbotage", and the Trendelenburg position for its beneficial effects on the cardiovascular system.

In 1930, a new long-acting local anaesthetic, nupercaine, was introduced and used for spinal anaesthesia by Keyes and McLellan (1930). They described a 0.5% concentration of the drug in 6% glucose, a preparation of higher specific gravity than C.S.F. and this preparation has been known since as "heavy" nupercaine. This drug was used in the present studies.

Spinal anaesthesia became extremely popular in the 1930's and 1940's, frequently being administered by the surgeon before performing the operation. However, by the late 1940's controversy about the safety of spinal anaesthesia began to surface, but this was not for the first time.

As early as the beginning of the century, worries had been expressed about the aetiology of occasionally occurring neurological sequelae (Brownlee, 1911). The debate began in earnest when Kennedy, Effron and Perry (1950) published a paper entitled "The grave spinal cord paralyses caused by spinal analgesia." They reported seven previous cases and added twelve new ones. Unfortunately the anaesthetic procedures were not fully detailed but the conclusions were forthright: "Paralysis below the waist is too great a price to pay for the surgeon to have a relaxed field of operation."

However, it was the now famous, and widely reported, "Wooley and Roe" court case which caused the greatest scare and, perhaps illogically, destroyed the confidence of many anaesthetists in the safety of spinal anaesthesia. In 1947, two patients named Wooley and Roe who were on the same operating list, became permanently paralysed below the waist after receiving spinal anaesthesia for relatively minor procedures. The judgement in the "Woolley and Roe" case which followed (Cope, 1954) was that phenol in the solution used to sterilise the outside of the ampoules of local anaesthetic, had leaked into the local anaesthetic through invisible cracks in the ampoules.

In the same year (1954) as the "Wooley and Roe" case was published in the anaesthetic literature, Dripps and Vandam (1954) published results of long term follow-up of 10,098 patients who had received spinal anaesthesia. They failed to discover any major neurological sequelae. However, this reassuring study did not dispel the rising tide of disquiet in many anaesthetists' minds and spinal anaesthesia subsequently showed a marked decline in favour, reflected in the fall in sales of suitable drugs (Lake, 1958).

It was a decade before the first signs of a re-awakening of interest in spinal anaesthesia became evident when Lee (1967) stated that "Spinal analgesia has a definite place in modern practice and should be employed rather more frequently than it is in 1967." He considered that there was no consensus of opinion as to the real cause of the neurological lesions.

A considerable boost to confidence in the safety of spinal anaesthesia was given when Noble and Murray (1971) published a review of 78,746 spinal anaesthetics given in a Canadian teaching hospital over a ten year period and found no serious permanent complications. The authors did consider that where neurological complication had followed spinal anaesthesia, they were most likely to have been due to chronic adhesive arachnoiditis (Noble and Murray, 1971). The clinical course may be delayed for weeks or months and is due to a proliferative arachnoidal reaction which may eventually produce an interference with the blood supply to the arachnoid mater and to the spinal cord and nerve roots (Greene, 1961). The reaction may be due to a toxin or irritant which could be the local anaesthetic drug itself or a contaminant. An idiosyncratic or allergic reaction in certain patients could also be a possible aetiology (Noble and Murray, 1971). The existing evidence would seem to indicate that the complication of chronic adhesive arachnoiditis is an exceedingly rare event with modern drugs and techniques.

Marinacci and Courville (1958) examined 482 patients with neurological complications alleged to be due to spinal anaesthesia and found that in all but 4 there were neurological complaints due to other, entirely unrelated conditions, commonly infectious neuronitis or peripheral neuropathy.

Perhaps as a result of the large and reassuring clinical studies, spinal anaesthesia is now enjoying a renaissance of interest. Surveys of the use of spinal anaesthesia in Scotland were carried out in 1976 and 1981 (Robertson, Lewerentz and Holmes, 1978; Robertson, 1983). These studies indicated that while 40% of consultants who replied to questionnaires used spinal anaesthesia for some purposes in 1976, 75% did so in 1981. There was a corresponding increase in frequency of use and decline in anxiety over medico-legal consequences.

A reassessment of spinal anaesthesia in comparison with modern general anaesthesia would seem timely.

[1.9] Comparison of Spinal and General Anaesthesia

As already mentioned, interest in this comparison as regards crude mortality dates back to 1911 when Brownlee (1911) reported results presented to the German Surgical Society (9 patients died out of 71,000 who had spinal anaesthesia, compared with 21 deaths out of 71,000 who received general anaesthesia).

The comparative incidence of post-operative chest complications has been a subject of interest but studies have been inconclusive. Dripps and Deming (1946) showed an 11% incidence of atelectasis and pneumonia following upper abdominal surgery under general anaesthesia but only 4.2% after surgery performed under spinal block. However, when the patients receiving general anaesthesia were subjected to vigorous and extensive chest physiotherapy, the rate of chest complications fell to that of the spinal group. Urbach, Lee, Sheely et al, (1964) in a controlled series, compared spinal and general anaesthesia for inguinal hernia repair but found no significant differences in complications between the groups.

Honkonen et al (1971) compared post-operative complications in patients with fractured neck of femur and found the post-operative incidence of pneumonia, pulmonary thromboembolism and myocardial infarction to be similar. The mortality rates were 3% after general anaesthesia and 10% after spinal anaesthesia. However, the validity of the results is questionable as patients were not randomly allocated to each group or matched, and indeed the patients selected for general anaesthesia were less ill.

McLaren, Stockwell and Reid (1978) compared spinal and general anaesthesia for repair of fractured neck of femur in a study of 53 patients and found a mortality rate of 31% by 4 weeks after surgery in those who had general anaesthesia but the spinal group had a significantly lower mortality rate at the end of 4 weeks of 3.8%. This study aroused much interest and has been widely quoted. However, although randomly allocated, patient numbers were relatively small. In comparison with the studies forming the present thesis, where patients were unselected, in the study by McLaren et al, a degree of selectivity was applied, and patients had to fulfil certain criteria before admission to the study. The general anaesthetic group received muscle relaxants and intermittent positive pressure ventilation (IPPV). The spinal group patients received a low dose unilateral block and were sedated with nitrous oxide and an althesin infusion. Spreadbury (1980) found early mortality after correction of fractured neck of femur to be much higher (30%) after anaesthesia including IPPV and muscle relaxation, than after ketamine alone (3.3%). However, long term mortality rates were similar in each group.

[1.10] Logistics of Studies

The studies comprising the present thesis were all conducted on patients admitted to the Western Infirmary, Glasgow, one of the major teaching hospitals in the Glasgow area. The Department of Orthopaedic Surgery has 40 beds for acute admissions in the Western Infirmary, and beds for elective surgery and convalescence in the associated Gartnavel General Hospital.

The number of patients admitted to the Western Infirmary with fracture of the femoral neck is approximately 400 per year. They occupy 37%, on average, of the acute orthopaedic beds and the length of stay in the Western Infirmary (acute beds) for most patients is of the order of 5 to 15 days. Patients are then transferred to convalescent beds in Gartnavel General Hospital or returned direct to the referring hospital.

All patients in the studies to be presented had surgical treatment of fractured neck of femur carried out in the Western Infirmary theatre suite on Level 5 of the "Phase I" building. This is a modern suite comprising 4 theatres, one of which is devoted entirely to emergency orthopaedic surgery. There is an adjacent recovery area of 6 beds, a transfer and reception area, and an immediately adjacent 10 bedded Intensive Therapy Unit. The blood gas and oxygen analysis facilities in the Intensive Therapy Unit were used for the majority of the studies with back-up facilities from the anaesthetic laboratories if the equipment was out of order, which occurred on a few occasions.

[1.11] **Patients studied**

Patients included in the study were those presented for surgical correction of fractured neck of femur on the Monday operating session, excluding those requiring primary hip prosthesis.

It was the policy in the Western Infirmary to operate on all patients with fractured neck of femur on the first day after admission (excluding Sundays) unless they would not obviously benefit from the procedure. All patients received an intravenous infusion of crystalloid fluid for at least 12 hours before operation in order to prevent the dehydration and hypovolaemia which commonly occur in this group of elderly patients who generally have an inadequate oral fluid intake. Blood loss and oedema at the fracture site are other important contributary factors producing hypovolaemia which may lead to dangerous falls in arterial pressure under anaesthesia, especially under spinal block (Atkinson, Rushman and Lee, 1977). Only two patients were considered unsuitable for inclusion in the present studies. One had a haemoglobin concentration of 5.2 g $dlitre^{-1}$ and the other had a serum potassium concentration of 2.1 mmol $litre^{-1}$. A further two patients had to be excluded later for technical reasons (see below). Patients received no premedicant drugs, but some had analgesia administered during the night prior to surgery. Many of the patients suffered from a variety of medical problems common to their age group which will be detailed in later chapters.

[1.12] Pre-operative Assessment

Details of past medical history, drug and fluid therapy, and main physical findings were recorded. As the scope of the studies was extended and as follow-up was lengthened, it became apparent that some form of comparative assessment of pre-operative condition was desirable. A scoring system seemed appropriate and would be, of necessity, retrospective. The author recognises the limitations and possible inaccuracies of such a system but feels that it is justifiable and may be helpful.

The fitness classification of the American Society of Anesthesiologists (1963) was considered. This allocates one of five scores on the following basis:

"1" A normal healthy patient

"2" A patient with mild systemic disease

"3" A patient with a severe systemic disease that limits activity, but is not incapacitating

"4" A patient with an incapacitating systemic disease that is a constant threat to life

"5" A moribund patient not expected to survive 24 hours with or without an operation

The above classification, while familiar to most anaesthetists, is not completely satisfactory for the purposes of the present studies, mainly because very few patients would have fallen into categories "1" or "5". The author thus decided to define a simple system of fitness classification which could be used not only to compare overall fitness, but to indicate roughly the presence and degree of dysfunction of cardiovascular, respiratory and central nervous systems. The scoring system devised was on a scale of 1 to 3 defined as:

"1" Normal or minor disease or dysfunction

"2" Significant disease or dysfunction of moderate severity

"3" Severe or multiple disorders or disease processes

Before being seen by the anaesthetist, patients were randomly allocated to receive spinal or general anaesthesia. After induction of anaesthesia they were transferred to the operating table in theatre.

[1.13] Surgical Techniques

Surgery consisted of reduction and internal fixation of the fracture by nail or nail and plate techniques. X-ray image intensifier equipment was used to assist in performance of the surgical procedure. The orthopaedic surgeons were usually of senior registrar status, with the same surgeon on each Monday over a 3 month period. After the operation was completed the patients were transferred to the adjacent recovery area where they remained for 1 to 5 hours before transfer back to the original ward.

[1.14] Anaesthetic Techniques

Both techniques chosen had been in routine use in the Western Infirmary for this category of patient and were considered to be as simple, safe and reliable as possible.

a) General Anaesthesia.

General anaesthesia was induced with althesin (Glaxo) 1.0-3.0 ml i.v. Following the administration of suxamethonium 50 mg the trachea was intubated with a cuffed tube. Anaesthesia was maintained with 66% nitrous oxide and 0.75-1.25% halothane in oxygen. The patients breathed spontaneously via a semi-closed breathing system with carbon dioxide absorption, with a fresh gas flow of 3 litre min^{-1}. At the end of anaesthesia endo-tracheal toilet was performed before deflation of the cuff and removal of the endo-tracheal tube. At the time of the study, oxygen was not routinely administered to this type of patient in the post-operative period.

b) Spinal Anaesthesia.

1.2-1.5 ml of hyperbaric cinchocaine ("heavy nupercaine") was injected slowly (without barbotage) into the subarachnoid space at the 3rd or 4th lumbar interspace via a 22 gauge "spinal" needle. The block was performed with the patient in the horizontal and lateral position with the fractured hip dependent. Discomfort caused by turning to this position was transient and minimized by gentle handling. Two minutes after injection the patient was turned to the supine position and remained horizontal. Small doses of intravenous diazepam were given if sedation was thought necessary. The blocks achieved were bilateral so as to abolish the discomfort of lying on the orthopaedic table, but levels of block were not assessed in order to minimise disturbance of the patients. Arterial pressure was measured by oscillotonometer. The electrocardiogram and peripheral pulse (by digital plethysmography) were monitored. Axillary temperature was measured at times of blood sampling. In two patients it proved impossible to perform lumbar puncture and those patients were excluded from the study and given general anaesthesia.

[1.15] Evolution of Studies

The initial study plan was a comparison of the effects of anaesthetic technique on blood gas results in the immediate peri-operative period. The changes in arterial oxygenation in the first hour after general anaesthesia were then examined in detail in a small number of patients.

When early post-operative mortality results were examined and a trend was found towards a difference between the groups, it was decided that larger numbers of patients were needed. The scope of the studies was also extended. An investigation of comparative incidence of deep venous thrombosis was initiated in an attempt to explain whether the differences in early post-operative mortality might be linked with a difference in incidence of thromboembolism.

A study of blood viscosity changes was also initiated. By chance, the wife of a junior anaesthetic colleague was working in the field of blood rheology in another hospital, Glasgow Royal Infirmary. Since there was no previous work comparing spinal and general anaesthesia and effects on viscosity, this part of the study was embarked upon out of curiosity and with no working hypothesis at that time.

After results of early post-operative mortality for all patients studied had been analysed, a difference in mortality between the groups was confirmed. It was felt wise, before drawing far reaching conclusions about the relative safety of the anaesthetic techniques, to examine the outcome in the patients already studied over a much longer period, and a retrospective follow-up of the outcome over the first year after operation was initiated.

CHAPTER 2

BLOOD GAS STUDIES

SECTION I

Comparison of Arterial Blood Gas Data in the Peri-operative Period in Patients Receiving Spinal or General Anaesthesia

[2.1] Introduction

Arterial oxygen tension tends to decrease with advancing age (Raine and Bishop, 1963; Conway, Payne and Tomlin, 1965; Marshall and Millar, 1965; Davis and Spence, 1972; Gillies, Petrie, Morgan et al, 1977). It has also been suggested that patients with fractured neck of femur have arterial pO_2 values even lower than would be predicted on the basis of age alone (Phillips and Tomlin, 1977; Martin 1977).

In patients having surgical correction of fractured neck of femur under general anaesthesia, Wishart, Williams and Smith (1977) found that there was a small but significant deterioration in arterial oxygenation by one hour after surgery compared with pre-operative values. This occurred whether the patient was artificially ventilated or was allowed to breathe spontaneously through either a "circle" or an "open" breathing system. While studies in a variety of patients have suggested that deterioration in arterial blood gas values does not occur after spinal anaesthesia (de Jong, 1965; Catenacci and Sampathachar, 1969; Paskin, Rodman and Smith, 1969), the effect of spinal anaesthesia on blood gas data in patients with fractured neck of femur does not seem to have been previously described. The present study was performed to compare the effects of spinal and general anaesthesia on pulmonary function as assessed by arterial blood gas data, before, during and after surgery.

[2.2] Patients and Methods

100 unselected patients presenting for internal fixation of fractured neck of femur were randomly allocated to receive spinal anaesthesia by subarachnoid block (SAB Group) or general anaesthesia (GA Group) using the previously described methods (chapter 1.14).

Details were noted of previous medical history and of current drug therapy. The scoring system described in chapter 1 was used, subsequently allocating scores of 1 to 3 on the basis of the patient's overall physical state, and that of the cardio-vascular (CVS), central nervous (CNS), and respiratory (RS) systems. Detailed description of the type of medical problems encountered and pre-admission drug therapy is given in chapter 5.

In the theatre reception area the patient's axillary temperature was measured with a clinical mercury thermometer and 2 ml of arterial blood was withdrawn anaerobically into a heparinised plastic syringe from the radial artery. The samples were withdrawn with the patient in the supine position before transfer from bed to the theatre trolley. Venous samples for haemoglobin (Hb) estimation were also taken in the first 50 patients. Nine patients in the SAB group received small doses of diazepam i.v. and one patient required metoclopramide for nausea.

Arterial and venous (50 patients only) samples were again withdrawn 1 hour after induction of anaesthesia and at 1 hour after the end of the surgical procedure. When oxygen therapy had been given in the immediate post-operative period, this was discontinued (if considered safe to do so) and the patient breathed room air for at least 20 minutes prior to the post-operative arterial blood sample being taken. 2 patients (both in the GA group) were considered too unwell to permit the discontinuation of oxygen therapy. The arterial samples were analysed immediately after withdrawal for pO_2, pCO_2, pH and base excess using a Radiometer ABL1 automated blood-gas analyser. Corrections were later applied for the differences between electrode temperature and that of the patient, using a standard temperature correction programme on a Hewlett Packard programmable calculator.

[2.3] Accuracy of Analysis

The ABL1 automated blood gas analyser has been shown by Selman and Tait (1976) to have an accuracy comparable with standard blood gas analysis equipment with standard deviations of: pH electrode +/- 0.002 units, pO_2 electrode (for tonometered blood) +/- 0.133 kPa, pCO_2 electrode +/- 0.175 kPa. The machine used for the present studies was situated in the Intensive Therapy Unit adjacent to the theatre suite and was subject to a careful daily maintenance and calibration regime by technicians from the anaesthetic department.

[2.4] Results

The distribution of fitness scores is displayed in table 1. There were no statistically significant differences between the groups in the number of patients allocated to each score (by chi-square test). Where the number of patients scoring "3" was so small as to render the chi-square test invalid, these patients were excluded from the test. Sex distribution was not significantly different between the groups (chi-square test). In the GA group there were 40 females and 11 males, and the SAB group consisted of 35 females and 14 males. General details of the patients studied are given in table 2. There were no significant differences between the groups (by unpaired student's t test) in respect of mean age, temperature, duration of surgery, blood loss, volume of fluid infused or the interval between admission to hospital and time of surgery. The mean delay of around 2 days between admission and surgery occurred because the majority of patients in this study were operated upon on Monday mornings and no surgery on fractured necks of femur was performed at weekends after Saturday lunch-time (with the exception of primary hip prosthesis). Table 3 displays pre-operative and minimum intra-operative values of systolic arterial pressure in each group. Mean systolic pressure fell significantly from pre-operative values in both groups ($p<0.001$). The decrease was significantly greater ($p<0.05$) in the SAB group (mean decrease 64 mm Hg) compared with the GA group (45 mm Hg), as might be expected as a result of the sympathetic blockade produced by spinal anaesthesia.

Fitness Scores (see Chapter 1)	"1"		"2"		"3"	
	GA	SAB	GA	SAB	GA	SAB
"Overall" scores	21	22	24	17	6	8
CVS scores	35	25	14	19	2	3
CNS scores	26	26	23	19	2	2
RS scores	41	35	6	8	4	4

NUMBER OF PATIENTS ALLOCATED TO EACH SCORE IN EACH PRE-OPERATIVE "FITNESS" CATEGORY (Blood gas study)

TABLE 1

	GA Group	(Range)	SAB Group	(Range)
Age (y)	74.5 +/- 2.3	(21-96)	76.8 +/- 1.4	(57-93)
Temperature (^{o}C) before operation	36.7 +/- 0.1	(35-38.4)	36.7 +/- 0.1	(35.8-38.5)
Temperature (^{o}C) after operation	36.0 +/- 0.1	(33.3-37.4)	36.1 +/- 0.1	(35.0-37.6)
Duration of surgery (min)	76.5 +/- 4.0	(45-220)	77.8 +/- 3.2	(40-135)
Estimated blood loss (ml)	264 +/- 46	(55-2250)	261 +/- 47	(50-2100)
Crystalloid infused during surgery (ml)	928 +/- 61	(100-1500)	1018 +/- 56	(400-2000)
Hb Before operation (g $dlitre^{-1}$)	11.6 +/- 0.33	(7.5-14.4)	11.9 +/- 0.41	(8.7-15.8)
Admission to surgery interval (days)	1.9 +/- 0.3	(< 1-14)	2.1 +/- 0.4	(< 1-19)

GENERAL FEATURES (Blood gas study) (mean +/- SEM)

TABLE 2

	GA Group	SAB Group
Before operation	147 +/- 6	146 +/- 6
Minimum systolic pressure during operation	102 +/- 5	82 +/- 4

SYSTOLIC ARTERIAL PRESSURES (mm Hg) (mean +/- SEM)

TABLE 3

All patients received an intra-operative fluid infusion. Two patients in the GA group received blood transfusions during operation. Intra-operative infusion of plasma protein solution or plasma expander was given to 6 patients in the GA group and 8 in the SAB group. Haemoglobin (Hb) concentration was measured in the first 50 patients only. Mean post-operative Hb concentration fell significantly from pre-operative values in both groups ($p<0.001$). The extent of the fall was not significantly different being 1.2 g $dlitre^{-1}$ in the GA group and 1.8 g $dlitre^{-1}$ in the SAB group.

Mean arterial blood gas values in each group are displayed in table 4, and the changes from pre-operative to post-operative values in table 5. Pre-operative arterial pO_2 values were low in both groups (overall mean 9.04 kPa). By one hour after surgery, the mean PaO_2 in the GA group had decreased significantly by 0.68 kPa from the pre-operative value. There was, however, no change in mean PaO_2 in the SAB group either during or after surgery. All blood gas measurements in SAB group were made with the patient breathing room air. PaO_2 values in the GA group during operation are not quoted as these patients received an FIO_2 of 0.33.

Regression analysis of the blood-gas data (figures 1-4), failed to reveal a correlation between age and PaO_2, either in the pre-operative or post-operative samples. Pre-operative $PaCO_2$ values were low in both groups (mean 4.35 kPa), but intra-operative $PaCO_2$ was significantly higher in the GA group than in the SAB group. Intra-operative $PaCO_2$ values were, however, not significantly different from pre-operative values in either group (table 4).

		GA Group	SAB Group
PaO_2	Pre-op	9.14 +/- 0.16	8.94 +/- 0.10
	60 min intra-op	-	8.91 +/- 0.24
	60 min post-op	8.53 +/- 0.19 *	9.19 +/- 9.25 *
$PaCO_2$	Pre-op	4.34 +/- 0.08	4.36 +/- 0.10
	60 min intra-op	5.16 +/- 0.15 **	4.36 +/- 0.09 **
	60 min post-op	4.39 +/- 0.09	4.38 +/- 0.09
pH (units)	Pre-op	7.462 +/- 0.005	7.46 +/- 0.008
	60 min intra-op	7.367 +/- 0.01	7.438 +/- 0.007
	60 min post-op	7.425 +/- 0.005	7.439 +/- 0.006
Base excess (mmol $litre^{-1}$)	Pre-op	-0.03 +/- 0.32	-0.18 +/- 0.46
	60 min intra-op	-3.1 +/- 0.36 ***	-1.65 +/- 0.39 ***
	60 min post-op	-2.44 +/- 0.31	-1.62 +/- 0.4

ARTERIAL BLOOD-GAS MEASUREMENTS (FIO_2 = 0.209) BEFORE INDUCTION, 60 MIN AFTER INDUCTION, 60 MIN AFTER END OF ANAESTHESIA

(mean values +/- SEM)

Intra-op PaO_2 values in GA group (see text).

Significant differences between starred groups by unpaired t test

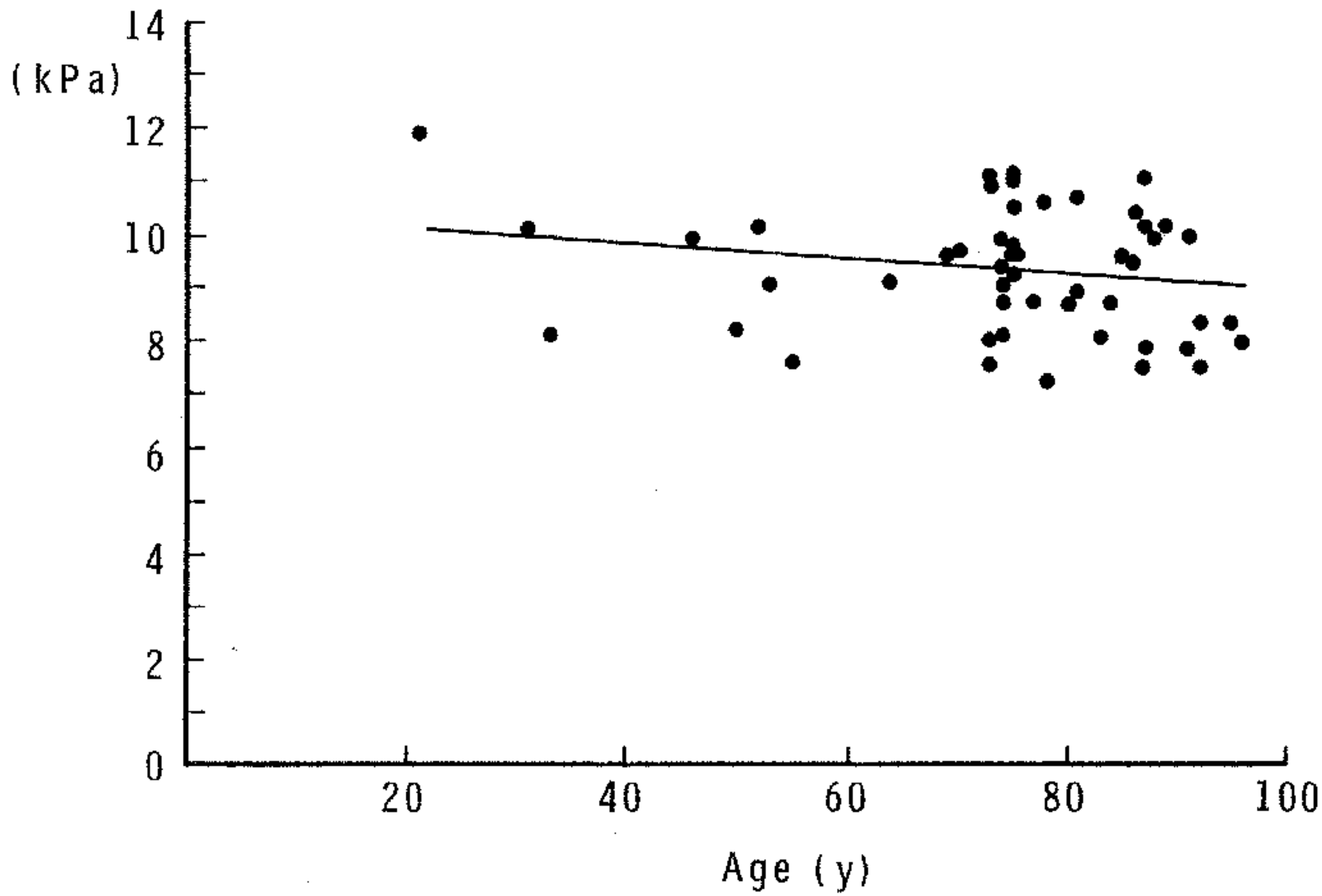
* $p < 0.05$; ** $p < 0.001$; *** $p < 0.01$

TABLE 4

	GA Group	SAB Group
PaO_2 (kPa)	+ 0.675 +/- 0.6*	-0.124 +/- 0.17
$PaCO_2$ (kPa)	- 0.031 +/- 0.05	-0.019 +/- 0.07
pH (units)	+ 0.037 +/- 0.005*	+0.029 +/- 0.005*
Base excess (mmol $litre^{-1}$)	+ 2.274 +/- 0.24*	+1.548 +/- 0.24*
Axillary temperature (^{o}C)	+ 0.606 +/- 0.156*	+0.635 +/- 0.12*

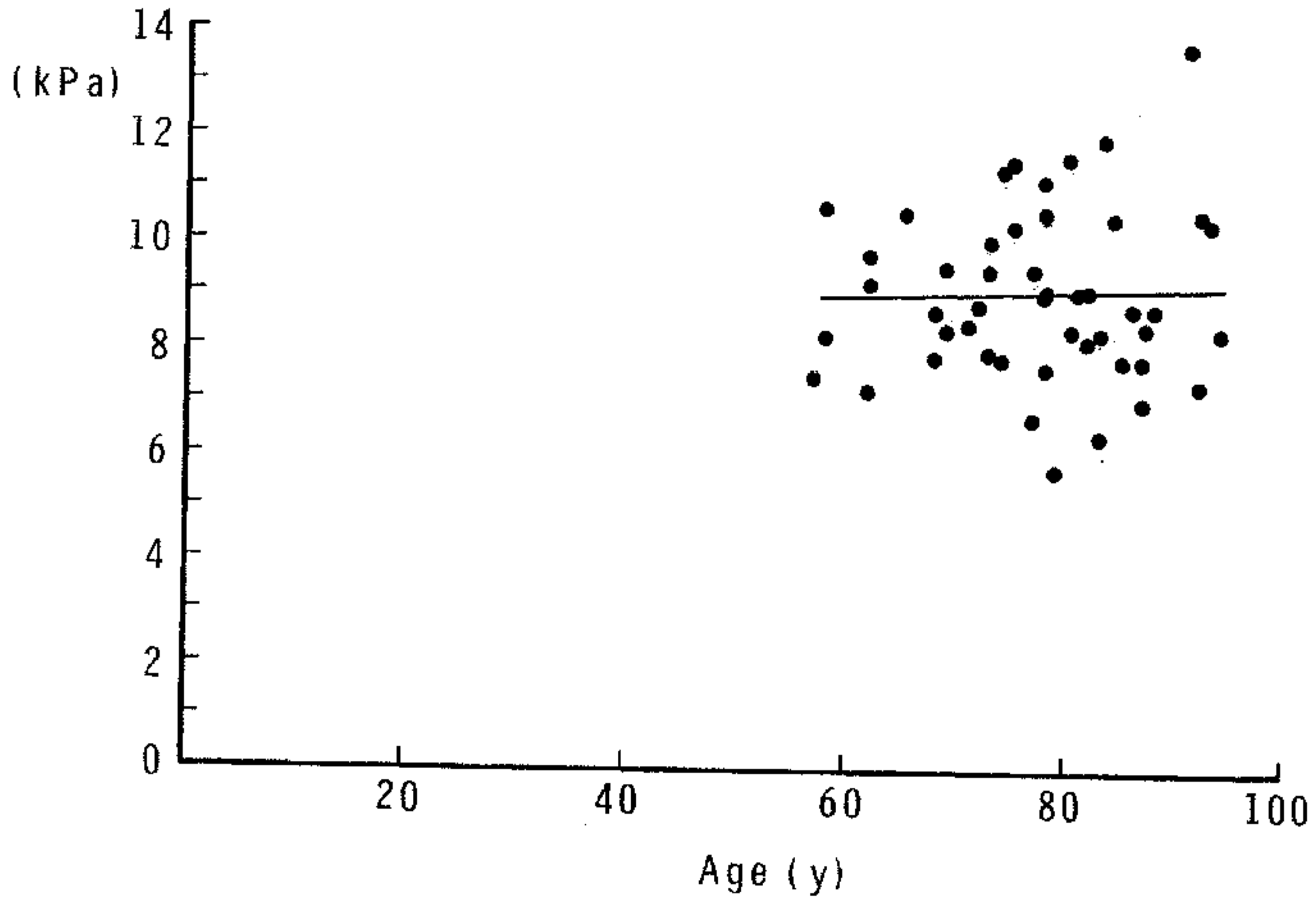
CHANGES (mean +/- SEM) IN BLOOD-GAS MEASUREMENTS (value before operation minus value after operation) IN EACH GROUP * $P < 0.001$ (paired Student's t test)

TABLE 5



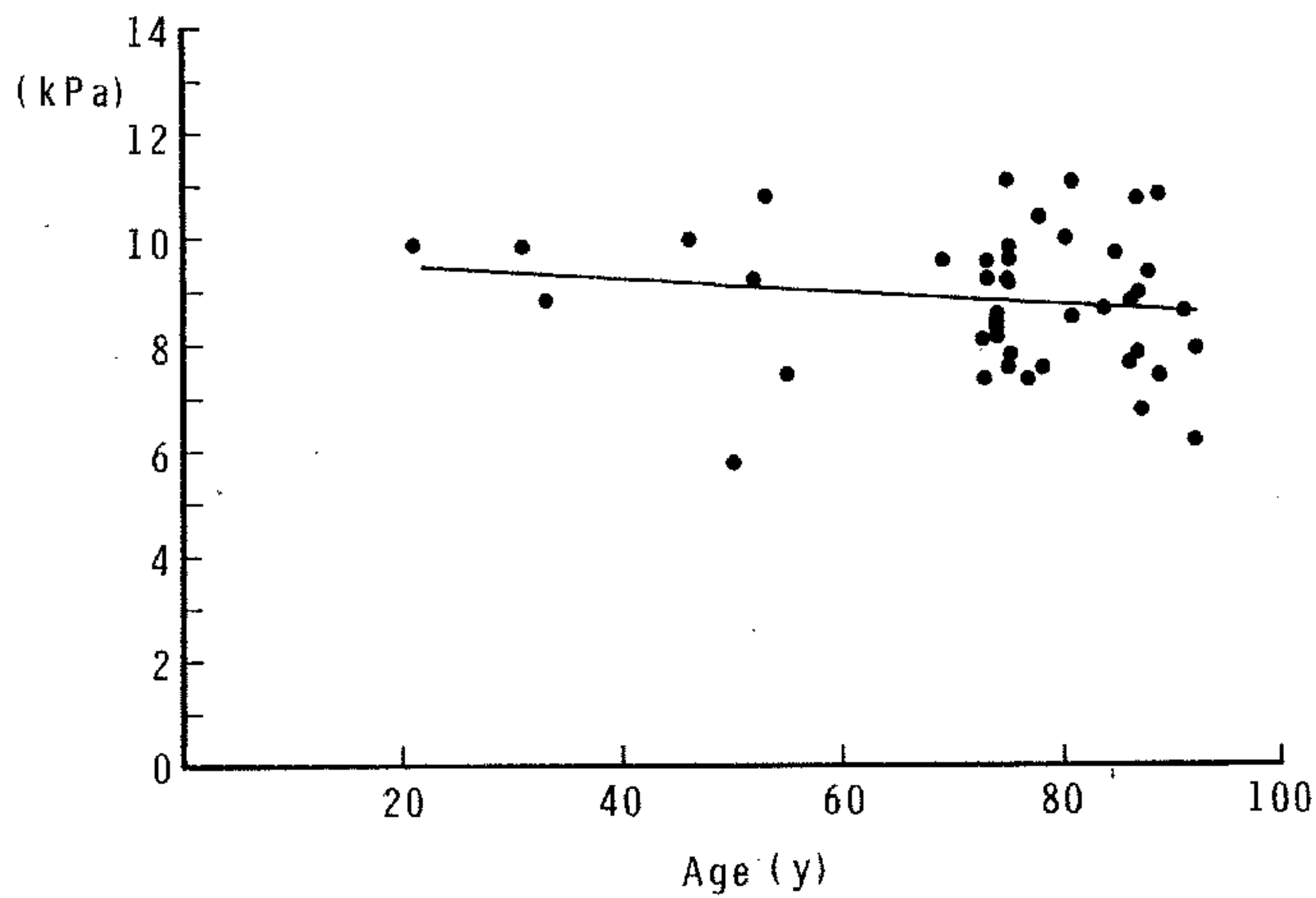
Pre-operative pO_2 plotted against age (GA group)

FIGURE 1



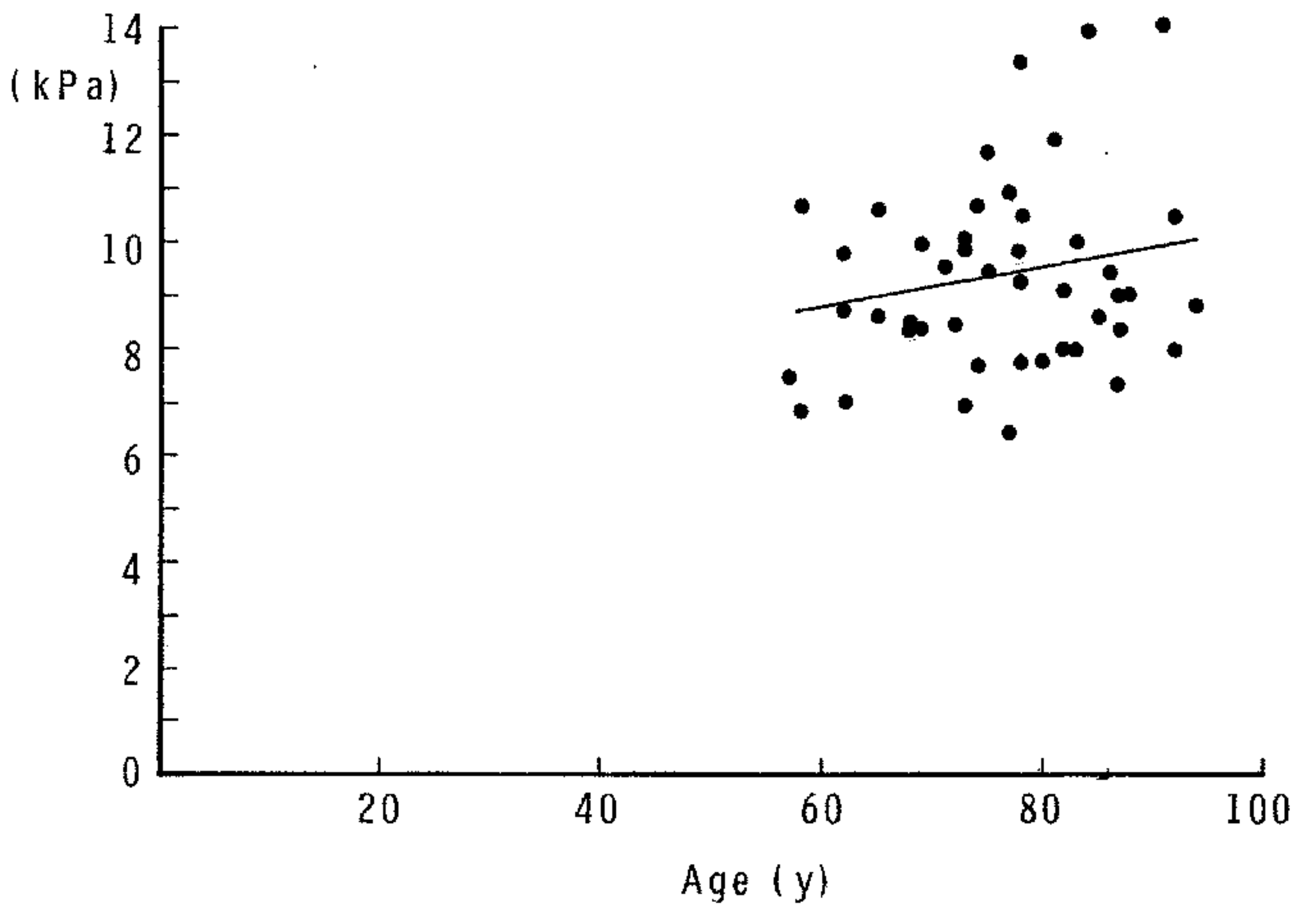
Pre-operative pO_2 plotted against age (SAB group)

FIGURE 2



Post-operative pO_2 plotted against age (GA group)

FIGURE 3



Post-operative pO_2 plotted against age (SAB group)

FIGURE 4

The intra-operative decrease in pH and increase in base deficit in both groups, whilst statistically significant were not clinically noteworthy. Both groups showed a significant fall in temperature by 1 hour after operation. The axillary temperature in one patient in the GA group fell to 33.3°C.

[2.5] Discussion

The patients having repair of fractured neck of femur under spinal anaesthesia showed no significant changes in mean pO_2 or pCO_2 during or after operation. The patients in the GA group, in contrast to the SAB group, showed a small but significant decrease in mean PaO_2 from pre-operative values of 0.68 kPa by one hour after surgery.

De Jong, (1965), found that in 14 patients undergoing various major surgical procedures under spinal or epidural block, intra-operative arterial blood gas data showed no significant change from pre-operative values. The levels of block achieved varied from T10 to C5 and all patients received some form of sedation. Only 6 of the patients were fit, normal patients. 11 of the patients breathed added oxygen at some point during the surgical procedure. Because of these variables it is difficult to draw conclusions from that study. Catenacci and Sampathachar (1969) showed an increase in PaO_2 in obese patients after induction of high spinal anaesthetic block to a level of T4 to T8. There was no significant change in arterial pO_2 in non-obese patients after a similar level of block was induced. No significant changes in blood gases occur after spinal anaesthesia in patients with chronic obstructive airways disease (Paskin et al, 1969). Little change was found in total ventilation under high spinal block by Askrog, Smith and Eckenhoff (1964) but there was some increase in physiological dead space.

Wishart et al (1977) found a similar decrease in arterial oxygenation to that seen in the present study in patients having repair of fractured neck of femur using 3 different techniques of general anaesthesia, (halothane and oxygen via closed circuit; halothane, nitrous oxide and oxygen via a Magill system; and artificial ventilation with 66% nitrous oxide in oxygen with pancuronium providing neuromuscular blockade).

Patients in the present study had an overall mean PaO_2 before induction of anaesthesia of 9.04 kPa. The question arises as to whether this value is lower than one might expect in a general population of similar age group. The values in the present study are in agreement with those in comparable patients in other recent series, (Wishart et al, 1977; Phillips and Tomlin, 1977; McLaren, Stockwell and Reid, 1978). Martin, 1977, found a lower pre-operative mean PaO_2 (8.56 kPa) in a similar group of patients to those in the present study. If it were permissible to extrapolate published regression lines for age against PaO_2 (Raine and Bishop, 1963; Gillies et al, 1977) into the age range of the present study, then the pre-operative PaO_2 values would seem smaller than expected. However, the majority of data from which these regression lines were derived were from patients under 60 years of age and extrapolation of regression lines is statistically unacceptable.

Clinically unsuspected hypoxaemia often occurs soon after fractures, especially those of long bones (Tachakra and Sevitt, 1975), but that study found a relatively low incidence of hypoxaemia after hip fracture (14 out of 31 patients). The rapid development of hypoxaemia would be consistent with the "fat embolus" syndrome. The hypoxia has previously been considered to be due to fat globules from either the traumatised area or plasma fat lodging in the pulmonary capillaries (Saldeen, 1970a). However, Saldeen (1970a), in autopsy material, found fibrin in pulmonary vessels more often in "fat embolism" than other traumatic cases and concluded that intravascular coagulation in the lung could occur in "fat embolism". In rats (Saldeen, 1970b) experimentally induced fat embolism produced a similar histological picture in the lungs to that occurring after injection of thromboplastin. Heparin and fibrinolysin counteracted the effects of injected fat. Modig, Busch, Olerud et al (1975) found that the reductions of arterial blood pressure and pO_2 in patients undergoing total hip replacement were not related to fat droplets in the lungs or acrylic monomer from the cement used in fixation of the prosthesis, but closely correlated with tissue thromboplastin products reaching the pulmonary circulation. Thromboplastins are also released during fractures of the lower limb or when a fracture is moved (Modig, 1977). Thromboplastin gives rise to thrombin with generation of microemboli which are trapped in the pulmonary microcirculation. This leads to disturbances of ventilation-perfusion ratios and hence a decrease in PaO_2. At their most severe these events lead to the development of clinical "fat embolism" with shock lung and other organ dysfunction, via complex mechanisms which need not be discussed here.

Another possible explanation for the pre-operative hypoxia could be the supine position or prolonged recumbency. Ward, Tolas, Benveniste et al (1966) examined the PaO_2 of 100 elderly patients. 50 patients (mean age 72 years) in the sitting position had a mean of PaO_2 of 11.2 kPa, while the other group of 50 patients (mean age 73 years) in the supine position had a mean PaO_2 of 10.24 kPa. Prolonged recumbency of 10 days has been shown to increase the mean alveolar-arterial O_2 partial pressure difference from 1.2 kPa to 2.5 kPa in young healthy men (Cardus, 1967).

In view of the deterioration of PaO_2 post-operatively in the GA group, it was decided to study in detail, changes in arterial blood gases during the first hour after anaesthesia.

SECTION II

Analysis of Arterial Blood Gas Data after General Anaesthesia with Particular Reference to the First Hour After the End of Anaesthesia

[2.6] Introduction

As described previously, patients undergoing repair of fractured neck of femur under general anaesthesia show a significant reduction in arterial oxygen tension by 1 hour after the end of anaesthesia. As this occurs in patients who are already tending to be hypoxaemic before induction of anaesthesia, it was decided to examine in detail the changes in arterial blood gas data in the first hour after anaesthesia had been discontinued.

[2.7] Patients and Methods

20 patients were studied who had been randomly allocated to receive general anaesthesia. However, because of calibration problems with the oxygen electrode (detailed later) the results from the first 10 patients could not be taken as valid, and were abandoned. The patients were not consecutive as the nature of the study did not allow time for more than one patient to be studied per operating session. The pre-operative preparation and method of general anaesthesia were as described previously.

An arterial sample was withdrawn from the radial artery by direct puncture with a 23 gauge needle into a heparinised plastic syringe from the supine patient in bed in the theatre reception area. After induction of general anaesthesia a radial artery was cannulated with a 20 gauge "teflon" cannula to facilitate frequent arterial blood sampling. An arterial sample was withdrawn intra-operatively at 1 hour after induction of anaesthesia. Towards the end of the operative procedure the inspired oxygen percentage of 33% was checked by sampling from the inspiratory limb of the circle system and analysing oxygen concentration on a Servomex oxygen analyser. On each occasion the concentration proved correct within 0.5%. After the end of the surgical procedure the patient was transferred to the recovery area while remaining connected to the anaesthetic machine with the concentrations of anaesthetic agents unchanged. Blood gas samples were then taken in the recovery area while simulating conditions which could be expected to be encountered at the end of anaesthesia and during the usual period of transfer to the recovery area.

As soon as possible in the recovery area, the endotracheal tube was disconnected from the anaesthetic system and the patient then allowed to breathe room air. Arterial blood samples were taken from the intra-arterial catheter at the time of disconnection of anaesthetic gases. Further samples were taken at the following times after disconnection; 1, 2, 3, 4, 6, 8, 10, 20, 30, 40, 50, and 60 minutes. Samples were stored in ice until analysis was performed as soon as possible on the Radiometer ABL1 automated blood gas analyser. This had been fitted with an oxygen electrode specially supplied by Radiometer Ltd which did not exhibit calibration drift with exposure to halothane-containing blood samples. Calibration was checked before and after each set of samples. All results were later corrected for the difference between the patient's axillary temperature and the electrode temperature using a standard correction programme for blood gases on a programmable calculator. When airway reflexes returned the tracheal tube was removed.

[2.8] Investigation of Calibration Error

During studies in the first 10 patients, it was noticed that an unacceptable degree of calibration drift was occurring but only with certain samples. The problem could not be demonstrated when blood samples from volunteers were used even when the conditions of rapid multiple analyses were duplicated. It was fortuitous that after 9 fruitless investigations of the problem, the tenth sample came from a dog anaesthetised with halothane. On that occasion the calibration drift was clearly seen and further investigation instigated.

16 ml of venous blood was taken from a normal volunteer and 8 ml of the sample tonometered with 12% oxygen and 5.6% carbon dioxide in nitrogen and the other 8 ml tonometered with the same gas mixture with the addition of 1% halothane. Samples from the first 8 ml of tonometered blood were analysed sequentially in the ABL1 blood gas analyser which was calibrated before and after the measurements were made. This procedure was repeated with the second 8 ml tonometered aliquot.

Results showed (table 6) that in the absence of halothane there was little variation in measured pO_2 (coefficient of variation 1.13%). However, in the samples tonometered with halothane there was a progressive increase in measured pO_2 from 10.95 kPa to 14.72 kPa at the second measurement on the 6th sample.

Time (min)	Sample	Tonometry without halothane pO_2 (k Pa)	Tonometry with halothane pO_2 (k Pa)
0	Calibration	17.813	17.613
3	1	11.507	10.947
6	2	11.587	11.107
9	3	11.707	11.147
12	4	11.427	11.387
15	5	11.347	11.947
18	6	11.427	12.80
21	6 (repeat)	-	14.72
24	Calibration	17.613	23.467
+ 2 hours	Calibration	17.610	20.000

pO_2 MEASUREMENTS OBTAINED WITH THE ABL 1 BLOOD GAS ANALYSER WITH 2 ALIQUOTS OF BLOOD TONOMETERED WITH AND WITHOUT 1% HALOTHANE

TABLE 6

Subsequent calibration revealed persistent over-reading of 2.39 kPa. Only the pO_2 electrode revealed this instability with halothane. Exposure of the pO_2 electrode to blood containing 1% halothane resulted in a gradual upward drift in calibration such that one hour later, it over-read by 10% and this effect persisted for the subsequent 6 hours. This problem was reported in 1971 (Severinghaus, Weiskopf, Nishimura et al, 1971) but seems not to be widely known as an important source of error. The effect is variable between electrodes and as calibration errors were not noticed until the frequent PaO_2 analyses were performed starting with the 93rd patient, it is probable that the errors on previous electrodes were insignificant. However, the effect of any error of this type would be to cause the post-operative pO_2 values in the GA group to be overestimated by about 10%. The majority (80%) of arterial samples from patients receiving general anaesthesia were not preceded by samples containing halothane. In the case of samples from patients who were subsequent on the list to patients who had halothane, the time which elapsed from the first halothane sample (intra-operative) until the pre-operative sample from the patient about to receive spinal anaesthesia was of the order of 5-20 minutes. Thus, the effect on subsequent samples from the SAB group would have been variable, increasing for the intra-operative and post-operative samples.

It was realised that the calibration error might have affected some of the results presented in the first part of this chapter but when the results were examined from the 10 patients from the SAB group in whom these errors might have occurred, a mean decrease was found in PaO_2 at 1 hour after surgery of 0.086 kPa from the pre-operative value. This compares with a mean increase over the same period of 0.124 kPa when all patients in the SAB group are considered. This suggests that any errors occurring in the main part of the study were insignificant and it is likely that a different electrode, less affected by halothane was in use for most of the main study. Indeed if the results from the 10 patients possibly affected were removed from the study, the overall effect would be to increase the mean post-operative PaO_2 rather than decrease it. The results from these patients have therefore been retained.

Following publication of the findings with the ABL1 pO_2 electrode (Douglas, McKenzie, Ledingham et al, 1979) a replacement electrode was received from Radiometer Ltd. which was unaffected by halothane. This electrode was used for the present part of the study.

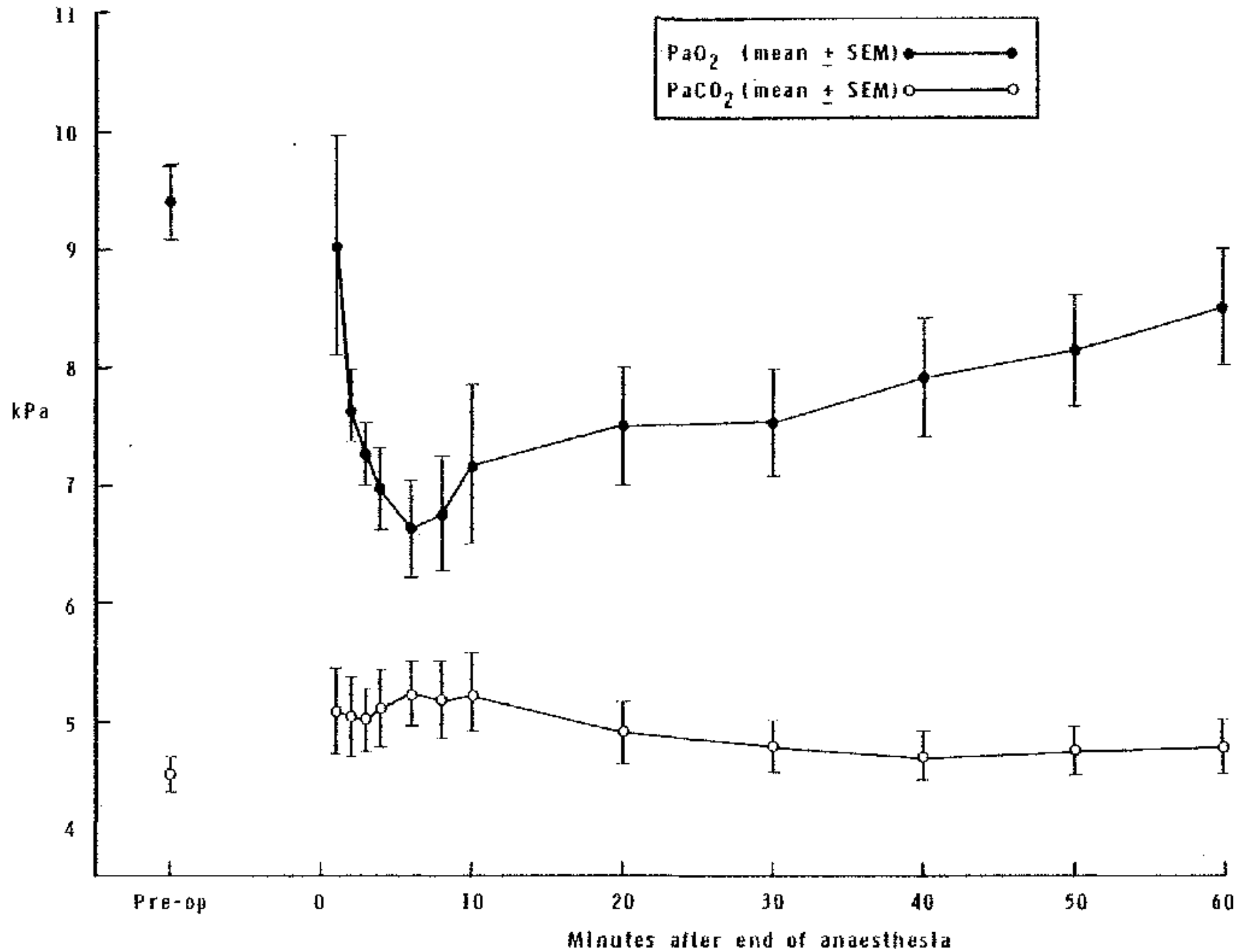
[2.9] Results

Figure 5 shows the means (+/- S.E.M.) of arterial pO_2 and pCO_2 pre-operatively and at intervals up to one hour post-operatively. There was a dramatic and highly significant fall ($p<0.001$ by paired student's t test) in mean PaO_2 reaching the lowest mean of 6.65 kPa six minutes after the end of anaesthesia. The mean PaO_2 thereafter gradually increased to 8.5 kPa at the end of one hour. Mean $PaCO_2$ showed a small increase from pre-operative values which was greater in the first 10 minutes and reduced over the next 20 minutes to a stable value of around 4.8 kPa. This is consistent with the known respiratory depressant characteristics of halothane anaesthesia (Deutsch, Linde, Dripps et al, 1962). At no point were $PaCO_2$ values above accepted normal values. The pre-operative $PaCO_2$ values were low, as seen in the previous study.

The mean PaO_2 value at some of the sampling times are displayed with the scatter of data in figure 6. This reveals that some patients had extremely low arterial pO_2 values with several patients achieving repeated values of less than 6.5 kPa. In order to display changes in individual patients, the raw data are presented in table 7.

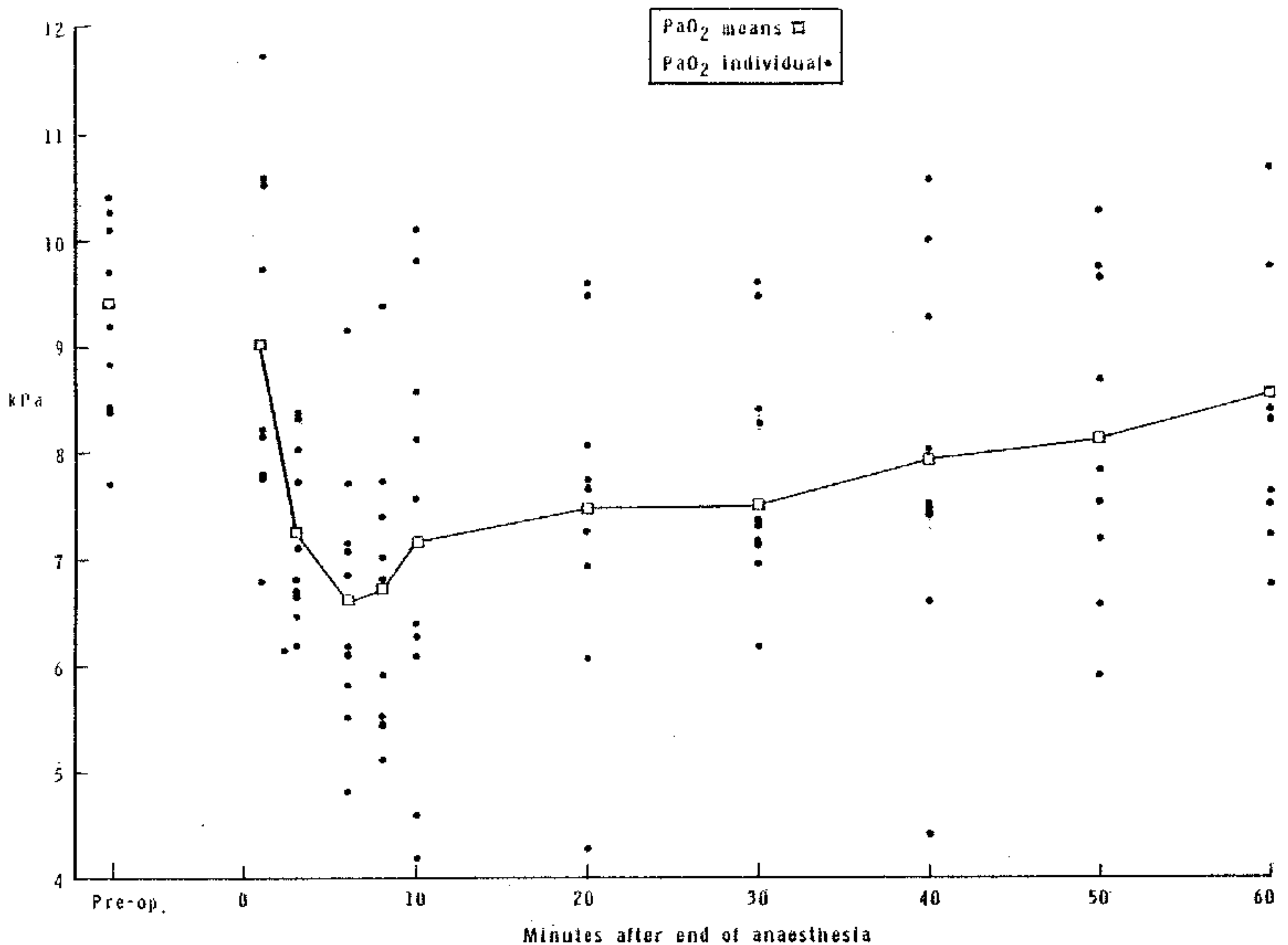
[2.10] Discussion

The profound hypoxaemia seen in the early post-operative period in several of the patients studied, is of obvious clinical significance, as considerable arterial oxygen desaturation would be likely to occur at the values found. The effect was sufficiently prolonged in some patients to be alarming in retrospect. However, there was no clinical suspicion that severe hypoxaemia was occurring despite patients being observed closely and almost continuously over the period of the study, both by the author and recovery nursing staff. The results were not corrected for temperature and closely examined, until all the ten patients whose results are presented had been studied. When the pattern of hypoxaemia was then seen it was not felt justified to continue to study any more patients in this manner, as a raised inspired oxygen concentration was obviously necessary in at least 50% of patients, despite the normal practice at that time of allowing patients to breathe room air post-operatively.



Mean PaO_2 and $PaCO_2$ over first hour after general anaesthesia

FIGURE 5



Scatter of PaO_2 over first hour after general anaesthesia

FIGURE 6

Individual Patients	Pre-op	Intra-op	0	1	2	3	4	6	8	10	20	30	40	50	60
A	10.4	9.2	10.5	8.2	7.1	6.7	6.7	6.2	6.8	9.8	8.1	8.3	7.9	8.1	8.3
B	8.5	/	8.9	7.7	6.5	6.4	6.2	4.8	5.9	6.3	7.0	7.3	7.5	7.8	7.6
C	10.3	15.4	13.4	8.9	7.2	6.7	/	7.0	7.7	8.1	7.7	8.4	10.0	10.2	10.4
D	9.7	14.7	13.9	9.7	8.5	8.0	7.7	6.8	/	6.3	7.3	7.3	7.4	7.5	7.6
E	10.1	15.6	14.2	11.7	8.5	7.1	6.3	6.1	5.1	4.6	4.3	4.3	4.5	5.9	/
F	8.4	9.2	9.2	7.8	7.0	6.8	5.6	5.5	5.5	4.2	6.9	7.0	7.4	7.2	7.2
G	7.7	8.0	7.4	6.8	6.4	6.2	6.1	5.8	5.6	6.1	6.1	6.2	6.5	6.6	6.7
H	10.7	13.8	14.3	10.5	8.6	8.4	8.3	9.1	9.4	10.1	9.6	9.6	10.5	9.7	9.7
I	9.0	16.2	16.0	10.6	9.0	8.4	8.3	7.1	7.0	8.6	9.5	9.3	9.3	9.6	10.6
J	9.2	10.2	11.9	8.1	7.6	7.7	7.3	7.7	7.4	7.6	7.6	7.2	8.0	8.6	8.4

Pre-op Intra-op // Minutes after Disconnection from Anaesthetic Gases

PaO_2 VALUES IN FIRST HOUR AFTER GENERAL ANAESTHESIA.

ALL PATIENTS BREATHING ROOM AIR EXCEPT FOR INTRA-OPERATIVE SAMPLE (FIO_2 = 0.33)

TABLE 7

The study simulated the conditions which occur if patients are transferred direct from anaesthetic gases with an inspired oxygen content of 33%, to room air. Fink (1955) described the occurrence of hypoxaemia after general anaesthesia with nitrous oxide in oxygen. The degree of desaturation was worst in the first 5 minutes after the patient was allowed to breathe room air. FInk did not note the occurrence of hypoxaemia after 10 to 20 minutes into the post-operative phase as the patients were then given oxygen by face mask.

Many other authors have described the occurrence of a degree of arterial hypoxaemia lasting for many hours after general anaesthesia. Nunn and Payne (1962) studied 24 healthy adults undergoing minor procedures under anaesthesia with various volatile agents with spontaneous respiration with or without nitrous oxide. The patients breathed 100% oxygen before extubation. Mean arterial pO_2 values in the first 3 hours after operation were around 58 mm Hg (7.7 kPa). The range showed that the lowest values occurred at 5 minutes after the end of anaesthesia and the lowest value was 40 mm Hg (5.32 kPa). The age of the patients was not stated.

Conway and Payne (1963) studied 21 patients having various procedures under general anaesthesia with halothane in oxygen and found arterial oxygen desaturation in every patient when measured between 1 and 2 hours after the end of anaesthesia. Comparison with the present author's results are difficult, as saturation values and not partial pressures are quoted. Conway and Payne (1963) found that the hypoxaemia responded readily to a raised inspired oxygen tension. Nunn (1965) showed a negative correlation between age and post-operative pO_2.

However, most of the data refers to patients under 70 years of age and is derived both from the author's results and pooled data from other series. It is noteworthy that few PaO_2 values are less than 50 mm Hg (6.65 kPa). Thus, the present findings are in line with other studies although exhibiting a more severe degree of hypoxaemia. The effects of the common practice of breathing 100% oxygen for 2 to 3 minutes at the end of anaesthesia were not studied. However, it the opinion of the author that this practice would not necessarily prevent severe hypoxaemia occurring when the patient subsequently breathed room air. Whether it is justifiable to test this hypothesis is doubtful, as added oxygen in the early post-operative period would seem essential, is relatively easy to administer and is almost never completely contra-indicated.

[2.11] Aetiology of Post-operative Hypoxaemia

This subject has been reviewed by Spence and Alexander (1972), and Bay, Nunn and Prys-Roberts (1968). The present study did not attempt to elucidate the particular factors occurring in the patients studied but a discussion of the possible factors is of interest. The hypoxaemia seen bears a remarkable resemblance in pattern over the first 10 minutes to that described by Fink (1953), but the degree of hypoxia was more profound in the present study. Fink, in his classic account, described the occurrence of diffusion hypoxia occurring because of the dilution of alveolar oxygen by the large volume of nitrous oxide being eliminated in the early stages of recovery from anaesthesia with this agent. The maximum effect should be over by 10 minutes after the end of anaesthesia. However, the explanation of the hypoxaemia seen in the present study seems unlikely to be solely diffusion hypoxia (Fink effect).

The other possibilities are:

1) Hypoventilation
2) Diffusion defect
3) Excessive desaturation of mixed venous blood
4) Venous admixture - "shunt"
5) Ventilation-perfusion abnormality

1) Hypoventilation

The mean $PaCO_2$ while showing a small rise in the first post-operative hour was well within, and indeed below, normal in this study. Hypoventilation is thus unlikely to be an important factor, assuming no major reduction in carbon dioxide production.

2) Diffusion defect

A specific defect in oxygen diffusion across the alveolar membrane in the presence of normal carbon dioxide diffusion seems unlikely and can be discounted.

3) Excessive desaturation of mixed venous blood

This may be caused by inadequate oxygen delivery to the tissues and may be due to a depressed cardiac output, or a cardiac output inadequately compensating for increased metabolic demands or anaemia. Low cardiac output may be a feature in the group of patients studied, as halothane is a cardiac depressant (Deutsch et al, 1962). A degree of anaemia may have been a minor factor.

Increased metabolic demands would occur if shivering took place. Bay et al (1968) studied patients in the early post-operative period and found no correlation between presence or absence of raised oxygen consumption (caused by shivering) and arterial pO_2. The patients in that study were, however, relatively young and were mostly able to raise cardiac output and respiratory exchange in line with metabolic demand. This may not be the case in the present group of patients, but shivering was not frequent in the present study.

4) Venous admixture ("shunt")

Shunting is at the extreme end of the spectrum of ventilation-perfusion abnormalities, where parts of the lung are perfused but not ventilated resulting in venous admixture. A good response to relatively low levels of added inspired oxygen would suggest that frank shunting plays little part in this situation. Some confirmatory evidence that the hypoxia would respond to a modest increase in inspired FIO_2 is shown by the mean intra-operative PaO_2 value of 14.27 kPa (+/- 0.74) in the first 25 patients studied in the GA group (FIO_2 = 0.33).

5) Ventilation-perfusion abnormality

A disturbance in the ratios of ventilation and perfusion in the lungs is a very strong possibility (Nunn and Payne, 1962; Conway and Payne, 1963; Bay et al, 1968). Alexander, Spence, Parikh et al (1972) have suggested that the fall in functional residual capacity which occurs under anaesthesia (Hewlett, Hulands, Nunn et al, 1974), persists into the post-operative period and leads to closure of some small airways and hence underventilation of some segments of the lung with normal perfusion.

Thus, a combination of diffusion hypoxia, ventilation-perfusion defect and perhaps inadequate cardiac output may account for the pronounced hypoxaemia observed in this study.

[2.12] Conclusions

Patients with fractured neck of femur tend to be hypoxaemic before surgery but suffer no further deterioration in oxygenation in the immediate peri-operative period if surgery is performed under spinal anaesthesia. However after general anaesthesia, if patients breathe room air, profound hypoxaemia may occur in the first hour and especially in the first 10 minutes after the end of anaesthesia. Thus, the present study would suggest the importance of absolutely continuous administration of added oxygen for at least one hour after repair of fractured neck of femur under general anaesthesia, and demonstrates the severity of arterial hypoxaemia which might occur if added oxygen is not given, particularly during the time of transfer to the recovery area.

Confirmation of the aetiology of the hypoxaemia would be of considerable interest. On a practical level, many anaesthetists habitually allow patients to breathe 100% oxygen for a variable period before disconnection from the anaesthetic gases. As discussed above, it is debatable whether it would be worthwhile to examine the changes in PaO_2 after this procedure, to determine whether the hypoxaemia which was demonstrated in the present study would be less marked. Any such study would have to be carried out with caution and analysis of samples carried out immediately so that hypoxaemia detected could be treated. It would be valuable to confirm that added oxygen by conventional high-flow face mask is indeed effective in preventing hypoxaemia in the early period after general anaesthesia for hip fracture, although there is little ground for suspicion that this would not be the case, on the basis of clinical experience.

Patients requiring primary hip prosthesis were excluded from the present studies as the insertion of prosthesis and cement might be expected to produce cardio-vascular and respiratory effects, as have been seen after total hip replacement (Modig and Malmberg, 1975; Modig, 1976). Some pilot studies by the present author revealed quite marked changes in arterial oxygenation around the time of prosthesis insertion. Investigations of blood gas changes both related to method of anaesthesia and prosthesis insertion might be a worthwhile field of investigation.

CHAPTER 3

THE EFFECT OF ANAESTHETIC TECHNIQUE ON THE INCIDENCE OF DEEP VENOUS THROMBOSIS IN PATIENTS WITH FRACTURED NECK OF FEMUR

[3.1] Introduction

At the time that this study was undertaken, to the author's knowledge, there were no reports in the literature of the comparative effects of general and spinal anaesthesia on the incidence of deep venous thrombosis (DVT). This study was undertaken as there was evidence of reduced mortality in the SAB group in the initial phase of the study (details in chapter 5). The timing of the deaths strongly suggested a difference in frequency of thromboembolic events.

[3.2] Incidence of Deep Venous Thrombosis (DVT) after Hip Fracture

Patients with fracture of the femoral neck are probably at highest risk of developing DVT and fatal pulmonary thromboembolism of any group of patients. Sevitt and Gallaghar, (1961) showed that, at autopsy, 83% of patients who died after femoral neck fracture had DVT, and of these, 46% showed evidence of pulmonary thromboembolism. All those with pulmonary thromboembolism also had DVT, but many of the pulmonary emboli had not been diagnosed clinically. The incidence of DVT rose with the length of time survived after the fracture. Patients who survived less than 4 days had an incidence of 19%, after 4 to 7 days survival, 47% had DVT and after 8 to 14 days, 88% had DVT. Field, Kakkar and Nicolaides (1972) found a 75% incidence of DVT after per-trochanteric fracture of the femur. Xabegras, Gray and Ham (1978) found DVT in 48% of patients not given anti-coagulant prophylaxis after fractured neck of femur. In another study Moskovitz, Ellenberg, Feffer et al (1978) found DVT in 40% of patients after hip fracture whether they had received anti-coagulant prophylaxis or not.

Assessment of incidence of DVT by clinical methods is utterly unreliable (Flank, Kakkar and Clark, 1968) and any assessment must be by more objective methods.

[3.3] Available Methods of Detection of Deep Venous Thrombosis

The validity of any study of DVT incidence is crucially dependent on the accuracy of the method of detection used. A discussion of the reasons for selection of venography as the method of choice in this study is appropriate. The use of purely clinical assessment of incidence of DVT is notoriously inaccurate except when signs are gross (McLachlin, Richards and Paterson, 1962). As few as 50% of patients with calf tenderness after operation do, in fact, have DVT, and over 60% of patients with proven DVT have no physical signs (Browse, 1978).

Methods of detection (Browse, 1978) include: doppler flow detector; impedance plethysmography; thermography; fibrinogen uptake test; isotope venography and contrast venography (phlebography). For screening purposes, some false positive results are acceptable. The fibrinogen uptake test, doppler technique and impedance plethysmography are adequate techniques for some applications but Browse considered that the "only acceptable method for diagnosis of existing thrombosis is phlebography" (Browse, 1978).

The fibrinogen uptake test utilises radioactive labelled fibrinogen which is injected and subsequently incorporated in any clots which form and can be detected by noninvasive scanning. It has been used widely in studies of post-operative deep venous thrombosis, but its use in studying the true incidence of venous thrombosis after hip fracture surgery has been shown by Morris and Mitchell (1977a) to yield inaccurate results. They compared results of fibrinogen uptake test with post-mortem dissection of leg veins in 31 patients with hip fractures who died during or within 7 days of the period of fibrinogen uptake tests. Results of the tests in the thigh area on the side of the hip fracture proved valueless and the criteria for confident isotope diagnosis of venous thrombosis in the uninjured thigh could not be determined. Assessing uptake in the calf was more successful but underestimated the incidence of venous thrombosis providing 6 false negative cases. They concluded that while the accuracy of fibrinogen uptake test was limited to the lower leg in patients with hip fractures, this might not be a disadvantage, as the calf veins are those most often affected in this condition. (As will be seen, this does not agree with the findings in the present study in whom 8 of the 24 patients with DVT did not have calf vein thrombosis).

Field et al (1972) found that the fibrinogen uptake test in comparison with venography had a significant false positive rate of 24% and a false negative rate of 8%, thus being inaccurate in 32% of patients. They found that it was inaccurate in the regions of the proximal femoral vein, the pelvic region and near the wound, and in that study, thrombi often occurred in large proximal veins.

In a comparison of the fibrinogen uptake test and venography after elective hip replacement surgery, Loudon, McGarrity, Vallance et al (1978) found that the fibrinogen uptake test yielded a false positive rate of 30%. They concluded that venography is required where accuracy is paramount. For these reasons the present study used venography exclusively in the assessment of the comparative incidence of deep venous thrombosis.

Possible complications of venography include reaction to contrast medium, precipitation of DVT or dislodging thrombus (Culver, Crawford, Gardiner et al, 1970). However, Thomas (1971) considered venography to be very safe.

[3.4] Patients and Methods

40 patients, were allocated randomly to receive either general or spinal anaesthesia as previously described.

Table 8 outlines general characteristics of the patients studied. There were no significant differences in mean age (by Student's t test) or sex distribution (by Fisher's test) with 16 females and 4 males in the GA group, and 14 females and 6 males in the SAB group.

Table 9 shows the allocation of overall and cardio-vascular "fitness" scores in the same manner as described previously (chapter 1). There were no significant differences in allocation of scores by Fisher's test.

Patients underwent venography at 7 to 10 days after operation. The method was as described by Louden et al (1978).

	GA Group	(Range)	SAB Group	(Range)	
Age (y)	72.3 +/- 2.8	(33 - 87)	73.9 +/- 4.1	(19 - 94)	
Admission to surgery interval (days)	1.8 +/- 0.16	(1 - 3)	2.0 +/- 0.18	(1 - 4)	
Pre-operative serum urea (mmol $litre^{-1}$)	6.1 +/- 0.6	(1.5 - 10.6)	8.4 +/- 1.2	(2.4 - 22.1)	
Estimated blood loss (ml)	243 +/- 47	(85 - 990)	348 +/- 64	(60 - 1200)	
Fluid infused (ml)	923 +/- 68	(1300 - 1500)	1300 +/- 94	(700 - 2200)	$p < 0.01$
Length of operation (min)	79 +/- 4.1	(60 - 130)	93.5 +/- 5.6	(60 - 150)	$p < 0.05$

GENERAL FEATURES (DVT study) (mean +/- SEM)

TABLE 8

Fitness Scores (see Chapter 1)	"1"		"2"		"3"	
	GA	SAB	GA	SAB	GA	SAB
"Overall" Scores	10	10	9	9	1	1
CVS Scores	13	11	7	8	0	1

NUMBER OF PATIENTS ALLOCATED TO "FITNESS" SCORES

(DVT study)

TABLE 9

The patient was placed on a screening table with 30° anti-Trendelenberg tilt. A butterfly needle of 19 or 21 gauge was inserted percutaneously into a dorsal vein of the foot. The retrogade direction was preferred. A tourniquet was applied above the ankle and 50ml of Conray 280 was quickly injected. The filling of the deep venous system was screened and films taken over calf, knee and thigh. A video tape recording was made and a further 20 to 30ml of contrast medium were often required. The filling of the iliac system was demonstrated by calf compression or by elevation of the leg. The same procedure was followed in each leg and the veins were flushed with heparinised saline. Statistical analyses were by Student's t test and Fisher's test as appropriate.

[3.5] Results

There were no significant differences in pre-operative mean blood urea concentrations, interval between admission and surgery, or estimated blood loss between the groups (table 8). However, mean length of operation was significantly longer in the SAB group (93.5 minutes) than in the GA group (79 minutes). The mean volume of fluid infused was also significantly greater in the the SAB group (1300ml) than in the GA group (923ml).

Table 10 records the venographic incidence of DVT in each anaesthetic group with details of incidence by lateralisation. The incidence of DVT in the SAB group (40%) was significantly lower than in the GA group (76.2%) by Fisher's test ($p<0.05$). 10% of patients in the SAB group had unilateral DVT in the opposite leg to that with the fracture. 45% of patients in the GA group had unilateral DVT but all occurred on the same side as the fracture. Bilateral DVT occurred in 8 of the 16 patients with DVT in the GA group and 3 out of 8 with DVT in the SAB group. Clinical evidence of DVT was only noted in 3 patients, all in the SAB group.

Table 11 displays sites of thrombi as demonstrated on the venograms. Many patients, of course, had thrombi at more than one site which leads to total numbers of thrombi exceeding the number of patients in the study.

Table 12 compares mean age and length of operation in those patients with and without DVT with the two anaesthetic groups amalgamated. The mean age of patients with DVT (69.7years) was significantly younger ($p<0.05$) than that of patients without DVT (78.2 years). The mean length of operation, however, was not significantly different.

When age and length of operation in each anaesthetic group were examined in patients with and without DVT (table 13), mean length of operation in those who developed DVT was significantly longer in the SAB group.

There were no significant differences in outcome in the year following operation (table 14). Only two patients with DVT died within one month of operation, both in the GA group (on the 4th and 9th day). Detailed analysis of outcome for all patients studied for the thesis is presented later (chapter 5).

[3.6] Discussion

This study demonstrates that the incidence of DVT in the immediate post-operative period was 76% after general anaesthesia but only 40% after spinal anaesthesia.

	GA (n=20)	SAB (n=20)
DVT present	16 (75%) *	8 (40%) *
Bilateral DVT	8 (40%)	3 (15%)
Unilateral Same side as surgery	9 (45%)	3 (15%)
Unilateral Other side	0	2 (10%)
Clinically	0	3 (15%)

* $p < 0.05$

INCIDENCE OF DVT

TABLE 10

	GA Group (n=20)		SAB Group (n=20)	
	SIDE OF OPERATION	OTHER SIDE	SIDE OF OPERATION	OTHER SIDE
ILIAC	3	1	0	1
FEMORAL	10	2	5	2
POPLITEAL	3	1	3	2
CALF	9	7	5	4

SITES OF DVT

TABLE 11

	With DVT (n=24)	Without DVT (n=16)
Age (years)	69.7 +/- 3.5 *	78.24 +/- 2.8 *
Length of operation (min)	85.54 +/- 4.2	88.82 +/- 7.3

*$p < 0.05$

AGE AND DURATION OF SURGERY (mean +/- SEM) IN THOSE WITH AND WITHOUT DVT (anaesthetic groups combined)

TABLE 12

	With DVT		Without DVT	
	GA (n=16)	SAB (n=8)	GA (n=4)	SAB (n=12)
Age (years)	71.8 +/-3.2	65.37 +/-8.4	74 +/-4.9	80 +/-3.4
Length of operation (mins)	76.5 +/-3.4 *	101.2 +/-7.5 *	65.8 +/-19.2	91.7 +/-9.0

* $p < 0.01$

AGE AND DURATION OF SURGERY IN THOSE WITH AND WITHOUT DVT

(in each anaesthetic group)

TABLE 13

	GA Group	SAB Group
Hospital Deaths	4	3
Returned Home	13	14
Died at Home	1	0
Remained in Hospital	1	2
Psychogeriatric Care	1	1
Community Care	1	0

OUTCOME (DVT study)

TABLE 14

Although the groups were well matched for age, sex distribution, pre-operative fitness, delay before operation and intra-operative blood loss, the groups were not identical in two respects. The patients in the SAB group had a longer mean duration of operation and received significantly more fluid (table 8). The greater duration of operation may well have been due to the extra time taken to perform the spinal block, as the anaesthetic time was included in the recorded length of operation. There is no other obvious explanation for the difference as operating conditions were not noticeably different between the two groups, either subjectively, or objectively (blood loss). The greater volume of fluid received by the patients in the SAB group may be explained by the common practice of giving fluid to counteract the fall in arterial blood pressure resulting from vasodilation produced by spinal anaesthesia.

Longer operations might be expected to increase the risk of DVT formation. In those patients who did develop DVT, the mean length of operation was significantly longer in the SAB group (table 13) which could suggest that protective mechanisms might be operating in that group or, conversely, precipitating factors were occurring in the GA group. However, it must be remembered that length of operation was greater overall in the SAB group.

When the two anaesthetic groups are combined (table 12), the mean age of those patients with DVT is significantly lower than that of patients without DVT. This is difficult to reconcile with clear evidence showing that DVT incidence rises with age (Sevitt and Gallaghar, 1961).

Despite the substantial difference in incidence of DVT, there were no noticeable differences in outcome in this part of the study (table 14). It is important, however, to look at long term outcome in the whole thesis study group, and this is presented in chapter 5. Having presented the evidence that anaesthetic technique seems to affect incidence of DVT, other evidence from the literature will be examined and possible mechanisms discussed. A review of other methods of DVT prophylaxis also seems relevant. The overall clinical implications will be discussed fully in chapter 5, as reduction of DVT incidence is not necessarily an end in itself, although the patho-physiological mechanisms are of great interest.

[3.7] Other Studies of Effects of Anaesthesic Technique on DVT Incidence

Only one other study (published after the present study had been completed) compares the incidence of DVT with spinal or general anaesthesia in patients with fractured neck of femur (Davis, Quince and Laurenson, 1980). That study used the fibrinogen uptake test to assess incidence of DVT and this methodology renders the results highly questionable, for the reasons described earlier (chapter 3.3). However, the pattern of results are in broad agreement with the present study. The incidence of DVT in the general anaesthetic group was 28 out of 37 patients (76%) and 17 out of 37 patients (46%) receiving spinal anaesthesia, a statistically significant difference ($p<0.05$). The technique of general anaesthesia involved intermittent positive pressure ventilation with nitrous oxide, opiate, and muscle relaxant (pancuronium) in a generous dose (mean 6mg). It has been suggested, but not proved (to the author's knowledge) that IPPV and/or muscle relaxant drugs may be themselves a precipitating factor in the development of post-operative DVT (Laaksonen, Arola, Hannelin et al, 1973). The use of techniques of general anaesthesia for repair of fractured neck of femur involving IPPV and muscle relaxants may be associated with a high early post-operative mortality (McLaren et al, 1980; Spreadbury, 1980). This will be discussed in more detail later.

In hip replacement surgery, two studies provide excellent confirmatory evidence of the comparative effect of spinal or epidural anaesthesia on DVT incidence. Thorburn, Louden and Vallance (1980) compared the frequency of DVT after total hip replacement in patients receiving general or subarachnoid spinal anaesthesia. All patients received both fibrinogen uptake test and venography. DVT was said to be present if a positive fibrinogen uptake test was associated with a venographic abnormality. Of 47 patients receiving general anaesthesia, 25 (53%) had DVT, and of 38 patients receiving spinal anaesthesia 11 (29%) had DVT. The spinal anaesthetic group therefore had a significantly lower frequency of DVT ($p<0.05$). The general anaesthetic technique employed IPPV and muscle relaxants to provide suitable conditions for the surgical procedure. Spinal anaesthesia provides excellent muscle relaxation by virtue of central neural blockade of motor fibres.

Modig, Borg, Karlstrom et al (1983b) compared the influence of epidural and general anaesthesia on the incidence of DVT and isotopically detected pulmonary embolism after total hip replacement. In a very carefully conducted study, bilateral venography and chest radiography combined with perfusion lung scans were performed 14 days before and 11 days after hip replacement operation. 30 patients received general anaesthesia with IPPV, opiate and relaxant, and 30 received epidural anaesthesia which was continued for the first 24 hours post-operatively. The authors sub-divide the DVT results and do not give total incidence in each anaesthetic group. The incidence of DVT was significantly lower in the epidural group when popliteal and femoral areas or calf and thigh veins were compared. Presumably, breakdown of the figures was necessary to achieve statistical significance although this is not stated by the authors. Significantly more patients had positive perfusion lung scan suggesting pulmonary embolism in the GA group (33%) than in the epidural group (10%).

The incidence of DVT after open prostatectomy under epidural or general anaesthesia was compared by Hendolin, Mattila and Poikolainen (1981). 21 patients received general anaesthesia with IPPV, opiate and muscle relaxant, and 17 patients received epidural anaesthesia continued until the morning after operation. The fibrinogen uptake test was used to screen patients before surgery, on the day of operation, and on 5 subsequent occasions up to the 7th post-operative day. A positive fibrinogen uptake test was an indication for venography. 52% of the patients in the GA group and 12% of those in the epidural group developed thrombi detected by fibrinogen uptake test within 4 days of prostatectomy and this difference was statistically significant ($p<0.02$). Venography was positive in 9 of the 13 patients with a positive fibrinogen uptake test. However, as the authors do not state the relative distribution of positive venograms between the groups, some doubt must be cast on the validity of the conclusions drawn from this study. Clinical signs of DVT were observed in 6 patients, all in the general anaesthetic group.

Thus, despite the reservations expressed above, the studies of Thorburn et al (1980), Modig, Borg, Karlstrom et al (1983b) and Hendolin et al (1981) all show similar trends, with a reduced incidence of DVT associated with the use of spinal or epidural anaesthesia in comparison with general anaesthesia. The study of Davis et al (1980) must probably be discounted because of the methodology.

Before discussion of the possible mechanisms by which anaesthetic technique may affect DVT, the aetiological and risk factors of DVT will be reviewed with particular reference to the circumstances relevant to the surgical and trauma patient.

[3.8] Aetiology of Deep Vein Thrombosis

Three major factors are thought to be implicated in the pathogenesis of deep venous thrombosis and are attributed to Virchow ("Virchow's Triad"): changes in the vessel wall, changes in blood flow, and changes in the blood (Morris and Mitchell, 1977c).

1) Changes in the vessel wall

Clearly, vessel wall injury may occur at the time of the fracture. Endothelial damage may also occur as a result of pressure on the deep veins of the calf muscles which are flaccid on the operating table. During hip replacement surgery, Stamatakis, Kakkar, Sagar et al (1977) have shown that very severe distortion of the common femoral vein occurs as a result of manipulation of the operative leg and this may cause endothelial damage which can initiate thrombus formation.

2) Changes in blood flow

a) Immobility both before, during and after surgery will tend to cause sluggish venous blood flow due to depression of the venous pump mechanism in the lower limb.

b) Blood viscosity changes in the peri-operative period and their importance in the aetiology of DVT are fully discussed in chapter 4.

c) Low cardiac output in the unfit elderly patient will also contribute to a reduced limb blood flow. Anaesthesia, whether general or regional, may also cause major changes in cardiac output and lower limb blood flow (Clark and Cotton, 1968; Kemble, 1971; Modig, Malmberg and Karlstrom, 1980) and this will be discussed below.

3) Changes in the blood

The effects of injury, anaesthesia and surgery are extremely complex (Brozovic, 1977). One recent study (Richard, Buller, Bovill et al, 1983) found no changes in indices of coagulation or fibrinolysis after minor surgery (ophthalmic) under either general or local anaesthesia. However after major surgery the picture is very different, and the effects of anaesthesia and surgery can be difficult to separate. The major changes have been reviewed by Brozovic (1977).

a) Clotting factors

Factor VIII levels rise within the first 24 hours after operation and may remain elevated for many days (Brozovic, 1978). Factor V levels, while falling initially after operation, subsequently rise as a result of increased synthesis.

b) Fibrinolytic "shutdown"

Chakrabarti, Hocking and Fearnley (1969) showed that, after surgery, fibrinolytic shutdown occurred which lasted for up to 10 days. Brozovic (1977) postulated inadequate production and release of plasminogen activator, acceleration of its clearance from the circulation and also possibly, a deficiency of plasminogen or excessive amount of inhibitors.

c) Antithrombin III

Antithrombin III (heparin cofactor) is a glycoprotein capable of inhibiting coagulation and levels have been found to be low after surgery from the first to the sixth post-operative days (Brozovic, 1977).

d) Acute phase reactants

The "Acute Phase" reaction results in a rise of plasma glycoproteins, of which fibrinogen is probably the most important in the present context, particularly in its effects on viscosity (see chapter 4).

e) Platelets

Platelet numbers and adhesiveness are increased after surgery (Wright, 1942), and aggregation is enhanced (Emmons and Mitchell, 1965).

[3.9] Additional Risk Factors

While trauma and surgery are themselves important risk factors for the development of DVT, other risk factors have been clearly defined. The subject has been reviewed by Morris and Mitchell (1977c).

a) Immobility

Immobility seems to be a major risk factor in the development of DVT, but the underlying disease process requiring bed rest must also be considered. Gibbs (1957) in a post-mortem study of a variety of medical and surgical patients, showed a rapid rise in the frequency of DVT with length of bed rest before death, from zero after 2 days in bed to 100% after 14 days. Sevitt and Gallaghar (1961) confirmed these findings with a post-mortem study showing DVT in less than 20% of patients confined to bed for less than 4 days, rising to almost 90% of those confined to bed for 1 to 2 weeks.

b) Age

Post-mortem studies have shown that frequency of DVT and pulmonary embolism increases with age (Sevitt and Gallaghar, 1961). The occurrence of DVT in the post-operative period has also been shown to rise with increasing age (Kakkar, Howe, Nicolaides et al, 1970). In a study of patients dying after trauma or burns, Sevitt and Gallaghar (1961) showed that the incidence of DVT detected at post-mortem rose with age from around 42% in the 31 to 45 age group, to over 70% in those over 60 years of age. However, as noted by Morris and Mitchell (1977c), the elderly take longer to recover from illness and tend to be immobilised for longer, and these may be more important factors than age alone.

c) Obesity

Obesity has been shown to be a risk factor in patients who have undergone surgical operations (Coon and Collar, 1959)

d) Heart Disease

Post-mortem studies have also confirmed that heart disease, in particular, cardiac failure, increases the risk of venous thromboembolism (Coon and Coller, 1959).

e) Previous episode of DVT

Kakkar et al (1970) showed that the incidence of post-operative DVT was significantly greater in those who had had a previous episode even although it had occurred some years previously.

f) Varicose veins

While the presence of varicose veins is a significant risk factor in young patients, Kakkar et al (1970) have shown that their presence had no significant effect on the incidence of thrombosis in those over 60 years of age.

f) Malignant disease

Malignancy is a significant risk factor (Kakkar et al, 1970) but none of the patients in the present study was known to be suffering from malignancy although pathological fracture of the neck of femur from secondary tumour deposits is not very uncommon.

g) Length of operation

Soumolainen, Kettunen, Rissanen et al (1983) found a increased incidence of DVT when hip surgery operations exceeded 150 minutes. Long operations for hip fracture may also increase mortality (Lorhan and Shelby, 1964).

i) Other factors

Other risk factors such as pregnancy and the contraceptive pill are not relevant to the present studies.

[3.10] Risk factors in the present study

It was not practicable to delineate each risk factor in the present study, but with the exception of those features previously mentioned, the two groups can be regarded as well matched. Duration of immobility before operation (delay before surgery), length of operation, age and cardiac status have been examined and were similar in both groups. However, it was not practicable to weigh the patients, or to rely on a history of previous DVT as clinical diagnosis is completely unsatisfactory.

[3.11] Mechanisms of Effect of Anaesthetic Technique on DVT

1) General Anaesthesia

The induction of general anaesthesia has been shown to reduce lower limb blood flow substantially (Clark and Cotton, 1968; Kemble, 1971). Clark and Cotton measured venous blood flow by a thermal dilution technique in the popliteal and external iliac veins. At both sites, flow rates were reduced by at least 50% immediately following induction of anaesthesia by intra-venous thiopentone. The flow rates remained low throughout operation under inhalational anaesthesia with halothane until anaesthesia was lightened towards the end of the procedure, when flow rates progressively increased towards pre-anaesthetic values. Electrical stimulation of calf muscles produced substantial increases in venous flow in some of the patients studied. The authors postulate that the initial rapid decrease of flow following induction of anaesthesia may either be a result of the reduction in cardiac output known to be caused by thiopentone, or possibly a re-distribution of blood to other regions of the body. The associated inactivity of the calf muscles also may contribute to flow reduction. Kemble (1971) also found a peri-operative decrease in venous blood flow of about 50%, using radioactive hippuran in patients undergoing a variety of surgery under general anaesthesia. Venous flow had returned to the pre-operative level by the day following operation.

Intermittent positive pressure ventilation (IPPV), by increasing mean intra-thoracic pressure, might be expected to further impede venous return and increase the likelihood of stasis in the deep veins of the pelvis and lower limbs. Laaksonen et al (1973) randomly allocated 107 patients undergoing elective surgery of various types to receive two methods of general anaesthesia, one group were given IPPV and muscle relaxation, and the other group breathed spontaneously, with inhalational or regional anaesthesia. The fibrinogen uptake test was employed to detect post-operative DVT. No significant difference was observed overall between the test and control groups with DVT detected in 41% of patients in each group. The time taken for spontaneous lysis of the thrombi was slightly longer in the group who had received muscle relaxation but the difference was not statistically significant. The authors conclude that the maintenance of spontaneous breathing during surgery may be important for prophylaxis against thrombosis in the elderly, but do not substantiate this with the presented evidence. Indeed, their use of the fibrinogen uptake test to detect DVT and the fact that some of the patients in the spontaneous ventilation group received regional anaesthesia renders their results meaningless.

The case against IPPV/relaxant techniques as regards liability to increase the risk of DVT must be regarded, at present, as unproven. However, the use of relatively large doses of non-depolarising muscle relaxant drugs in the elderly, who may not handle their excretion efficiently, might well be expected to lead to residual paralysis and hence delay return of function of the lower limb venous pump. The recent introduction of shorter acting non-depolarising muscle relaxants (atracurium and vecuronium) may, however, considerably reduce the risks of residual paralysis occurring in the elderly (see chapter 6).

Lower limb blood flow is also affected by the rheological state of the blood. The effects of anaesthesia on blood rheology are discussed in full in chapter 4.

General anaesthetic agents have been shown to enhance fibrinolysis (Simpson, Radford, Forster et al, 1982) but the effect was least with halothane. The implications of this remain unclear.

Lichtenfeld, Schiffer and Helrich (1979) found no effect of general anaesthetic agents, including nitrous oxide and halothane, on platelet function. However, Zahavi, Price and Kakkar (1980) found enhanced platelet activation and release associated with halothane anaesthesia.

2) Spinal/Epidural Anaesthesia

Modig et al (1980) have used venous occlusion plethysmography to compare lower limb blood flow in 2 groups of patients undergoing total hip replacement under general anaesthesia with IPPV or epidural anaesthesia continued for 24 hours. They found that arterial in-flow, venous emptying rate and venous capacity were all higher in the patients receiving epidural block. This improvement in flow in the epidural group was most pronounced immediately after the end of surgery and at 3 hours after operation. They concluded that this hyperkinetic lower limb circulation provided an unfavourable milieu for the formation and the propagation of thrombi. The most likely causes of the increase in lower limb circulation during epidural anaesthesia are the sympathetic blockade produced and rheological changes (discussed in chapter 4). There is every reason to suspect that spinal anaesthesia would produce the same effects as it will also produce a fairly comparable degree of sympathetic blockade in the lower limb.

Modig, Borg, Bagge et al (1983a) found that fibrinolysis inhibition activity was significantly less after epidural anaesthesia (continued for 24 hours) than after general anaesthesia for hip replacement. Concentration of plasminogen activators increased significantly after epidural anaesthesia but not after general anaesthesia and at the 3rd post-operative day plasminogen activator levels were significantly reduced from pre-anaesthetic levels in the general anaesthetic group but not in the epidural anaesthetic group. Thus any thrombi formed in the patients with epidural block would be more liable to be lysed. Modig, Borg, Bagge et al (1983a), also showed that activation of factor VIII was significantly less after epidural anaesthesia compared with general anaesthesia for total hip replacement. Simpson et al (1982) found enhancement of fibrinolysis after epidural block combined with light general anaesthesia in patients undergoing hysterectomy.

Local anaesthetic agents are themselves known to inhibit platelet adhesion (O'Brian, 1961), platelet aggregation and release (Feinstein, Fiekers and Fraser, 1976; Cazenave, Benveniste and Mustard, 1979) and leucocyte migration and aggregation (Giddon and Lindhe, 1972). Lignocaine given as an intravenous infusion intra-operatively and for 6 post-operative days significantly reduced the incidence of DVT in comparison with a control group given 5% dextrose in a study of patients having hip replacement surgery (Cooke, Lloyd, Bowcock et al, 1977).

It is well documented that significant plasma levels of local anaesthetic are obtained during epidural blockade (Ward, Bonica, Freund et al, 1965). However, the extent to which subarachnoid local anaesthetic drugs are absorbed systemically was uninvestigated until 1979, when Giasi, D'Agostino, and Covino (1979) showed that equal amounts of lignocaine injected into the lumbar subarachnoid or epidural spaces produced similar blood levels of the drug. Much larger doses of local anaesthetic agent are required to produce a given level of sensory block via the epidural route, and for the same level of sensory block, epidural anaesthesia results in a lesser degree of sympathetic blockade. It is not known what systemic blood levels of cinchocaine (nupercaine) result after subarachnoid spinal administration, but direct or indirect effects of systemically absorbed local anaesthetic agent may be a significant part of any protective mechanism.

If, as is usual, patients are allowed to breathe spontaneously during surgical procedures under spinal or epidural anaesthesia a negative mean intra-thoracic pressure is maintained, assisting venous return from the lower limbs. This factor would also be present in patients under general anaesthesia with spontaneous ventilation, as was the case in the present study.

A feature common to many studies comparing general with spinal or epidural anaesthesia is the reduced blood loss seen with the regional anaesthetic technique. This, in turn, may lead to a reduction in blood transfusion requirements and it has been suggested (Modig, Borg, Karlstrom et al, 1983b) that blood transfusion may be a predisposing factor in the development of deep venous thrombosis, possibly because stored blood may contain increased amounts of platelet factors 3 and 4. The studies quoted above (Modig, Borg, Karlstrom et al, 1983b; Hendolin et al, 1981; Thorburn et al, 1980) all showed a reduction in blood loss and blood transfusion requirement in the regional anaesthetic groups when compared with the GA groups. These studies were not able, however, to demonstrate that there was a causal association between the increased blood loss, and higher incidence of DVT in the GA groups and Modig, Borg, Karlstrom et al (1983b) could not correlate amount of blood loss with appearance of DVT.

[3.12] Other Methods of Prophylaxis

The literature on the prophylaxis of deep vein thrombosis is vast, and in many respects contradictory. Morris and Mitchell (1976a), have shown that, despite the established high incidence of DVT and pulmonary emboli in patients with fractured neck of femur, 51% of orthopaedic surgeons (answering a questionnaire) did not use any form of DVT prophylaxis in this type of patient and only 15% used any aid to the diagnosis of venous thrombosis other than clinical signs.

Prophylaxis of deep venous thrombosis can of course be an end in itself, to avoid post-thrombotic swelling and ulceration of the leg or the much rarer event of heart failure from thromboembolic pulmonary hypertension (Mitchell, 1979). However, Mitchell (1979) considered that survival was the only valid end point and in a succinct review of all prophylactic measures concluded that conventional anti-coagulation with warfarin remained the only regime for which a significant effect on total mortality has been shown.

The literature on DVT prophylaxis is so extensive that the present discussion will be confined to that on prophylaxis in patients with fractured neck of femur.

a) Oral anti-coagulation

Sevitt and Gallaghar (1959) compared two groups of 150 patients with hip fracture, of which one received phenindione anti-coagulation and the other no prophylactic treatment. The mortality rate was 28% in the control group and significantly lower at 17% in the treated group, with a 3 to 4 month follow-up. Clinical pulmonary embolism did not develop in any patient on anti-coagulation but was seen in 18% of the control series.

83% of patients who died in the control group had DVT at autopsy, with a comparable incidence of 14% in the treated group. The study, however, lacked an objective, accurate assessment of comparative DVT incidence in survivors. Morris and Mitchell (1976b) found that patients receiving warfarin after hip fracture had a reduced incidence of DVT detected by fibrinogen uptake test and at autopsy compared with controls, but showed no significant reduction in mortality in the treated group. However, numbers studied (160) may have been insufficient as there was a trend towards reduced mortality in the group receiving warfarin. However, Hamilton, Crawford, Gardiner et al (1970) found no significant reduction in venographically detected DVT in patients with hip fracture given phenindione anticoagulation compared with a control group.

b) Low dose heparin

Morris and Mitchell (1977b) could find no significant reduction in the incidence of DVT on fibrinogen uptake test in patients with hip fracture given low dose heparin when compared with a control group. Moskovitz et al (1978) also found that low dose heparin afforded no protection against thromboembolic events in patients after surgical repair of hip fracture. This is in contrast to the effectiveness of low dose heparin prophylaxis in general surgical patients demonstrated in a multicentre trial (Kakkar, Corrigan, and Fossard, 1975) and in patients having hip replacement surgery (Moskovitz et al, 1978).

c) Anti-platelet agents (dipyridamole, aspirin, flurbiprofen).

Morris and Mitchell (1977b) failed to show any prophylactic effect of the above agents against DVT as evaluated by fibrinogen uptake test in patients with hip fracture. Channon, and Wiley (1979) using venography also failed to find any prophylactic effect of aspirin in patients with hip fracture. However, Snook, Chrisman and Wilson (1981) showed a significant reduction in venographically detected DVT with aspirin prophylaxis after fractured neck of femur.

e) Defibrinating agents.

Lowe, Meek, Campbell et al (1978) have shown that the defibrinating agent, arvin, (ancrod) significantly reduced the incidence of venographically detected DVT after fractured neck of femur, by reduction of plasma fibrinogen and thus plasma and blood viscosity.

f) Dextran.

Dextran 70 has been shown by Bronge, Dahlgren and Lindquist (1971) to give a similar amount of protection against venographically detected DVT to that afforded by dicoumarol. However, that study did not have a control group with no prophylaxis. Ahlberg, Nylander, Robertson et al (1967) showed a significant reduction in venographically detected DVT using dextran prophylaxis in patients with fractured hips, while a control group given streptokinase showed no such reduction. Myrvold, Persson, Svensson et al (1973), using the fibrinogen uptake test, showed that heparin and dextran had equal prophylactic effects after fractured neck of femur, but they did not have a control group without prophylaxis.

g) Physical methods of prophylaxis.

Morris and Mitchell (1978) concluded that there was no evidence that physical methods of prophylaxis (e.g. early ambulation) had been shown to reduce the frequency of DVT assessed by objective methods. There do not appear to be any studies in patients with hip fracture of methods such as calf compression or graded compresion with stockings which have been found effective in other groups of patients (Nicolaides, Fernandes and Pollock, 1980; Ishak and Morley, 1981).

[3.13] Conclusions

The present study provides evidence that spinal anaesthesia significantly reduces the incidence of DVT after fractured neck of femur when compared with general anaesthesia. The few other comparative studies of general and regional anaesthesia and DVT all show a lower incidence of DVT in patients receiving regional anaesthesia, but as discussed, some of the studies are open to criticism.

General anaesthesia may itself precipitate DVT by contributing to stasis in the deep veins by cardiac output and viscosity changes.

Spinal anaesthesia may protect against DVT by increased lower limb blood flow, viscosity changes and possibly by effects on blood coagulability and the fibrinolytic system although the latter features have only been shown for other methods of administration of local anaesthetic agents.

The clinical importance of these conclusions is extremely difficult to assess, but further discussion and evidence for effects on mortality will be found in chapter 5.

Many unanswered questions remain in the vast area of deep venous thrombosis, pulmonary embolism and their prevention. In the field of anaesthesia, further studies on the effects of regional anaesthesia are needed. Investigations in other groups of patients at risk and studies on the effect of combination of regional and general anaesthetic techniques on DVT and on comparative effects of differing general anaesthetic techniques on thromboembolism are needed. Further clarification and confirmation of the mechanisms underlying differences in incidence of DVT related to anaesthetic technique are also required.

Investigations in this field are difficult, time consuming, full of pitfalls and the interpretation of results and their application to clinical practice requires most careful and critical analysis. These difficulties are daunting but the place of anaesthesia in reducing morbidity and mortality from thrombo-embolism may prove to be of considerable importance.

CHAPTER 4

THE EFFECT OF ANAESTHETIC TECHNIQUE ON BLOOD VISCOSITY AND ITS DETERMINANTS

[4.1] Introduction

One of the major factors which may influence blood flow in arterial, capillary and venous systems is the rheological property of blood. Blood flow in the deep veins of the leg may be significantly affected by blood viscosity and thus be expected to influence the liability to deep venous thrombosis. Dormandy and Edelman (1973) found that patients with established DVT confirmed by fibrinogen uptake test and phlebography had a higher blood viscosity than normal control subjects. They carried out a prospective study of patients undergoing general surgical or gynaecological operations and assessed the incidence of post-operative DVT by fibrinogen uptake test pre-operatively and on the 1st, 3rd, 5th, 7th and 9th post-operative days. Where positive scans were obtained, confirmatory venography was performed in most cases. Measured whole blood viscosity was significantly higher in those with DVT than those without DVT. The authors concluded that blood viscosity appeared to offer the first physico-chemical (as opposed to clinical) pre-disposing factor to have an excellent predictive value for the risk of occurrence of DVT. They also postulated that differences in viscosity may explain why patients with apparently the same risk factors do not have an equal risk of developing DVT.

Lowe et al (1978) showed that the administration of ancrod, a defibrinating agent, was associated with a significant reduction in DVT after repair of fractured neck of femur. DVT was detected by ascending venography or autopsy between 6 and 16 days after surgery. The incidence of DVT in the control group of 52 patients was 73% compared with 45% of the 53 patients who received ancrod. Ancrod reduces levels of plasma fibrinogen, one of the major determinants of blood viscosity. Mean blood viscosity fell by 8% in the control patients and 23% in the ancrod treated patients and the difference was statistically significant ($p<0.01$). Haematocrit had fallen by 15% in both groups and when this effect was eliminated by a correction nomogram, mean blood viscosity rose post-operatively in control patients but was reduced by 10% during ancrod treatment ($p<0.01$). Thus the deliberate reduction of blood viscosity in patients with fractured neck of femur was associated with a significant reduction in deep venous thrombosis. The reduction of DVT achieved in that study (Lowe et al, 1978) was of a similar order to that achieved in the present author's study in fractured neck of femur where differences between the groups were in anaesthetic technique employed.

Before the study presented here, there did not seem to be any information in the literature about comparative effects of general and regional anaesthesia on blood viscosity, although there are some scant and conflicting data about the effects of general anaesthesia on blood rheology.

[4.2] Measurement of Blood Viscosity

Whole blood does not behave in a "Newtonian" fashion and viscosity varies with flow rate (Replogle, Meiselmand and Merrill, 1967). The term "shear rate" implies that fluid moves in a manner similar to plains of liquid sliding past one another at a relative velocity termed "shear rate" and exerting a force on each other, "shear stress". Whole blood tends to display increasing viscosity with reducing shear rate. At very low velocity gradients there is intense aggregation and Rouleaux formation between red blood cells with resulting high viscosity. Replogle et al (1967) have outlined the approximate range of shear rates relevant to flow conditions found in the circulation. They considered that the range relevant to arterial and venous flow is somewhat greater than 100 sec^{-1} and shear rates relevant to capillary flow are in the range 0.01 to 100 sec^{-1}. Thus, in the present study the higher shear rate (94.5 sec^{-1}) will approximate to arterial and venous flow, and the lower shear rate (0.94 sec^{-1}) to flow in the micro-circulation. However, flow varies from very low levels at, or near, the wall of a vessel, rising as the the centre of the vessel is approached provided that flow is laminar.

The present study compares the effects of spinal and general anaesthesia on whole blood viscosity and its major determinants: haematocrit, plasma fibrinogen, and red cell deformability.

[4.3] Patients and Methods

20 patients were allocated randomly to the SAB or GA groups as previously described. None of the patients was taking

any medication known to interfere with coagulation. Venous blood samples were withdrawn on arrival in the reception area, 40 minutes after induction of anaesthesia, and 2 hours after the end of the surgical procedure. The samples were anti-coagulated with E.D.T.A. (1mg/ml) and measurements of viscosity, red cell deformability and haematocrit were made. Citrated blood was used for plasma fibrinogen estimations. It was only possible to make viscosity measurements on samples from 8 patients in each group but all other measurements were made on all 20 patients.

Whole blood viscosity was measured at 37°C using a Contraves LS30 rotational viscometer at high (94.5 sec^{-1}) and low (0.94 sec^{-1}) shear rates. In order to observe the effects of variables other than haematocrit, the viscosity results were "corrected" to a standard haematocrit of 0.45 using a regression equation from a population study (Dormandy, 1970). Haematocrit measurements were made with a Hawksley micro-haematocrit centrifuge spinning at 13,000G for 5 minutes.

Plasma fibrinogen was measured in citrated plasma by a thrombin time method using a Dade fibrometer and standards (Clauss, 1957).

There is no generally accepted method for assessing red cell deformability but filtration techniques are most commonly used at present (Dodds, Matthews, Bailey et al, 1980).

Red cell deformability was estimated by a method described by Reid, Barnes, Lock et al (1976) and modified by Drummond, Lowe, Belch et al (1980). The flow of whole blood through a 5 micron nucleopore filter was measured. The product of this volume and the haematocrit gave the volume of red cells filtered per minute, which is thought to be proportional to the deformability of red cells. The flow rate of red cells through this filter is dependant on their ability to deform in a manner akin to that which has been shown to occur in the capillary bed.

Statistical analysis was by paired and unpaired student 't' test as appropriate.

[4.4] Results

Table 15 shows general details of patients studied. Patients were matched for sex distribution, with 6 females and 4 males in each group. There were no significant differences in mean age, estimated blood loss or maximum falls in systolic arterial pressures between the groups. However the mean volume of fluid administered to the SAB group was almost double that given to the GA group for reasons already discussed in chapter 3.

[4.5] Viscosity

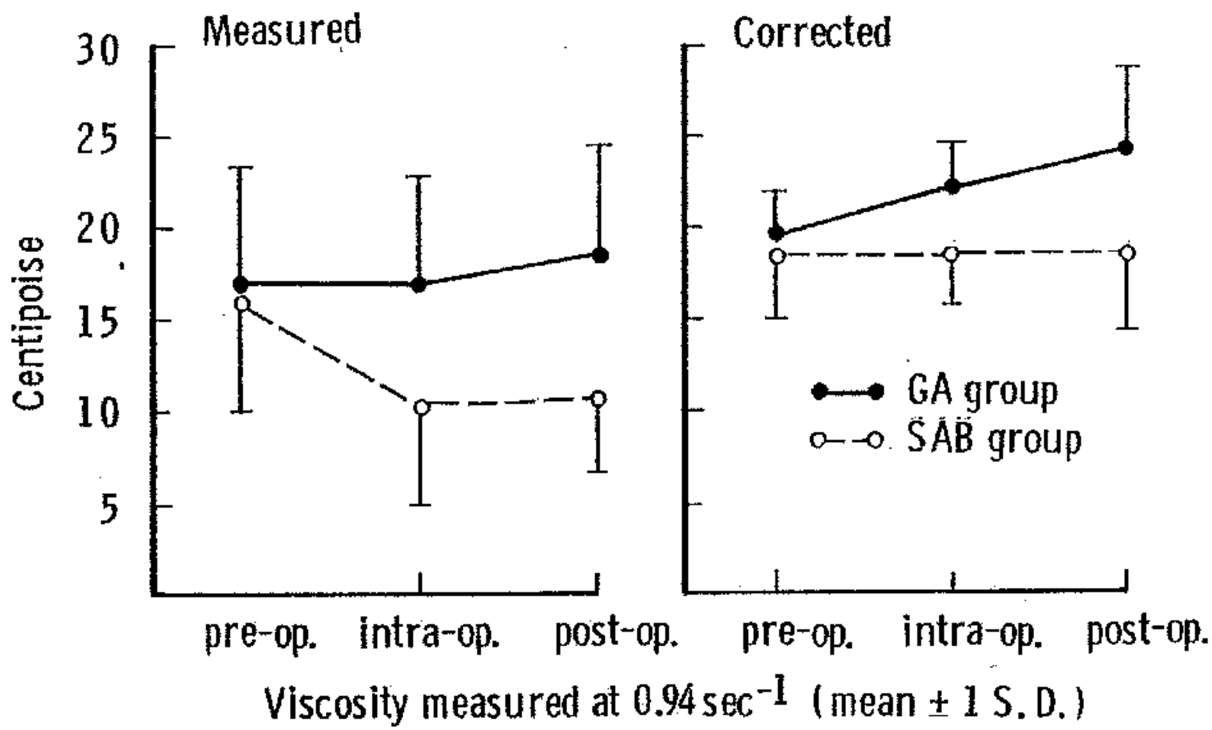
Figures 7 and 8 show changes in blood viscosity (centipoise) in the immediate peri-operative period. Figure 7 shows the viscosity measured at low shear rate (0.94 sec^{-1}). The figures headed "uncorrected" demonstrate viscosity changes as actually measured, while the right hand section of the figures displays the measurements "corrected" to a standard haematocrit of 0.45. Figure 8 demonstrates the same data measured at a high shear rate (94.5 sec^{-1}). Tables 16 and 17 display more detailed results. Corrected and uncorrected measurements are best discussed separately.

	GA (n=10)	SAB (n=10)
Age (y)	71.2 +/- 2.4	75.3 +/- 3.6
Total fluids given (ml)	970 +/- 80*	1,800 +/- 150*
Estimated blood loss (ml)	251 +/- 26	275 +/- 47
Max.fall in systolic arterial pressure (mm Hg)	57 +/- 3	61 +/- 4.6

GENERAL DETAILS OF PATIENTS STUDIED (mean +/- SEM) (Viscosity Study)

* $p < 0.01$

TABLE 15



Measured
Corrected
30
25
20
15
10
5
Centipoise
GA group
SAB group
pre-op.
intra-op.
post-op.
pre-op.
intra-op.
post-op.
Viscosity measured at 0.94 sec^{-1} (mean ± 1 S.D.)

FIGURE 7

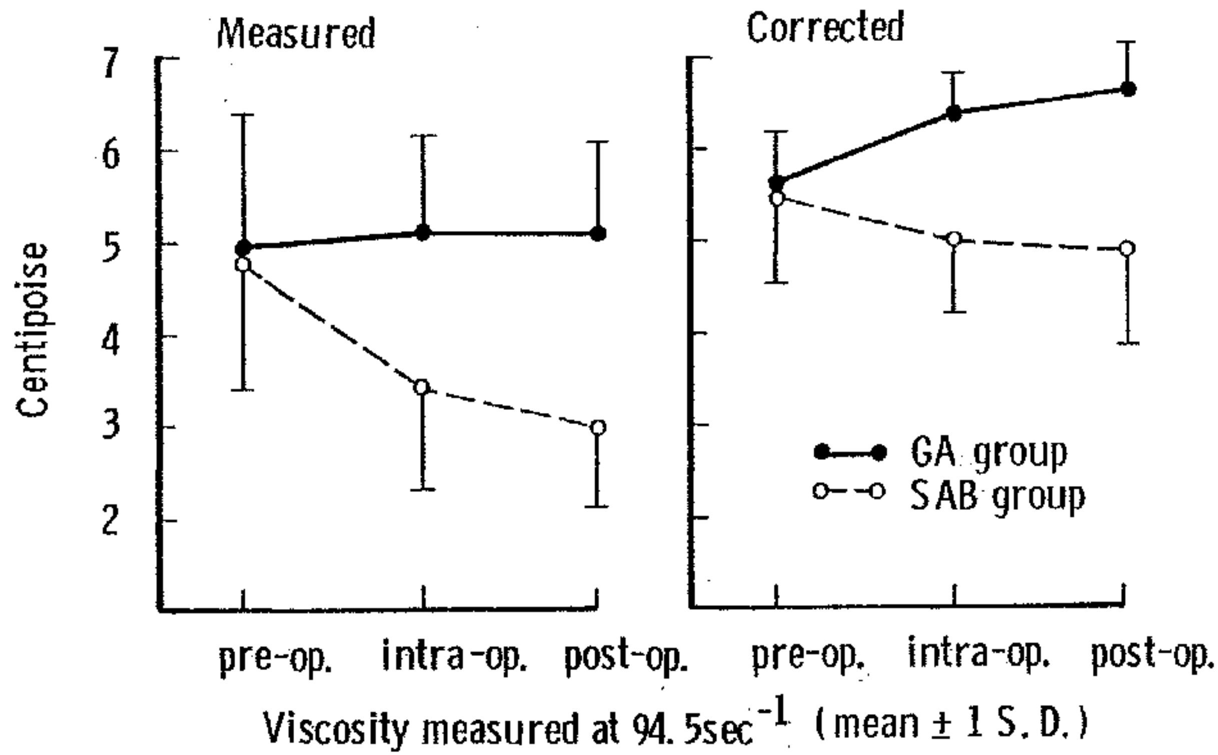

Measured
Corrected
Centipoise
7
6
5
4
3
2
GA group
SAB group
pre-op.
intra-op.
post-op.
pre-op.
intra-op.
post-op.
Viscosity measured at 94.5sec^{-1} (mean ± 1 S.D.)

FIGURE 8

	GA Group (n=8)		SAB Group (n=8)	
	Measured	Corrected	Measured	Corrected
Pre-op	16.75 +/- 6.5	18.83 +/- 3.3	16.05 +/- 5.2	18.48 +/- 3.3
Intra-op	16.76 +/- 5.9	22.40 +/- 2.32	10.39 +/- 5.3	18.26 +/- 3.58
Post-op	18.15 +/- 7.16	24.64 +/- 4.41	10.96 +/- 4.2	17.41 +/- 2.3

VISCOSITY (centipoise) mean +/- 1 S.D.
at 0.94 sec^{-1}

TABLE 16

	GA Group (n=8)		SAB Group (n=8)	
	Measured	Corrected	Measured	Corrected
Pre-op	4.96 +/- 1.42	5.59 +/- 0.63	4.96 +/- 1.6	5.69 +/- 0.93
Intra-op	5.05 +/- 1.11	6.40 +/- 0.44	3.47 +/- 1.12	5.06 +/- 0.78
Post-op	5.08 +/- 0.96	6.71 +/- 0.49	3.04 +/- 0.91	4.96 +/- 1.02

VISCOSITY (centipoise) mean +/- 1 S.D. at 94.5 sec^{-1}

TABLE 17

a) Uncorrected viscosity.

Pre-operatively there were no significant differences in mean viscosity. However mean viscosity was significantly lower in the SAB group in comparison with the GA group ($p<0.05$) both intra-operatively and post-operatively at both shear rates.

In the SAB group, at both shear rates, mean viscosity had fallen significantly from pre-operative values by the time of the intra-operative sample ($p<0.01$), and the effect persisted post-operatively. There were no changes in uncorrected viscosity in the GA group.

b) Corrected viscosity.

At both shear rates the mean post-operative "corrected" viscosity was significantly higher in the GA group compared with the SAB group ($p<0.02$). Mean intra-operative and post-operative viscosity had risen significantly from pre-operative values in the GA group at both shear rates. In the SAB group, "corrected" viscosity values did not change significantly although there was a trend towards a fall in viscosity at high shear rates.

[4.6] Determinants of Viscosity

a) Haematocrit.

Mean haematocrit measurements in each anaesthetic group, before, during and after surgery are shown in table 18. Mean pre-operative haematocrit values were not significantly different between the groups and there was no significant change in haematocrit during or after surgery in the GA group. However, mean haematocrit fell significantly in the SAB group ($p<0.05$).

	GA (n=10)	SAB (n=10)
Pre-operative	0.41 +/- 0.5	0.40 +/- 0.2
Intra-operative	0.39 +/- 0.4	0.33 +/- 0.2
Post-operative	0.38 +/- 0.5	0.33 +/- 0.1

HAEMATOCRIT (mean +/- S.D.)

TABLE 18

b) Plasma fibrinogen.

Mean plasma fibrinogen levels are shown in table 19. There were no significant differences between the groups at any of the measurement times.

c) Red cell deformability.

Red cell deformability expressed as volume of red cells filtered per minute is displayed in figure 9 and table 20. Deformability was significantly increased ($p<0.02$) in the SAB group intra-operatively returning to pre-operative levels by the time of the post-operative sample. In contrast deformability was significantly reduced from pre-operative values in the GA group ($p<0.02$) both during and after surgery. Values remained significantly different post-operatively ($p<0.05$).

[4.7] Discussion

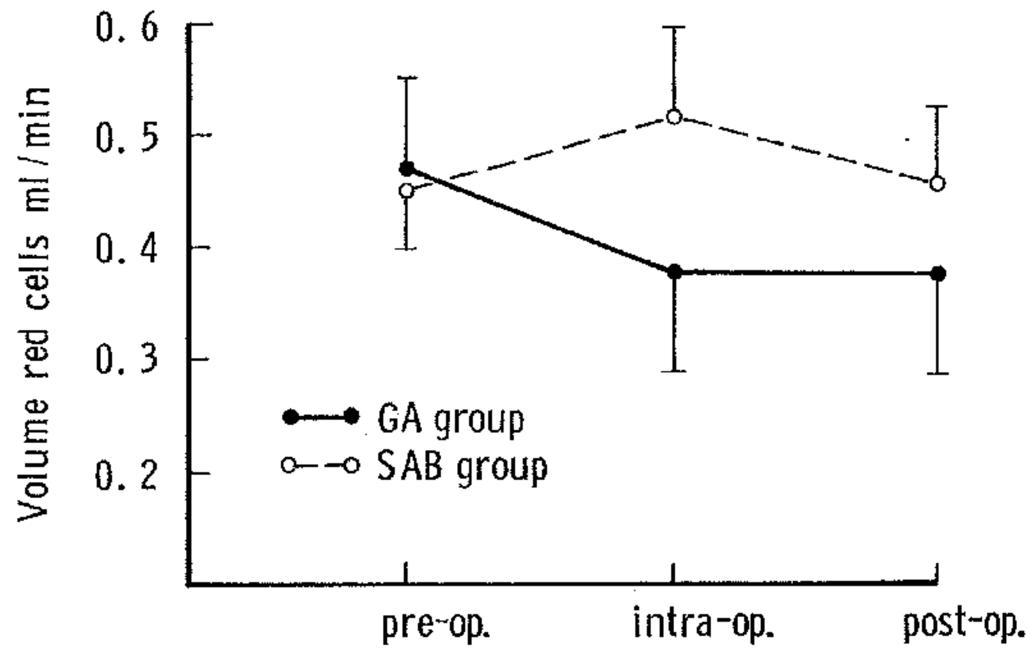
Measured whole blood viscosity fell significantly after spinal anaesthesia and the effect persisted into the post-operative period. No changes in measured viscosity were seen in the GA group.

Unquestionably, the changes were mainly the result of reduction in haematocrit. However when this effect is eliminated there remains a significant difference in viscosity between the groups at the time of the post-operative sample. As plasma fibrinogen levels were unchanged, the difference in viscosity is almost certainly explained by the changes in red cell deformability. Although these changes in deformability were most marked intra-operatively, deformability remained significantly different between the groups post-operatively.

	GA (n=10)	SAB (n=10)
Pre-operative	3.2 +/- 0.7	3.5 +/- 0.9
Intra-operative	3.2 +/- 0.4	3.5 +/- 0.8
Post-operative	3.3 +/- 0.6	3.6 +/- 0.8

FIBRINOGEN glitre^{-1} (mean +/- S.D.)

TABLE 19



Red cell deformability (mean ± 1 S. D.)

FIGURE 9

	GA Group (n=10)	SAB Group (n=10)
Pre-op	0.48 +/- 0.07	0.45 +/- 0.06
Intra-op	0.37 +/- 0.08	0.52 +/- 0.08
Post-op	0.37 +/- 0.07	0.45 +/- 0.08

RED CELL DEFORMABILITY (mean +/- 1 S.D.)

volume of red cells (ml/min)

TABLE 20

The increased deformability may well have been an important contributary factor in the fall in viscosity in the SAB group, although the fall in "corrected" viscosity did not achieve statistical significance. The decreased deformability after general anaesthesia is reflected in the rises in "corrected" viscosity. Thus, if haematocrit had remained constant, patients in the GA group would have had a rise in whole blood viscosity.

The implications of these results can be viewed firstly in the context of the effect of changes in viscosity on flow in the deep veins and thus liability to DVT, and secondly for the possible implications as regards perfusion of the micro-circulation of vital organs.

The significant fall in viscosity in the SAB group might be expected to improve blood flow to the limbs, reduce venous stasis and reduce the incidence of DVT. Viscosity differences were thus very likely to have been a significant factor in the difference in DVT incidence seen between the anaesthetic groups (chapter 3). The studies by Dormandy and Edelman (1973) and Loudon et al (1978) strongly support a direct relationship between viscosity and liability to DVT. However, Janvrin, Davies and Greenhalgh (1980) found a higher incidence of DVT in patients given intravenous fluid compared with a control group kept "dry" in a study of patients having various abdominal surgical operations. Despite a lower haematocrit, the group given fluid were found to be more hypercoagulable. Tocantins, Carroll and Holburn (1951) found that dilution of blood accelerated coagulation. This work requires further confirmation as the findings are somewhat bizarre.

The clinical importance of the changes in red cell deformability changes is not fully understood. Dintenfass (1981) considered that the deformability of red cells would have a great effect on flow in small vessels as the apparent viscosity of blood rises suddenly and dramatically below a certain blood vessel diameter. The diameter at which this phenomenon occurs is critically dependent on the deformability of the red cells. Thus the effects of spinal anaesthesia on red cell deformability may be important in perfusion of the microcirculation. Improved myocardial perfusion and reduced peripheral resistance could be expected to improve cardiac output and further improve lower limb blood flow.

Evidence is now emerging that where there is compromised circulation, the rheological properties of the blood may be critical in determining the adequacy of perfusion. Bailey, Yates, Johnston et al (1979) examined healing of amputations in diabetic patients and found a direct correlation between pre-operative haematocrit and success of operation. All 18 amputations done in patients with a pre-operative haemoglobin less than 12.0 g $dlitre^{-1}$ healed successfully, whilst all 30 amputations in patients with a pre-operative haemoglobin greater than 13.0 g $dlitre^{-1}$, failed to heal. They concluded that the most likely explanation for this was the correlation between viscosity and blood flow.

A very close correlation has been shown between haemoglobin, blood viscosity and total cerebral blood flow (Thomas, Marshall, Ross Russell et al, 1977), demonstrating that haemodilution resulted in an overall improvement in oxygen delivery. In patients with intermittent claudication (Yates, Andrews, Berent et al, 1979), reduction of haematocrit resulted in a rise of 13% in actual haemoglobin delivery at rest, and 100% rise in delivery at peak flow.

While the present study seems the only one to document comparative viscosity changes with regional and general anaesthesia, other studies have examined the effects of general anaesthesia on viscosity. However, limitations in methodology used renders meaningful interpretation difficult in many cases. Firstly, the published evidence on the effects on viscosity of anaesthetic agents used in the present study will be considered and then the evidence existing about other anaesthetic agents will be briefly presented.

[4.8] General Anaesthetic Agents and Viscosity

a) Althesin (alphaxolone-alphadolone)

Althesin was the induction agent used in the GA group in the present study. It is a mixture of two steroid agents in a solubilising agent, cremophor. (Althesin is currently unavailable in Britain having been withdrawn by the manufacturers because of continuing reports of adverse reactions thought to be associated with the solubilising agent). Gramstad and Stovner (1979) found that plasma viscosity decreased significantly after induction with althesin and diazepam. This effect was also seen when any agents containing cremophor were added to blood "in vitro". However, the results must be viewed with suspicion as the authors used the Wells-Brookfield cone-in-plate viscometer which is recognised to be inaccurate at the low shear rates used (Gordon and Ravin, 1978). Orr, Davidson, Russell et al (1982) repeated the study using an althesin infusion to induce anaesthesia and found only a very small reduction in whole blood viscosity which was only significant at one shear rate (0.945 sec^{-1}). They also found that red cell deformability was unchanged. Studies "in vitro" revealed that when haemodilutional effects were eliminated, plasma viscosity was not reduced by the addition of cremophor or althesin. The small reductions in haematocrit and plasma viscosity they observed in vivo, were considered to be secondary to the effects of sedation and the vasodilatation resulting from it, which might be expected to lead to a redistribution of extra-cellular fluid into the intra-vascular compartment. The converse of this has been demonstrated by Cohn (1966) who found that vasoconstriction raised haematocrit.

As althesin has a short plasma half-life, any effect it might have had on viscosity would be expected to have disappeared by the time the intra-operative sample was taken in the present study.

b) Halothane.

Halothane, the volatile halogenated anaesthetic agent, was used to maintain anaesthesia in the present study. Aronson, Levesque, Charm et al (1968) could find no change in blood viscosity at a variety of shear rates when halothane was added to whole blood in vitro. However, that study used the Wells-Brookfield viscometer which is inaccurate at low shear rates. Magora, London, Eimerl et al (1974) found a significant reduction in whole blood viscosity in patients under halothane anaesthesia. However, they also found a significant reduction in haematocrit and fibrinogen levels indicating haemodilution and the reduction in viscosity might be entirely attributed to this effect. They did not examine red cell deformability and also used the Wells-Brookfield viscometer. The reduction in viscosity was only apparent at two relatively high shear rates (46 sec^{-1} and 230 sec^{-1}).

Drummond, Drummond, McKenzie et al (1980) have shown a dose-related decrease in red cell deformability when halothane was added "in vitro" to whole blood, in concentrations similar to those found in clinical situations confirming the effects seen in the present study. Albert, Jain and Shadid (1964) found a decrease in blood viscosity during anaesthesia with halothane but did not take account of differing shear rates thus rendering the results of dubious value.

c) Nitrous oxide.

There seems to be no evidence whatsoever in the literature on the effects of nitrous oxide on blood viscosity.

d) Other anaesthetic agents.

Magora et al (1974) found that blood viscosity decreased during anaesthesia with cyclopropane. However, after thiopentone they showed that there was no change in viscosity despite a reduction in haematocrit. Viscosity was unchanged after ketamine and was associated with an increase in haematocrit. It is difficult to draw conclusions from these measurements as values were not corrected to a standard haematocrit and red cell deformability was not measured. Aronson et al (1968) find no effect of cyclopropane on viscosity at differing shear rates when added to blood "in vitro", but found a small trend towards reduced plasma viscosity with methoxyflurane.

[4.9] Mechanisms of Effect of Anaesthetic Agents on Blood Viscosity

Administration of spinal or epidural anaesthesia is usually accompanied by the administration of intravenous fluids to compensate for the expansion of intravascular volume caused by sympathetic blockade. This will tend to decrease haematocrit as seen in the present study. The effect is more marked in the elderly, as cardio-vascular compensatory reflexes are less efficient and less tolerant of changes in blood volume and hence patients require the administration of fluid (or vasopressor drugs) to maintain arterial pressure. As discussed earlier, vasodilatation may also cause a secondary fall in haematocrit consequent on reduced intra-vascular hydrostatic pressure.

Changes in deformability of red cells may be due to effects on the red cell membrane, haemoglobin, or the structural protein, spectin. However, explanation of the changes seen must inevitably be speculative but there is some supportive evidence.

Rosenburg (1980) found that halothane had a bi-phasic, dose-dependant action on membrane fluidity. Low concentrations of halothane caused decreased fluidity of a lipid bi-layer membrane but higher concentrations caused increased fluidity. Whether these results are relevant to erythrocyte membranes is not clear. However, in studies more relevant to the red cell membrane, Seeman and Roth (1972) found low concentrations of volatile anaesthetics to be anti-haemolytic but higher concentrations were in fact directly haemolytic, clearly implying some kind of effect on the membrane.

Internal structural alterations of the red cell are considered by Dormandy, Yates and Berent (1981) to be a possible mechanism of changes observed in red cell deformability. Barker, Brown, Drake et al (1975) observed changes in conformation of the haemoglobin molecule when exposed to clinical concentrations of halothane.

The changes in red cell deformability after spinal anaesthesia have not been documented previously and thus no work exists on their aetiology. However, the changes might be considered to be due to a primary effect of systemically absorbed local anaesthetic (although it is not known whether the local anaesthetic used in this study is, in fact, absorbed in significant concentrations). Another possible explanation might be a secondary effect by mechanisms as yet unknown but which possibly could include hormonal factors.

There is evidence that local anaesthetic agents have direct effects on the erythrocyte membrane. Seeman (1966) has shown that low concentrations of local anaesthetic agents, including cinchocaine, protect or stabilise human erythrocytes against haemolysis, whereas higher concentrations elicit a detergent haemolysis. Local anaesthetic agents are also known to affect sodium and potassium flux in human red cells (Andersen, 1968), which could have an effect on membrane fluidity. Local anaesthetic agents can also inhibit glucose transport in human erythrocytes (Lacko, Wittke and Lacko, 1978) and it is interesting that diabetic patients have reduced red cell deformability (Barnes, Locke, Scudder et al, 1976).

[4.10] Conclusions

The viscosity changes seen in the present study are in line with the differing incidence of DVT between the two anaesthetic groups. Spinal anaesthesia would appear to produce changes which are theoretically beneficial to blood flow in all parts of the circulation. The mechanisms of these changes are partly due to the alterations in haematocrit, but the increase in red cell deformability may also be of importance.

General anaesthesia, while not actually raising whole blood viscosity in this study, produced undesirable changes in red cell deformability which might be harmful in circumstances where perfusion of the microcirculation was already compromised and could contribute to the risk of post-operative thromboembolic complications. Where increased viscosity already exists or there is already reduced red cell deformability, as in diabetes (Barnes et al, 1976) then the use of halothane anaesthesia might be considered to be contra-indicated.

It must be noted that the number of patients studied was relatively small and confirmation of the results with larger numbers would seem advisable in the future.

The field of haemorheology and anaesthesia is relatively unexplored, and the possibilities for further research are considerable. Confirmation is needed of the results seen in the present study in different groups of patients and with different anaesthetic techniques, for example epidural anaesthesia. Investigation of mechanisms underlying the changes seen would be of great interest. Changes in viscosity and the effects on organ perfusion in the anaesthetised subject have not been explored, to the author's knowledge, although the difficulties of such studies are apparent. It is not possible to guess with the current state of knowledge, whether this whole area of research will ultimately prove to be of great importance to the anaesthetist but some of the studies presented have revealed fascinating and unsuspected effects of commonly used agents and techniques of anaesthesia.

CHAPTER 5

LONG TERM FOLLOW-UP AFTER SPINAL OR GENERAL ANAESTHESIA FOR REPAIR OF FRACTURED NECK OF FEMUR

[5.1] Introduction

When the studies comprising this thesis were commenced, long term follow-up of patients was not invisaged. However, short-term follow-up of the first 50 patients for 28 days after operation showed a trend, not statistically significant, towards a difference in mortality rates between the groups. When a larger number of patients were studied the difference was statistically significant. The pattern of mortality results was broadly similar to that found by McLaren et al (1978) in a study of spinal and general anaesthesia for repair of fractured neck of femur.

Because results in terms of early post-operative mortality were significantly better after spinal anaesthesia, the further use of general anaesthesia for the patient with hip fracture might be deemed unethical. However, it seemed that longer term, more detailed follow-up of the patients already studied was necessary before such a conclusion could be drawn. It was for these reasons that the follow-up study presented in this chapter was conducted retrospectively. It was decided that follow-up should be mainly aimed at the aquisition of "hard" data, for example death or survival, place and date of death or location of survivors. Any other information gathered would necessarily be of less value than if it had been gathered on a prospective basis.

[5.2] Patients and Methods

150 patients presenting for pin and plate repair of fractured neck of femur were allocated randomly to receive general or spinal anaesthesia as previously described. In 2 patients in the SAB group the sub-arachnoid space could not be identified. These patients were excluded from the study, and received general anaesthesia.

Follow-up was accomplished by perusal of case records and subsequently by questionnaire to patients' general practitioners and/or appropriate hospitals or institutions. In 3 patients it was necessary to obtain copies of death certificates from the Registrar General of Births, Marriages and Deaths as, in some cases, patients' General Practioner records had been destroyed after death. The cause of death was sought in all instances but in very few patients had autopsy examinations been carried out. The causes of death therefore, were based on the clinical impression of the certifying doctor and undue emphasis should not be placed on the accuracy of diagnosis.

Predicted mortality rates were derived by computing expected mortality in age bands for males and females for a population of similar size, age and sex distribution to that of the study population. Population mortality statistics were derived from the Annual Report of the Registrar General for Scotland, 1973.

[5.3] Results

Table 21 shows the age and sex distribution of the patients studied for each anaesthetic group. There were no significant differences in overall age or sex distribution (by chi-square test), with, as expected, approximately 74% of patients being female. Other general details of the patients studied are shown in table 22. There were no significant differences in intra-operative blood loss, duration of surgery or interval between admission and surgery. Mean pre-operative serum urea was significantly higher in the SAB group. Table 23 shows pre-operative "fitness" scores in a similar manner to that described in previous chapters. There were no significant differences between the groups in distribution of overall or specific system scores (by chi-square test).

The number of times in each group that the more common medical problems were present pre-operatively are displayed in table 24. When patients had more than one major problem this was added under each heading, thus the figures do not represent the numbers of patients but the number of times that the conditions were recorded. In a similar manner, common long term drug therapy in each group is shown (table 25). Too much emphasis should not be placed on tables 24 and 25 as they are only intended as an illustration of the general status of the study population.

Table 26 shows the sources from which patients were admitted in each anaesthetic group and there were no significant differences in the distribution of sources. In the general anaesthetic group 24 patients (34.8%) had a cervical fracture and 45 patients (65.2%) had a trochanteric fracture.

	GA			SAB		
(years)	M	F	Total	M	F	Total
< 65	7	5	12	8	3	11
65 - 69	0	4	4	0	11	11
70 - 74	6	11	17	4	4	8
75 - 79	3	13	16	4	9	13
80 - 84	0	8	8	3	12	15
85 - 89	1	11	12	2	5	7
90 +	0	6	6	1	7	8
Total	17	58	75	22	51	73

AGE AND SEX DISTRIBUTION

TABLE 21

	GA (n=75)	SAB (n=73)
Age (y)	74.2 +/- 1.7	75.4 +/- 1.4
Intra-operative blood loss (ml)	261 +/- 37	278 +/- 36
Duration of surgery (min)	77.2 +/- 3.2	82.2 +/- 2.6
Interval between admission and surgery (days)	1.9 +/- 0.2	2.0 +/- 0.2
Serum urea (mmol $litre^{-1}$)	6.0* +/- 0.3*	7.9* +/- 0.5*

* $p < 0.01$

GENERAL DETAILS OF PATIENTS STUDIED (mean +/- SEM)

TABLE 22

Fitness Scores	"1"		"2"		"3"	
(see Chapter 1)	GA	SAB	GA	SAB	GA	SAB
"Overall" scores	34	38	32	25	9	10
CVS scores	51	44	22	26	2	3
CNS scores	45	47	29	24	1	2
RS scores	62	56	9	13	4	4

NUMBER OF PATIENTS ALLOCATED TO EACH "FITNESS" SCORE

TABLE 23

	GA Group	SAB Group
Chronic obstructive airways disease	12	8
Active chest infection	4	2
Hypertension	6	4
Cardiac failure	3	6
Atrial Fibrillation	2	5
Raised Serum Urea (> 5 mmol litre^{-1})	27	36
Anaemia (Hb < 10 d litre^{-1})	4	3
Previous Cerebro-vascular accident	3	6
Previous Myocardial Infarction	3	1
Diabetes	2	3
Carcinoma	1	2

ASSOCIATED MEDICAL PROBLEMS - (pre-operative)
Number of patients in whom they occurred

TABLE 24

	GA Group	SAB Group
Diuretics	11	23
Digoxin	3	5
Oral diabetic therapy	1	3
Anti-hypertensive drug	1	1
Beta - blockers	0	11

SOME PRE-ADMISSION DRUG THERAPY
Number of patients taking each category of drug

TABLE 25

	GA (n=75)	SAB (n=73)
Home	64	66
Psychogeriatric	7	4
Geriatric care	4	3

SOURCE OF PATIENTS

TABLE 26

In the SAB group 24 (37.5%) had a cervical fracture and 40 (62.5%) had a trochanteric fracture. In 6 patients from the GA group and in 9 patients from the SAB group, the site of fracture was not determined from the notes. The distribution of sites of fracture was not significantly different between the two anaesthetic groups.

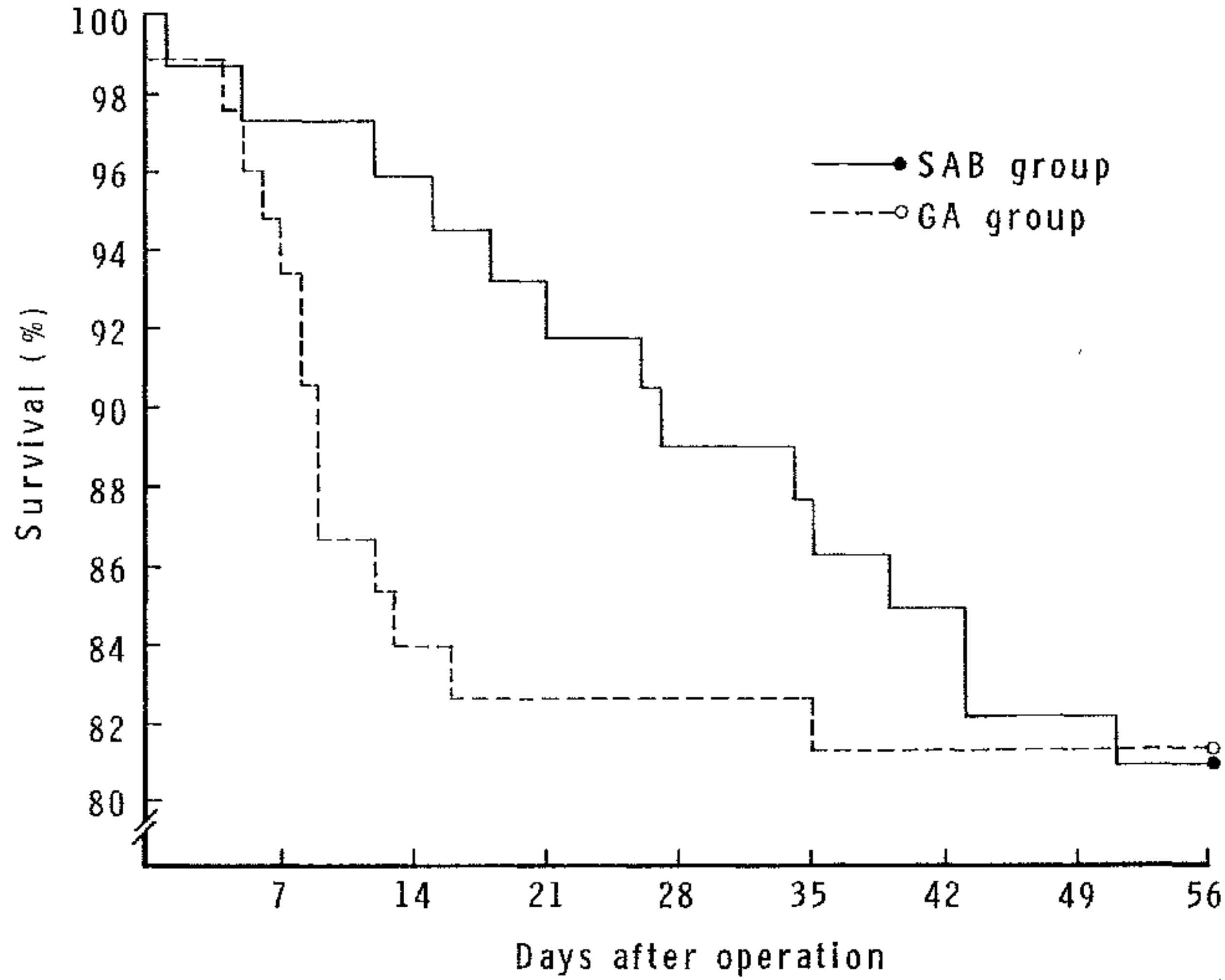
[5.4] Post-operative Mortality

Figure 10 displays the percentage survival in each anaesthetic group over the first 56 days after operation. There is a significant difference in the distribution of time of deaths between the anaesthetic groups. Between days 13 and 14, and 16 and 17, cumulative mortality is significantly lower in the SAB group ($p<0.05$) by Chi-square test with Yates' correction. The majority of the deaths are clustered between the 5th and 16th post-operative days in the GA group. There is no such pattern in the SAB group.

Despite these differences in early post-operative mortality, by 56 days after operation the survival rates in each group had become virtually identical.

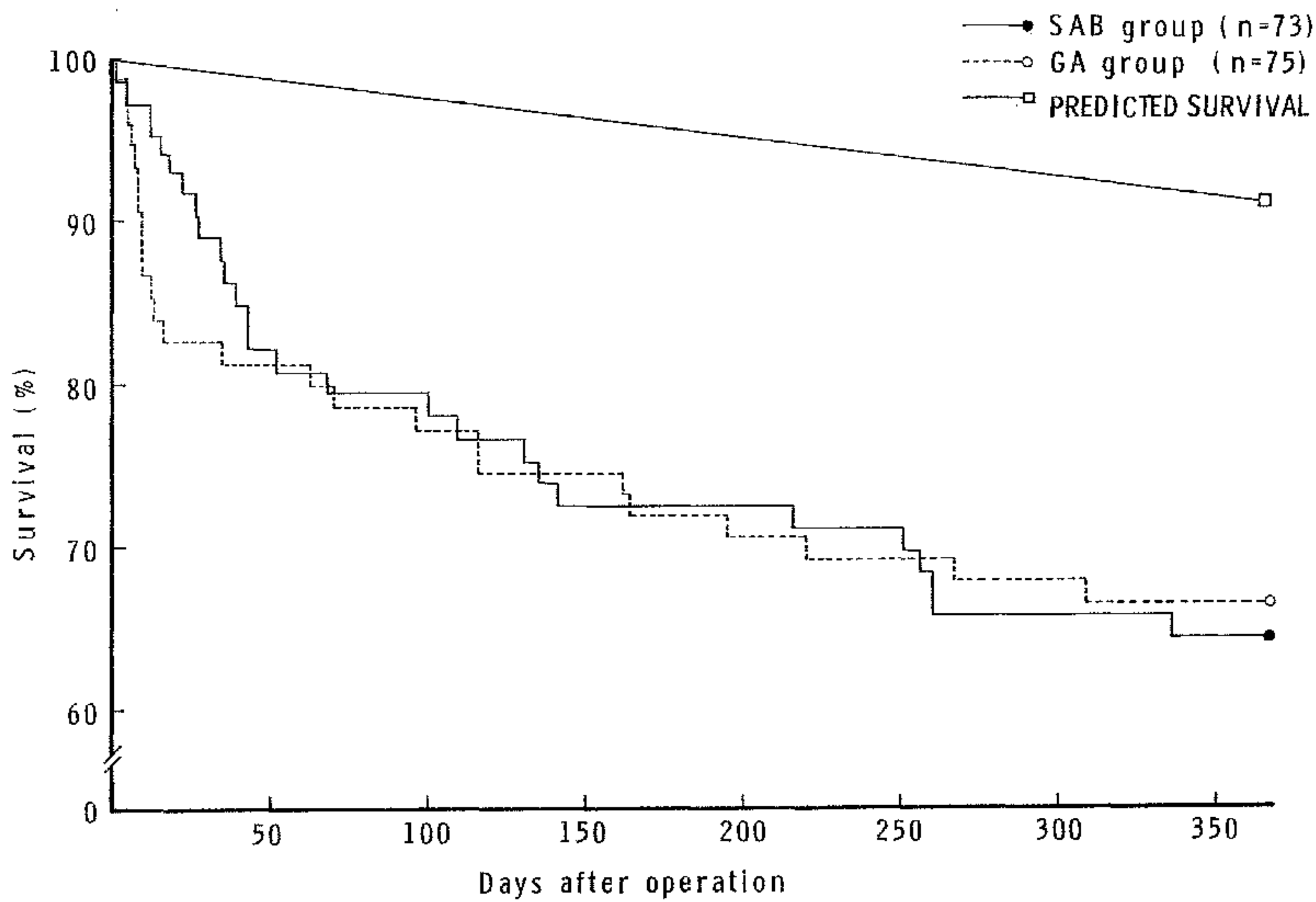
Observed and predicted survival rates for each group, over the first year after operation are displayed in figure 11. Table 27 shows the predicted number of deaths in the study groups in one year.

The monthly mortality rates in the study groups had returned to approximately equal to, or below, that predicted for the study population by the 8th month in both groups.



Survival over first 56 days after operation

FIGURE 10



Observed and predicted survival over year following operation

FIGURE 11

	GA (n=75)		SAB (n=73)	
	Male	Female	Male	Female
Predicted Annual number of Deaths	1.043 (6.14%)	5.680 (9.8%)	2.033 (9.25%)	4.648 (9.1%)
Total (m + f)	6.723 (8.96%)		6.681 (9.15%)	

AGE STANDARDISED PREDICTED MORTALITY
(based on Scottish Mortality Statistics, 1973)

TABLE 27

Mortality rates, in age groups, at 28, 100 and 365 days after operation are shown in tables 28 to 30. As expected, mortality rose with increasing age, but numbers in the sub-groups are too small for statistical validity.

Recorded causes of all deaths and the days on which they occurred are shown for each anaesthetic group in tables 31 and 32.

Table 33 relates mortality in the first 28 days and over the rest of the first post-operative year, to pre-operative system scores. Although mortality rates are higher in the groups with poorer "fitness" scores, these results do not achieve statistical significance. There are also no significant differences between anaesthetic groups in mortality rates in each "fitness" category (by chi-square test).

Mortality rates over the first 28 days in each anaesthetic group related to the site of fracture are shown in table 34 but no conclusions can be reliably drawn as numbers in the sub-groups are small.

The eventual location of survivors at the end of the year and the place of death of those not surviving are shown in table 35. Mean length of stay (+/- S.E.M.) in acute hospitals including patients who died, was similar, being 42.9 (+/- 7.9) days in the GA group and 38.8 (+/- 6.5) days in the SAB group. Mean length of stay in acute plus convalescent hospital care was, however, 82.9 (+/- 13.2) days in the GA group and 85.9 (+/- 13.3) days in the SAB group and there was also no significant difference between the groups in this respect.

Age (y)	GA Group	SAB Group
< 70	0 (0%)	0 (0%)
70 - 79	5 (15.1%)	2 (9.5%)
80 - 89	5 (25%)	3 (13.6%)
90 +	3 (50%)	3 (37.5%)
	13 (17.33%)	8 (10.9%)

DEATHS RELATED TO AGE. DAYS 0-28 AFTER OPERATION

TABLE 28

Age (y)	GA (n=75)	SAB (n=73)
< 70	0 (0%)	1 (4,5%)
70 - 79	8 (24.2%)	3 (14.3%)
80 - 89	5 (25%)	6 (27.2%)
90 +	4 (66.6%)	6 (75%)
	17 (22.66%)	16 (21.9%)

DEATHS RELATED TO AGE. DAY 0-100 AFTER OPERATION

TABLE 29

Age (y)	GA (n=75)	SAB (n=73)
< 70	1 (6.25%)	3 (13.6%)
70 - 79	12 (36.4%)	7 (35%)
80 - 89	7 (35%)	10 (45.4%)
90 +	5 (83.3%)	6 (75%)
	25 (33.3%)	26 (35.6%)

DEATHS IN FIRST YEAR AFTER OPERATION

TABLE 30

Causes of Death GA Group

No. of days after operation	Age	Sex	Recorded Cause of Death
0	89	F	Carcinoma, CCF, Haematemesis
4	87	F	CVA, Bronchopneumonia
5	85	M	PTE, pneumonia
6	86	F	Bronchopneumonia
7	91	F	PTE
8	74	M	Bronchopneumonia
8	74	F	? PTE
9	92	F	Pneumonia
9	78	M	Aortic thrombosis
9	74	F	Bronchopneumonia
12	73	F	Myocardial Infarction, CCF
13	92	F	Not known
16	88	F	Not known
35	91	F	Uraemia
63	73	F	Bronchopneumonia
70	75	M	Bronchopneumonia
96	75	F	Not known
116	72	M	Carcinoma
116	50	M	CVA + pulmonary oedema (autopsy)
162	78	F	Bronchopneumonia
164	87	F	Bronchopneumonia
195	73	M	Ruptured aortic aneurysm
221	75	F	Bronchopneumonia
267	87	F	Bronchopneumonia
308	95	F	Myocardial Infarction

Abbreviations: CCF Congestive cardiac failure
CVA Cerebro vascular accident
PTE Pulmonary thrombo embolism

RECORDED CAUSE AND TIME OF DEATH
GA Group

TABLE 31

Causes of Death SAB GROUP

No. of days after operation	Age	Sex	Recorded Cause of Death
1	92	F	Carcinoma, CCF
5	78	F	Pneumonia
12	84	F	Bronchopneumonia
15	87	M	Pneumonia, CCF
18	92	F	? CCF
21	90	F	Bronchopneumonia
26	76	M	PTE
27	83	F	Endotoxic shock, Cholecystitis
34	84	F	PTE
35	94	M	Left ventricular failure
39	94	F	Myocardial Infarction
43	77	M	Renal and hepatic failure
43	93	F	Aortic thombosis
51	81	F	? CCF
68	85	M	? Bronchopneumonia
100	67	F	Bronchopneumonia
109	88	F	Bronchopneumonia
131	63	F	Lymphosarcoma
135	82	F	CVA
141	81	M	? Pneumonia
216	78	F	Bronchopneumonia, CVA
251	78	F	Carcinoma
256	65	F	Pneumothorax
260	75	F	Bronchopneumonia
260	73	F	CVA
336	80	F	Bronchopneumonia

RECORDED CAUSE AND TIME OF DEATH

SAB Group

TABLE 32

FITNESS SCORES (see chapter 1)		"1" GA	"1" SAB	"2" GA	"2" SAB	"3" GA	"3" SAB
"Overall" scores	Total Allocated	34	38	32	25	9	10
Deaths (days)	0 - 28	3	2	5	3	5	3
	29 - 365	5	7	6	7	1	4
		8	9	11	10	6	7
CVS scores	Total Allocated	51	44	22	26	2	3
Deaths (days)	0 - 28	7	2	5	5	1	1
	29 - 365	8	11	3	6	1	1
		15	13	8	11	2	2
CNS scores	Total Allocated	45	47	29	24	1	2
Deaths (days)	0 - 28	5	7	8	1	0	0
	29 - 365	6	7	5	11	1	0
		11	14	13	12	1	0
RS scores	Total Allocated	62	56	9	13	4	4
Deaths (days)	0 - 28	9	5	1	1	3	2
	29 - 365	11	12	1	5	0	1
		20	17	2	6	3	3

NUMBER OF PATIENTS DYING IN EACH ANAESTHETIC GROUP RELATED TO PRE-OPERATIVE FITNESS SCORING ALLOCATION

TABLE 33

	GA Group			SAB Group		
SITE	Cervical	Trochanteric	Not Recorded	Cervical	Trochanteric	Not Recorded
Deaths	2 (8.3%)	10 (22.2%)	1	4 (16.6%)	4 (10%)	0

DEATHS RELATED TO SITE OF FRACTURE IN DAYS 0 - 28 AFTER OPERATION.

Percentage of deaths from each group

TABLE 34

	GA n = 75		SAB n = 73	
	Survivors	Deaths	Survivors	Deaths
Home	37	2	32	3
Community Care	3	-	3	-
Acute Hospital	-	17	-	16
Non-acute General Hospital	4	2	5	4
Psychogeriatric Hospital	4	4	3	3
Outcome not known	2		4	

LOCATION OF SURVIVORS AT THE END OF ONE YEAR AND NUMBER AND PLACE OF DEATHS

TABLE 35

8 patients in the GA group required psychogeriatric care but 6 of these had been admitted from such institutions. In the SAB group, 6 required psychogeriatric care, from which 4 of these had been admitted.

2 patients in the GA group and 6 in the SAB group required re-operation of the fracture repair.

[5.5] Discussion

The most important findings of this study are, that while spinal anaesthesia is associated with a significantly lower early post-operative mortality than general anaesthesia, the long term mortality and outcome of both anaesthetic groups are virtually identical. Discussion of the pattern of early post-operative mortality is of interest, despite the fact that the differences observed are short lived and would have been most misleading if follow-up had not been of sufficient duration.

[5.6] Early Post-operative Mortality

It is important to emphasise that discussion of factors leading to the differences seen in mortality rates between the anaesthetic groups in the early post-operative period, are speculative and by no means proven. However, from the data already presented in earlier chapters of this thesis and from other sources, a very plausible working hypothesis may be presented which would however, be extremely difficult to prove conclusively.

The hypothesis is that the differences in mortality rates can be explained by differences in the frequency of thrombo-embolic phenomena.

The differences between the groups in respect of DVT have been discussed at length in chapter 3 and probably offer the strongest supportive evidence for the hypothesis.

Fatal pulmonary thrombo-embolism would seem more likely in the group with the higher incidence of DVT although, as discussed earlier (chapter 3), this is not an assertion one can make with certainty and a reduction in DVT incidence is not necessarily accompanied by a reduction in overall mortality.

A full discussion about blood viscosity has already been presented but it is worth re-iterating that, apart from effects on liability to DVT and thus, pulmonary thrombo-embolism, changes in blood viscosity might be expected to affect perfusion and risk of thrombosis in the arterial system. Thus, incidence of myocardial infarction and cerebro-vascular accident might be affected. The changes in viscosity found are certainly in line with the working hypothesis, as is the other evidence (already presented) of different changes in blood coagulability associated with the anaesthetic techniques.

The clustering of deaths in the GA group between the 6th and 16th post-operative days is classically that thought to be characteristic of pulmonary thrombo-embolism. There is no such pattern of clustering in the SAB group.

The lists of causes of death in the first 28 days after operation (tables 31 and 32) certainly show a preponderence of thrombotic and thrombo-embolic causes of death in the GA group. However because of the inaccuracy of recorded cause of death in the absence of post-mortem examination, and because, for example, pulmonary embolism may be misdiagnosed as pneumonia (and vice versa) no great weight may be attributed to this evidence.

In order to prove the hypothesis, post-mortem examination would need to be performed on all patients dying in the first month or so after surgery, in both anaesthetic groups. It would, to say the least, be difficult and costly to mount such an exercise, and it has not, to the author's knowledge, been attempted in any study invoving comparisons of anaesthetic technique. Riska (1970) studied 470 patients with fractured neck of femur and obtained post-mortem examinations in 82 of the 87 patients who died within one month of the fracture. Pneumonia was the cause of death in 25.3% of patients, pulmonary embolus in 19.5%, stroke in 12.6%, myocardial infarction in 9.2% and a variety of other causes in the remainder.

[5.7] Other Studies

Two other studies have shown a significant effect of anaesthetic technique on post-operative mortality after fractured neck of femur.

The study by McLaren et al (1978) caused considerable interest in British anaesthetic circles. 53 patients were allocated to receive general anaesthesia (with IPPV) or spinal anaesthesia. As discussed earlier (chapter 1.9), despite substantial differences in methodology from the present study, a significantly reduced early post-operative mortality was associated with spinal (3.8%) compared with general anaesthesia (31%). The patients were, however, only followed up for 28 days, and as has become clear from the present study and that of Spreadbury (1980), that is an inadequate length of follow-up. A difference in incidence of thrombo-embolism was also considered by McLaren et al (1978) to be the most likely explanation of the mortality differences although their study did not attempt to elucidate this.

Spreadbury (1980) compared general anaesthesia including controlled ventilation (with details of techniques left to the choice of the anaesthetist) and anaesthesia with ketamine with or without diazepam. Only those previously ambulant and fit for immediate operation were included. It was thus a very selective study, and the groups were not comparable, the ketamine group having a significantly shorter mean operating time and more senior anaesthetist and surgeon. Fitness "scores" were also not equally distributed. The "relaxant" group received a variety of anaesthetic agents. However, despite these qualifications it is interesting that there was a significantly lower mortality rate in the ketamine group (3.3%) in the first 15 days after operation compared with the "relaxant" group (23.3%). However late deaths resulted in the eventual mortality rates being the same for both groups (30%). This pattern seems to be very similar to that seen in the present study although anaesthetic techniques used were completely different. Whether a difference in thromboembolic events also occurred in that study is unknown. Spreadbury condemns the technique of general anaesthesia with IPPV despite the identical long term outcome.

Other published studies comparing mortality rates after regional or general anaesthesia for fractured neck of femur have not shown any significant differences. Wickstrom, Holmberg and Stefansson (1983) compared five different anaesthetic techniques for repair of hip fracture and followed patients for 4 years after operation. 169 patients were studied and the techniques used included epidural, neurolept, ketamine, halothane and enflurane anaesthesia. No differences in outcome were found between the groups. Mortality at 1 month was only 6.5%, and at 6 months, 17.2%. 50.3% of patients were alive at 4 years after operation. Each group contained relatively few patients, numbers ranging from 19 to 54. They were significant differences in age distribution and distribution of site of fracture between the groups, thus severely limiting the interpretation and value of the study.

Davis and Laurenson (1981) in a study of 132 patients having repair of fractured neck of femur with spinal or general anaesthesia, found a mortality in the first 4 weeks after surgery of 4.7% in the SAB group and 13.2% in the GA group but this difference did not reach statistical significance.

[5.8] Long Term Outcome

In the present study, long term outcome was nearly identical in both anaesthetic groups. Mortality in the GA group "levelled off" to a certain extent about the 17th day after surgery. However, in the SAB group mortality did not begin to level off until the end of the second month (figure 11). It is difficult to explain the higher rate of mortality in the second month in the SAB group which leads to its "catching up" with the mortality of the GA group although it would seem that deaths were precipitated in the GA group while no such effect occurred in the SAB group.

The mean duration of stay when all hospital care is included is striking (84.4 days) especially when compared with a published figure of 35.3 days (Scottish Hospital Inpatient Statistics, 1978). The present study reasserts therefore the size of the problem and the enormous burden on resources that it represents.

It was not the purpose of these studies to produce predictors of outcome. However, as in other studies, mortality increases with age whether examined at 28 days, 100 days or one year after operation (tables 28-30). The extremely high mortality in the very elderly is, however, disturbing. Nonetheless it must be remembered that the operative treatment of fractured neck of femur is important as a method of pain relief, enabling mobilisation and greatly aiding nursing care. To condemn the very elderly to a miserable, immobile, painful end to their lives because of the "poor" results of operative treatment would seem most inhumane.

The trend toward an increased risk of mortality related to poor pre-operative condition is not a surprising finding. Caution must be exercised in evaluation of this aspect of the results as scores were assessed from the records after the completion of the study, and thus are not as accurate as a prospective assessment. However, in the author's opinion, they represent a useful assessment of the patients' fitness based on case histories available at the time of operation, and the scores were restricted to a scale of 1-3.

The percentage of all patients in the study who returned home was only 47.3%, a surprisingly low figure. However, this is the percentage of the whole study population. 131 patients were admitted from home and 79 (60.3%) of these returned. This compares with 70% of 50 patients in the study by Spreadbury (1980) but that study was selective and thus not comparable with the present study.

[5.9] Other Studies of Outcome Not Considering Anaesthetic Method

There is a great amount of literature on the subject of outcome after fractured neck of femur but the usefulness of any comparison of the present study with others is severely limited by the variability of many factors, including,

1. Operative or conservative treatment.
2. Delay before operative treatment.
3. Type of operative treatment.
4. Age, sex distribution and social background.
5. Length of hospitalization.
6. Type of post-operative management.
7. Length of follow-up and numbers lost to follow-up.

Further, mortality figures are frequently quoted as "hospital mortality" - a result which is meaningless as regards comparison between studies, as discharge and convalescent policies may profoundly affect the apparent results.

The mortality rates at 1 month in the present study were 11% in the SAB group and 17.3% in the GA group, an overall mortality rate of 14.2%. Riska (1970) found mortality in patients with surgically treated fractured neck of femur to be

12% at one month after operation, compared with 40% in those treated conservatively. That study included patients treated by primary hip prosthesis but this procedure was found to be associated with a slightly lower mortality rate (9.8%) although the difference was not significant.

Wickstrom et al (1982) found a mortality rate at one month of only 6.5% with a variety of anaesthetic techniques (mentioned previously). Jensen and Tondevold (1979) found a 10% mortality at one month in a large study of 1592 patients with hip fractures. Operative treatment did, however include primary prosthesis as well as "pin and plate" repair.

Mortality at 3 months after surgery was 21.6% in the present study. This compares with 22% in the study by Gordon (1971), and 17% in the large study by Jensen and Tondevold (1979). A study by Ohman, Bjorkegren and Fahlstrom (1969) found a mortality of 11.4% at 3 months. Karumo (1977) also found a low mortality at 3 months of 11.5%, but over 50% of patients received prophylactic oral anti-coagulation and this may well have been a crucial factor in the improved survival.

The mortality rate at one year after surgery is also quoted by several authors. In the present study it was 33.1%. Ohman et al (1969) found it to be 20% at one year, Beals (1972), 50%, Gordon (1971), 36.2%, Colbert and O'Muircheartaigh (1976), 28%, Jensen and Tondevold (1979), 27%, and Wickstrom et al (1982), 24.9%.

Return of observed mortality rates to that predicted for the study population was found to occur at 3 months after fracture by Alffram (1964). Colbert and O'Muircheartaigh (1976) found it to be at 6 months and Jensen and Tondevold (1979) at 1.6 years. This compares with approximately 8 months overall in the present study.

In summary, it appears that overall mortality results in the present study are broadly comparable with other published studies, bearing in mind the many variables that exist between studies. Further investigation of any effect of variation in general anaesthetic technique, particularly the use of controlled ventilation and muscle relaxants would seem indicated, particularly as the use of such techniques is considered by some anaesthetists to be desirable for many patients undergoing repair of hip fracture.

Comparison of length of stay is almost meaningless as it is affected by so many variables including available convalescent facilities. However one other study (Jensen and Tondevold, 1979) found mean stay in the acute hospital to be 24 days, compared with 42.9 days in the present study.

The percentage of patients admitted from home who returned there was 60.3% in the present study. Other quoted figures vary considerably, possibly because they often omit to say whether they include patients admitted from home. Various percentages of patients returning home are: 46% (Camblin, 1974), 52% (Poigenfurst and Schnabl, 1977), 55% (Smith and McLaughlan, 1975) and 67% (Ceder, Elmqvist and Svenson, 1981). Ceder , Lindberg and Odberg (1980) found that, in two series, 48% returned home in 1966 and 66% in 1972-1973. Jensen, Tondevold and Sorenson (1979), however, found that 82.4% of patients who had come from home returned there.

[5.10] Conclusions

The present study has demonstrated a high mortality and prolonged hospital stay in both anaesthetic groups with only 60.3% of those admitted from home returning there. There is, however, a significant reduction in early post-operative mortality in the SAB group for which the hypothesis of a difference in incidence of thrombo-embolic events has been put forward and supportive evidence presented.

Whether the reduction in early mortality associated with spinal anaesthesia is important is debatable but, certainly, spinal anaesthesia does not seem, on present evidence, to confer any long term benefit. It is not possible to say from the present study whether any individual patients might benefit. However, the difference in early mortality is of considerable theoretical interest, along with the confirmatory evidence presented in previous chapters and the possible implications for other groups of patients. Studies to show whether any long term advantages accrue in other groups of patients are required.

Studies are also required to assess whether spinal anaethesia is associated with reduced morbidity, with particular respect to confusional states in the elderly. Evidence exists of the superiority of epidural anaesthesia in this respect (Hole, Terjesen and Breivik, (1980). Only anecdotal evidence, based on feedback from nursing staff already aware of the anaesthetic technique used and the notoriously unreliable "clinical impression", has suggested the superiority of spinal anaesthesia in terms of a reduced incidence of confusional states after repair of fractured neck of femur. Any such study would need most careful psychological assessments before and after surgery by observers unaware of the anaesthetic technique used.

It may well be that there are advantages of spinal anaesthesia yet to be demonstrated, including effects on post-operative morbidity or mortality but, in the opinion of the author, the present study does not seem to support the view that spinal anaesthesia is an inherently superior technique to general anaesthesia for patients with fractured neck of femur.

CHAPTER 6

CHOICE OF ANAESTHETIC TECHNIQUE FOR PATIENTS HAVING REPAIR OF FRACTURED NECK OF FEMUR

[6.1] Introduction

There are a variety of anaesthetic techniques, in addition to those used in the studies comprising the present thesis, which could be used in patients having repair of fractured neck of femur. These include total intra-venous anaesthesia, local nerve blocks (femoral and sciatic), local anaesthetic infiltration and epidural anaesthesia and suitable combinations and permutations of these techniques. With the possible exception of epidural anaesthesia, none of the alternatives seems popular for this particular application in current British anaesthetic practice. In theory, many of the advantages and disadvantages of subarachnoid spinal anaesthesia will apply to epidural anaesthesia but the latter can be prolonged as necessary if a catheter is inserted into the epidural space. It is, however more likely to pose technical difficulty than spinal anaesthesia in the elderly patient with arthritic changes in the spine.

It is proposed, therefore, to restrict discussion on the choice of anaesthetic technique for fractured neck of femur to the comparative advantages and disadvantages of spinal and general anaesthesia, bearing in mind the findings already presented. In order to attempt to clarify discussion, the aspects will be presented under appropriate sub-headings.

[6.2] Duration of anaesthesia

Spinal anaesthesia administered as a single injection into the cerebro-spinal fluid (CSF) clearly has a limited duration of action. The duration will depend on many factors (Bryce-Smith, 1976) including the drug chosen, dose and volume injected, addition of vasoconstrictor, speed and site of injection, specific gravity relative to CSF, positioning of the patient, use of barbotage and use of supplementary analgesia or sedation. It is possible to insert a catheter into the C.S.F. for prolonged anaesthesia but this practice was abandoned many years ago because of the risk of severe "spinal" headache. The practical time limit of spinal anaesthesia is around 3 hours with a "high" block, but for the drug and dosage used in the present study, experience suggests a duration between 2 and 3 hours. This may be fairly close to the actual operating time required in many cases, and may be considered a source of anxiety to the anaesthetist. In the present study, duration of anaesthesia was adequate in all cases, but surgery was performed by experienced surgeons and thus was relatively quick.

By contrast, general anaesthesia can be made to last (for all practical purposes) as long as required, although very long anaesthesia may be undesirable and associated with problems of prolonged recovery, temperature control, fluid balance and in extreme cases, toxic effects of nitrous oxide (if used) on bone marrow and vitamin B_{12} metabolism (Skacel, Hewlett, Lewis et al, 1983).

[6.3] Technical Difficulty

Lumbar puncture in the elderly is certainly more difficult than in the younger patient, and may, in a proportion of patients prove impossible, even to the most experienced anaethetist. By comparison, on a technical level, general anaesthesia should be achievable in some form on every patient presented, although in some cases it may prove to be a major problem. This does not imply that the safe and smooth administration of general anaesthesia in this category of patient is easy, or should be left to the inexperienced anaesthetist.

[6.4] Time Taken for Induction

Spinal anaesthesia almost always takes more time to establish than general anaesthesia. Intra-venous access must be established and the patient positioned. The anaesthetist must "scrub-up" before performing lumbar puncture, a procedure which, if difficult, may take some time to perform. Once injected, the local anaesthetic agent will then take a finite time to act, a time which varies with the drug chosen but is usually between 5 and 20 minutes.

General anaesthesia will usually be induced intravenously and the trachea intubated. This procedure is normally followed by maintenance of anaesthesia by volatile or intravenous agents, or a suitable combination. Some anaesthetists will allow administration of anaesthetic agents by face mask. The time taken for these procedures is in the order of 5 to 10 minutes. Spinal anaesthesia will typically take up to twice as long, or longer if difficulties are encountered.

[6.5] Operating conditions

In patients with fractured neck of femur, there is no evidence that either method of anaesthesia provides superior operating conditions. Both can provide an adequate degree of muscle relaxation and, as shown in the present thesis, there is no evidence of any difference in blood loss in the hip fracture patient despite findings of reduced intra-operative blood loss associated with spinal anaesthesia for hip replacement surgery (Thorburn et al, 1980). Some surgeons (and anaesthetists) may dislike operating with a conscious or semi-conscious patient as it inhibits conversation during the procedure.

[6.6] Acceptability to the Patient

Most patients in Britain expect to receive general anaesthesia for major procedures although attitudes may be slowly changing with the widespread publicity given to the use of epidural anaesthesia in obstetrics. Performance of lumbar puncture demands that a patient is either in the sitting or lateral position. The former is impractical in the patient with a hip fracture because of pain and the lateral position is used. However, turning into the lateral position can still be very painful and skilled handling is necessary to minimise discomfort. Although not used at the time of the studies in this thesis, intravenous analgesia before turning the patient is now found by the author and others to be very helpful and the use of ketamine in analgesic doses has the advantages of lack of respiratory depression and maintenance of arterial pressure. There is a risk of hallucinations and confusion (Knox, Bovill, Clarke et al, 1970), but this should be minimal with small, subanaesthetic, analgesic doses (Slogoff, Allen, Wessels et al, 1974).

The induction of general anaesthesia can usually be achieved with little or no alteration in the position of the patient in bed, and this is obviously more pleasant.

Intra-operatively, an adequate spinal block will abolish all pain and frequently all sensation from the legs and operative site. The patient will often drift off to sleep, being pain-free, possibly for the first time since the fracture. However, the operative procedure may involve noisy drilling and hammering which can be distressing to the patient. Generalised discomfort may become apparent after lying on the operating table for a period of time. These problems can be partly alleviated by judicious use of sedation and/or analgesia.

General anaesthesia, of course, is not associated with any of these problems and thus may be considerably more pleasant for the patient.

[6.7] Post-operative Recovery

General anaesthesia can be followed by a number of major and minor sequelae (Owens, 1980). Nausea and vomiting, shivering and venous thrombo-phlebitis in the arm may occur. Prolonged sedation and disturbance of psycho-motor function may also be troublesome. Post-operative hypoxaemia has been fully discussed in chapter 2 of this thesis. The incidence of chest infection after general or spinal anaesthesia appears to be similar (Urbach et al, 1964).

The action of some drugs may persist unintentionally into the post-operative period and, for example, muscle relaxant drugs may be incompletely reversed. The occurence of muscle pains afer suxamethonium should not be a significant problem in the elderly, relatively immobile, patient (Burtles and Tunstall, 1961).

The most frequent sequelae of spinal anaesthesia are persistence of sensory and motor block for a short time after operation. The former may be considered beneficial, giving analgesia, but persistent motor block can be unpleasant. The most troublesome problem following spinal anaesthesia is "spinal" headache due to loss of CSF (Morris, 1972). The frequency of this complication depends on several factors including age, gauge of needle used, speed of mobilisation and state of hydration. It is presumably less likely in the elderly immobile patient with hip fracture. The incidence was not examined in the present study but no spontaneous reports occurred.

The more serious neurological sequelae which have been attributed to spinal anaesthesia have been discussed earlier in this thesis and permanent neurological problems seem to be of extreme rarity, if they occur at all.

[6.8] Other Complications

a) General Anaesthesia

The list of possible complications of general anaesthesia is too extensive to fully discuss here. A review may be found in "A Synopsis of Anaesthesia", (Atkinson, Rushman and Lee, 1977). The more common problems include hypotension, cardiac dysrhythmias, airway problems and difficulty in reversal of muscle relaxants. More rarely there may be adverse reactions to intravenous agents (Watkins, 1979), occasionally of a serious anaphylactic or anaphylactoid type. Very rarely, hepatitis may develop after the use of halothane (Moult and Sherlock, 1975) especially if repeated within a short period (e.g. 3 months). A rare, but often fatal complication occurring in association with general anaesthesia is malignant hyperpyrexia (Ellis, Keaney and Harriman, 1973) which may also be triggered by local anaesthetic agents.

b) Spinal anaesthesia

Dramatic falls in arterial blood pressure are undoubtedly the most common complication of spinal anaesthesia; indeed vasodilatation consequent upon sympathetic blockade is inherent in the technique. The hypovolaemic patient and those with impaired cardiovascular function for any reason, including drug therapy, are less able to compensate for this effect and the elderly patient with a fractured hip frequently is in this category. Unexpectedly high blocks occasionally occur and despite apparently succesful lumbar puncture complete failure of block does happen.

[6.9] Conclusions

As this thesis has demonstrated no long term benefits of spinal anaesthesia and because it has many practical disadvantages making it more difficult to manage and less predictable, the author has come to the conclusion that, with the present state of knowledge, general anaesthesia should be the preferred method of anaesthesia for patient undergoing surgical repair of fractured neck of femur.

Spinal anaesthesia however, is a very useful alternative technique which should continue to be taught to trainee anaesthetists by those experienced in its use. It may be reserved for patients for whom it might be expected to be beneficial. These might include patients with severe impairment of respiratory function, some cardiac conditions (congestive cardiac failure), diabetics, those with multiple problems or for whom general anaesthesia carries an increased risk for any other reason (drug sensitivity, porphyria etc.)

The effects of spinal anaesthesia on the incidence of deep vein thrombosis and blood viscosity are of considerable theoretical interest and future investigation of these effects would seem a fascinating and interesting field of research.

REFERENCES

Ahlberg, A., Nylander, G., Robertson, B., Cronberg, S. & Nilsson, I.M. (1967) Dextran in phrophylaxis of thrombosis in fractures of the hip.
Acta Chirurgica Scandinavica, Supplementum **387**, 83-85.

Albert, S.N., Jain, S.C. & Shadid, J.N. (1964) Studies on blood viscosity and its significance in anesthesia.
Medical Annals of the District of Columbia, **33**, 372-377.

Alexander, J.I., Spence, A.A., Parikh, R.K. & Stuart, B. (1973) The role of airway closure in postoperative hypoxaemia.
British Journal of Anaesthesia, **45**, 34-40.

Alffram, P.A. (1964) An epidemiologic study of cervical and trochanteric fractures of the femur in an urban population. Analysis of 1,664 cases with special reference to etiologic factors.
Acta Orthopaedica Scandinavica, Supplement **65**, 1-109.

Allen, H.L. & Metcalf, D.W. (1965) Fractured hip: a study of anesthesia in the aged.
Anesthesia and Analgesia (Cleveland), **44**, 408-412.

American Society of Anesthesiologists. (1963) New classification of physical status.
Anesthesiology, **24**, 111.

Andersen, N.B. (1968) The effect of local anesthetic and pH on sodium and potassium flux in human red cells.
The Journal of Pharmacology and Experimental Therapeutics, **163**, 393-406.

Annual Report of the Registrar General for Scotland (1973) Part 1 Mortality Statistics. Table B1.1. p.45. Edinburgh: H.M.S.O.

Aronson, H.B-Z., Levesque, P.R. Charm, S. & Etsten, B. (1968) Influence of anaesthetics on rheology of human blood. Canadian Anaesthetists' Society Journal, 15, 244-257.

Askrog, V.F., Smith, T.C. & Eckenhoff, J.E. (1964) Changes in pulmonary ventilation during spinal anesthesia. Surgery, Gynecology and Obstetrics, **119**, 563-567.

Atkinson, R.S., Rushman, G.B. & Lee, J.A. (1977) Synopsis of Anaesthesia. Bristol: Wright.

Bailey, M.J., Yates, C.J.P., Johnston, C.L.W., Somerville, P.G. & Dormandy, J.A. (1979) Preoperative haemoglobin as predictor of outcome of diabetic amputations. Lancet, **ii**, 168-170.

Barker, A.E. (1907) Clinical experiences with spinal analgesia in one hundred cases and some reflections on the procedure. British Medical Journal, **i**, 665-674.

Barker, A.E. (1908a) A second report on clinical experiences with spinal analgesia: with a second series of one hundred cases. British Medical Journal, **i**, 244-249.

Barker, A.E. (1908b) A third report on clinical experiences with spinal analgesia; with a third series of one hundred cases. British Medical Journal, **ii**, 453-455.

Barker, R.W., Brown, F.F., Drake, R., Halsey, M.J. & Richards, R.E. (1975) Nuclear magnetic resonance studies of anaesthetic interactions with haemoglobin. British Journal of Anaesthesia, **47**, 25-29.

Barnes, R., Brown, J.T., Garden, R.S. & Nicholl E.A. (1976) Subcapital fractures of the femur. A prospective review. Journal of Bone and Joint Surgery, **58**, 2-24.

Barnes, A.J., Locke, P., Scudder, P.R., Dormandy, T.L., Dormandy, J.A. & Slack, J. (1977) Is hyperviscosity a treatable component of diabetic microcirculatory disease? Lancet, ii, 789-791.

Bay, J., Nunn, J.F. & Prys-Roberts, C. (1968) Factors influencing arterial pO_2 during recovery from anaesthesia. British Journal of Anaesthesia, **40**, 398-407.

Beals, R.K. (1972) Survival following hip fracture. Long follow-up of 607 patients. Journal of Chronic Diseases, **25**, 235-244.

Bier, A. (1899) Experiments regarding the cocainization of the spinal cord. Zeitschrift fur Chirurgie, **51**, 361-369 [reprinted (1962) in Survey of Anesthesiology, **6**, 352-358].

Bronge, A., Dahlgren, S. & Lindquist, B. (1971) Prophylaxis against thrombosis in femoral neck fractures - a comparison between dextran 70 and dicumarol. Acta Chirurgica Scandinavica, **137**, 29-35.

Brownlee, A. (1911) General and spinal anaesthesia. Practitioner, **86**, 214-226.

Browse, N. (1978) Diagnosis of deep-vein thrombosis. British Medical Bulletin, **34**, 163-167.

Brozovic, M. (1977) Physiological mechanisms in coagulation and fibrinolysis. British Medical Bulletin, **33**, 231-238.

Bryce-Smith, R. (1976) The enigmas of spinal anaesthesia. Proceedings of the Royal Society of Medicine, **69**, 75-82.

Burtles, R. & Tunstall, M.E. (1961) Suxamethonium chloride and muscle pains. British Journal of Anaesthesia, **33**, 24-28.

Camblin, J.G. (1974) Five year retrospective study of femoral neck fractures.
Ulster Medical Journal, 43, 136-142.

Cardus, D. (1967) O_2 alveolar-arterial tension difference after 10 days recumbency in man.
Journal of Applied Physiology, 23, 934-937.

Catenacci, A.J. & Sampathachar, K.R. (1969) Ventilatory studies in the obese patient during spinal anaesthesia.
Anesthesia and Analgesia (Cleveland), 48, 48-54.

Cazenave, J-P., Benveniste, J. & Mustard, J.F. (1979) Aggregation of rabbit platelets by platelet-activating factor is independent of the release reaction and the arachidonate pathway and inhibited by membrane-active drugs.
Laboratory Investigation, 41, 275-285.

Ceder, L., Elmqvist, D. & Svensson, S-E. (1981) Cardiovascular and neurological function in elderly patients sustaining a fracture of the neck of the femur.
The Journal of Bone and Joint Surgery, 63, 560-566.

Ceder, L., Lindberg, L. & Odberg, E. (1980) Differentiated care of hip fracture in the elderly. Mean hospital days and results of rehabilitation.
Acta Orthopaedica Scandinavica, 51, 157-162.

Chakrabarti, R., Hocking, E.D. & Fearnley, G.R. (1969) Reaction pattern to three stresses - electroplexy, surgery, and myocardial infarction - of fibrinolysis and plasma fibrinogen.
Journal of Clinical Pathology, 22, 659-662.

Channon, G.M. & Wiley, A.M. (1979) Aspirin prophylaxis of venous thromboembolic disease following fracture of the upper femur.
Canadian Journal of Surgery, 22, 468-472.

Clark, C. & Cotton, L.T. (1968) Blood-flow in deep veins of leg. Recording technique and evaluation of methods to increase flow during operation.
British Journal of Surgery, **55**, 211-214.

Clauss, Von, A. (1957) Gerinnungsphysiologische schnellmethode zur bestimmung des fibrinogens.
Acta Haematologica Scandinavica, **17**, 237-246.

Cohn, J.N. (1966) Relationship of plasma volume changes to resistance and capacitance vessel effects of sympathomimetic amines and angiotensin in man.
Clinical Science, **30**, 267-278.

Colbert, D.S. & O'Muircheartaigh, I. (1976) Mortality after hip fracture and assessment of some contributory factors.
Irish Journal of Medical Sciences, **145**, 44-50.

Conway, C.M. & Payne, J.P. (1963) Post-operative hypoxaemia and oxygen therapy.
British Medical Journal, **i**, 844-845.

Conway, C.M., Payne, J.P. & Tomlin, P.J. (1965) Arterial oxygen tensions of patients awaiting surgery.
British Journal of Anaesthesia, **37**, 405-408.

Cooke, E.D., Lloyd, M.J., Bowcock, S.A.and Pilcher, M.F. (1977) Intravenous lignocaine in prevention of deep venous thrombosis after elective hip surgery.
Lancet, **ii**, 797-799.

Coon, W.W. & Coller, F.A. (1959) Clinicopathologic correlation in thromboembolism.
Surgery, Gynecology and Obstetrics, **109**, 259-269.

Cope, R.W. (1954) The Woolley and Roe case. Wooley and Roe versus Ministry of Health and others.
Anaesthesia, **9**, 249-270.

Corning, J.L. (1885) Spinal anaesthesia and local medication of the cord.
New York Medical Journal, **42**, 483-487. [Reprinted (1960) in "Classical File", Survey of Anaesthesiology, 4, 332-335].

Culver, D., Crawford, J.S., Gardiner, J.H. & Wiley, A.M. (1970) Venous thrombosis after fractures of the upper end of the femur. A study of incidence and site.
Journal of Bone and Joint Surgery, **52**, 61-69.

Davis, F.M. & Laurenson, V.G. (1981) Spinal anaesthesia or general anaesthesia for emergency hip surgery in elderly patients.
Anaesthesia and Intensive Care, **9**, 352-358.

Davis, F.M., Quince, M. & Laurenson, V.G. (1980) Deep vein thrombosis and anaesthetic technique in emergency hip surgery.
British Medical Journal, **ii**, 1528-1529.

Davis, A.G. & Spence, A.A. (1972) Postoperative hypoxemia and age.
Anesthesiology, **37**, 663-664.

Dean, H.P. (1907) Discussion on the relative value of inhalation and injection methods of inducing anaesthesia.
British Medical Journal, **ii**, 869-877.

de Jong, R.H. (1965) Arterial carbon dioxide and oxygen tensions during spinal block.
Journal of the American Medical Association, **191**, 94-98.

Deutsch, S., Linde, H.W., Dripps, R.D. & Price, H.L. (1962) Circulatory and respiratory actions of halothane in normal man.
Anesthesiology, **23**, 631-638.

Dintenfass, L. (1981) The clinical impact of the newer research in blood rheology: an overview.
Angiology, **32**, 217-229.

Dodds, A.J., Matthews, P.N., Bailey, M.J., Flute, P.T. & Dormandy, J.A. (1980) Changes in red cell deformability following surgery.
Thrombosis Research, **18**, 561-565.

Dormandy, J.A. (1970) Clinical significance of blood viscosity.
Annals of the Royal College of Surgeons, **47**, 211-228.

Dormandy, J.A. & Edelman, J.B. (1973) High blood viscosity: An aetiological factor in venous thrombosis.
British Journal of Surgery, **60**, 187-190.

Dormandy, J.A., Yates, C.J.P. & Berent, G.A. (1981) Clinical relevance of blood viscosity and red cell deformability including newer therapeutic aspects.
Angiology, 32, 236-242.

Douglas, I.H.S., McKenzie, P.J., Ledingham, I.McA. & Smith, G. (1978) Effect of halothane on PO_2 electrode (letter).
Lancet, ii, 1370-1371.

Dripps, R.D. & Deming, M.V.N. (1946) Postoperative atelectasis and pneumonia. Diagnosis, etiology and management based upon 1,240 cases of upper abdominal surgery.
Annals of Surgery, **124**, 94-110.

Dripps, R.D. & Vandam, L.D. (1954) Long-term follow-up of patients who received 10,098 spinal anesthetics. Failure to discover major neurological sequelae.
Journal of the American Medical Association, **156**, 1486-1491.

Drummond, A.R., Drummond, M.M., McKenzie, P.J., Lowe, G.D.O., Smith, G., Forbes, C.D. & Wishart, H.Y. (1980) The effects of general and spinal anaesthesia on red cell deformability and blood viscosity in patients undergoing surgery for fractured neck of femur.
In: Haemorheology and Diseases, Ed. Stoltz, J.F. & Drouin, P. pp. 445-450. Paris: Doin Editeurs.

Drummond, M.M., Lowe, G.D.O., Belch, J.J.F., Barbenel, J.C. & Forbes, C.D. (1980) An assessment of red cell deformability using a simple filtration method.
Journal of Clinical Pathology, **33**, 373-376.

Editorial (1976) Fractures near the hip.
British Medical Journal, **1**, 1237.

Ellis, F.R., Keaney, N.P. & Harriman, D.G.F. (1973) Histopathological and neuropharmacological aspects of malignant hyperpyrexia.
Proceedings of the Royal Society of Medicine, **66**, 66-67.

Emmons, P.R. & Mitchell, J.R.A. (1965) Postoperative changes in platelet-clumping activity.
Lancet, i, 71-75.

Feinstein, M.B., Fiekers, J. & Fraser, C. (1976) An analysis of the mechanism of local anesthetic inhibition of platelet aggregation and secretion.
Journal of Pharmacology and Experimental Therapeutics, **197**, 215-228.

Field, E.S., Kakkar, V.V. & Nicolaides, A.N. (1972) Deep vein thrombosis after myocardial infarction, prostatectomy and fracture of the femoral neck.
In: Thromboembolism: diagnosis and treatment. Ed. Kakkar, V.V. & Jouhar, A.J. Ch.10. pp. 123-129. London: Churchill Livingstone.

Fink, B.R. (1955) Diffusion anoxia.
Anesthesiology, **16**, 511-519.

Flanc, C., Kakkar, V.V. & Clarke, M.B. (1968) The detection of venous thrombosis of the legs using ^{125}I-labelled fibrinogen.
British Journal of Surgery, **55**, 742-747.

Fourneau, M.E. (1904) Stovaine, anesthesique local.
Bulletin des Sciences Pharmacologiques (Paris), **10**, 141-148.

Gallannaugh, S.C., Martin, A. & Millard, P.H. (1976) Regional survey of femoral neck fractures.
British Medical Journal, **ii**, 1496-1497.

Giasi, R.M., D'Agostino, E. & Covino, B.G. (1979) Absorption of lidocaine following subarachnoid and epidural administration.
Anesthesia and Analgesia (Cleveland), **58**, 360-363.

Gibbs, N.M. (1957) Venous thrombosis of the lower limbs with particular reference to bed-rest.
British Journal of Surgery, **45**, 209-236.

Giddon, D.B. & Lindhe, J. (1972) In vivo quantitation of local anesthetic suppression of leukocyte adherence.
American Journal of Pathology, **68**, 327-337.

Gillies, I.D.S., Petrie, A., Morgan, M. & Sykes, M.K. (1977) Analysis of possible factors influencing Pa_{O2} and $(PA_{O2}-Pa_{O2})$ in
patients awaiting operation.
British Journal of Anaesthesia, **49**, 427-437.

Gordon, P.C. (1971) The probability of death following a fracture of the hip.
Canadian Medical Association Journal, **105**, 47-51.

Gordon, R.J. & Ravin, M.B. (1978) Rheology and anesthesiology.
Anesthesia and Analgesia (Cleveland), **57**, 252-261.

Gramstad, L. & Stovner, J. (1979) Plasma viscosity and cremophor-containing anaesthetics.
British Journal of Anaesthesia, **51**, 1175-1179.

Greene, N.M. (1961) Neurological sequelae of spinal anesthesia.
Anesthesiology, **22**, 682-698.

Hamilton, H.W., Crawford, J.S., Gardiner, J.H. & Wiley, A.M. (1970) Venous thrombosis in patients with fracture of the upper end of the femur. A phlebographic study of the effect of prophylactic anticoagulation.
Journal of Bone and Joint Surgery, **52**, 268-289.

Hendolin, H., Mattila, M.A.K. & Poikolainen, E. (1981) The effect of lumbar epidural analgesia on the development of deep vein thrombosis of the legs after open prostatectomy.
Acta Chirurgica Scandinavica, **147**, 425-429.

Hewlett, A.M., Hulands, G.H., Nunn, J.F. & Heath, J.R. (1974) Functional residual capacity during anaesthesia. II: Spontaneous respiration.
British Journal of Anaesthesia, **46**, 479-494.

Hole, A., Terjesen, T. & Breivik, H. (1980) Epidural versus general anaesthesia for total hip arthroplasty in elderly patients.
Acta Anaesthesiologica Scandinavica, **24**, 279-287.

Honkonen, K., Tarkkanen, L. & Julkunen, H. (1971) Femoral neck fracture during and after surgery. With special reference to the type of anaesthesia used.
Acta Medica Scandinavica, **189**, 173-178.

Ishak, M.A. & Morley, K.D. (1981) Deep venous thrombosis after total hip arthroplasy: a prospective controlled study to determine the prophylactic effect of graded pressure stockings.
British Journal of Surgery, **68**, 429-432.

Janvrin, S.B., Davies, G. & Greenhalgh, R.M. (1980) Postoperative deep vein thrombosis caused by intravenous fluids during surgery.
British Journal of Surgery, **67**, 690-693.

Jensen, J.S. & Tondevold, E. (1979) Mortality after hip fractures.
Acta Orthopaedica Scandinavica, **50**, 161-167.

Jensen, J.S., Tondevold, E. & Hove Sorensen, P. (1979) Social rehabilitation following hip fractures.
Acta Orthopaedica Scandinavica, **50**, 777-785.

Kakkar, V.V., Corrigan, T.P. & Fossard, D.P. (1975) Prevention of fatal postoperative pulmonary embolism by low doses of heparin.
An international multicentre trial.
Lancet, **ii**, 45-51.

Kakkar, V.V., Howe, C.T., Nicolaides, A.N., Renney, J.T.G. & Clarke, M.B. (1970) Deep vein thrombosis of the leg. Is there a high risk group?
American Journal of Surgery, **120**, 527-530.

Karumo, I. (1977) Recovery and rehabilitation of elderly subjects with femoral neck fractures.
Annales Chirurgiae et Gynaecologiae, **66**, 170-176.

Keith, S. (1973) The hospital in-patient enquiry, 1970.
Health Trends, **5**, 13-14.

Kemble, J.V.H. (1971) The effect of surgical operation on leg venous flow measured with radioactive hippuran.
Postgraduate Medical Journal, **47**, 773-776.

Kennedy, F., Effron, A.S. & Perry, G. (1950) The grave spinal cord paralyses caused by spinal anesthesia.
Surgery, Gynecology and Obstetrics, **91**, 385-398.

Keyes, E.L. & McLellan, A.M. (1930) Preliminary report on a new local anesthetic (nupercain).
American Journal of Surgery, **9**, 1-7.

Knowelden, J., Buhr, A.J. & Dunbar, O. (1964) Incidence of fractures in persons over 35 years of age. A report to the M.R.C. working party on fractures in the elderly.
British Journal of Preventive and Social Medicine, **18**, 130-141.

Knox, J.W.D., Bovill, J.G., Clarke, R.S.J. & Dundee, J.W. (1970) Clinical studies of induction agents. XXXVI: Ketamine. British Journal of Anaesthesia, 42, 875-885.

Laaksonen, V.O., Arola, M.K.J., Hannelin, M., Inberg, M.V. & Kivisaari, A. (1973) Effect of anaesthesia on the incidence of postoperative lower limb thrombosis.
Annales Chirurgiae et Gynaecologiae Fenniae, 62, 304-317.

Labat, G.L. (1921) Latest achievements of the art of local, regional and spinal anaesthesia.
Annals of Surgery, 74, 673-683.

Lacko, L., Wittke, B. & Lacko, I. (1978) The pH-dependence of glucose transport inhibition by local anesthetics in human erythrocytes.
Experientia, 34, 26-28.

Lake, N.C. (1958) Spinal anaesthesia, the present position.
Lancet, i, 387-390.

Lee, A.J. (1967) Twenty years ago (Editorial)
Anaesthesia, 22, 342-346.

Lewis, F.A. (1981) Fracture of neck of the femur: changing incidence.
British Medical Journal, ii, 1217-1220.

Lichtenfeld, K.M., Schiffer, C.A. & Helrich, M. (1979) Platelet aggregation during and after general anesthesia and surgery.
Anesthesia and Analgesia (Cleveland), 58, 293-296.

Lorhan, P.H. & Shelby, E.A. (1964) Factors influencing mortality in hip fractures.
Anesthesia and Analgesia (Cleveland), 43, 539-543.

Loudon, J.R., McGarrity, G., Vallance, R., Baylis, A.C. & Graham, J. (1978) The fibrinogen uptake test after hip surgery.
British Journal of Surgery, 65, 616-618.

Lowe, G.D.O., Meek, D.R., Campbell, A.F., Forbes, C.D. & Prentice, C.R.M. (1978) Subcutaneous ancrod in prevention of deep-vein thrombosis after operation for fractured neck of femur.
Lancet, ii, 698-700.

Mackintosh R.R. & Lee J.A. (1973) History of Spinal Anaesthesia In: Lumbar Puncture and Spinal Analgesia, Ch.1. Edinburgh: Churchill Livingstone.

Magora, F., London, M., Eimerl, D. & Aronson, H.B. (1974) Blood viscosity during anaesthesia with halothane, cyclopropane, thiopentone and ketamine.
British Journal of Anaesthesia, **46**, 343-347.

Marinacci, A.A. & Courville, C.B. (1958) Electromyogram in evaluation of neurological complications of spinal anesthesia.
Journal of the American Medical Assocation, **168**, 1337-1345.

Marshall, B.E. & Millar, R.A. (1965) Some factors influencing post-operative hypoxaemia.
Anaesthesia, **20**, 408-428.

Martin, V.C. (1977) Hypoxaemia in elderly patients suffering from fractured neck of femur.
Anaesthesia, 32, 852-867.

McLachlin, J., Richards, T. & Paterson, J.C. (1962) An evaluation of clinical signs in the diagnosis of venous thrombosis.
Archives of Surgery, **85**, 738-744.

McLaren, A.D., Stockwell, M.C. & Reid, V.T. (1978) Anaesthetic techniques for surgical correction of fractured neck of femur.
Anaesthesia, **33**, 10-14.

Mitchell, J.R.A. (1979) Can we really prevent postoperative pulmonary emboli?
British Medical Journal, i, 1523-1524.

Modig, J. (1976) Respiration and circulation after total hip replacement surgery.A comparison between parenteral analgesics and lumbar epidural block.
Acta Anaesthesiologica Scandinavica, 20, 225-236.

Modig, J. (1977) Posttraumatic pulmonary microembolism.
Annals of Clinical Research, 9, 164-172.

Modig, J., Borg, T., Bagge, L. & Saldeen, T. (1983a) Role of extradural and of general anaesthesia in fibrinolysis and coagulation after total hip replacement.
British Journal of Anaesthesia, 55, 625-629.

Modig, J., Borg, T., Karlstrom, G., Maripuu, E. & Sahlstedt, B. (1983b) Thromboembolism after total hip replacement: role of epidural and general anesthesia.
Anesthesia and Analgesia (Cleveland), 62, 174-180.

Modig, J., Busch, C., Olerud, S., Saldeen, T. & Waernbaum, G. (1975) Arterial hypotension and hypoxaemia during total hip replacement: the importance of thromboplastic products, fat embolism and acrylic monomers.
Acta Anaesthesiologica Scandinavica, 19, 28-43.

Modig, J. & Malmberg, P. (1975) Pulmonary and circulatory reactions during total hip replacement surgery.
Acta Anaesthesiologica Scandinavica, 19, 219-237.

Modig, J., Malmberg, P. & Karlstrom, G. (1980) Effect of epidural versus general anaesthesia on calf blood flow.
Acta Anaesthesiologica Scandinavica, 24, 305-309.

Morris, D.D.B. (1972) Spinal and epidural analgesia: technique and complications.
In: A Practice of Anaesthesia, ed. Wylie, W.D. & Churchill-Davidson, H.C. Ch. 43. London: Lloyd-Luke Ltd.

Morris, G.K. & Mitchell, J.R.A. (1976a) Prevention and diagnosis of venous thrombosis in patients with hip fractures. A survey of current practice.
Lancet, ii, 867-869.

Morris, G.K. & Mitchell, J.R.A. (1976b) Warfarin sodium in prevention of deep venous thrombosis and pulmonary embolism in patients with fractured neck of femur.
Lancet, **ii**, 869-872.

Morris, G.K. & Mitchell, J.R.A. (1977a) Evaluation of ^{125}I-fibrinogen test for venous thrombosis in patients with hip fractures: comparison between isotope scanning and necropsy findings.
British Medical Journal, **i**, 264-266.

Morris, G.K. & Mitchell, J.R.A. (1977b) Preventing venous thromboembolism in elderly patients with hip fractures: studies of low-dose heparin, dipyridamole, aspirin, and flurbiprofen.
British Medical Journal, **i**, 535-537.

Morris, G.K. & Mitchell, J.R.A. (1977c) The aetiology of acute pulmonary embolism and the identification of high risk groups.
British Journal of Hospital Medicine, **18**, 6-12.

Morris, G.K. & Mitchell, J.R.A. (1978) Clinical management of venous thrombo-embolism.
Britsh Medical Bulletin, **34**, 169-175.

Moskovitz, P.A., Ellenberg, S.S., Feffer, H.L., Kenmore, P.I., Neviaser, R.J., Rubin, B.E. & Varma, V.M. (1978) Low-dose heparin for prevention of venous thromboembolism in total hip arthroplasty and surgical repair of hip fractures.
Journal of Bone and Joint Surgery, **60**, 1065-1070.

Moult, P.J.A. & Sherlock, S. (1975) Diagnosis of halothane-related hepatitis.
Proceedings of the Royal Society of Medicine, **68**, 768-769.

Myrvold, H.E., Persson, J.E., Svensson, B., Wallensten, S. & Vikterlof, K.J. (1973) Prevention of thrombo-embolism with dextran 70 and heparin in patients with femoral neck fractures.
Acta Chirurgica Scandinavica, **139**, 609-616.

Nicolaides, A.N., Fernandes, J.F. & Pollock, A.V. (1980) Intermittent sequential pneumatic compression of the legs in the prevention of venous stasis and postoperative deep venous thrombosis.
Surgery, **87**, 69-76.

Noble, A.B. & Murray, J.G. (1971) A review of the complications of spinal anaesthesia with experiences in Canadian teaching hospitals from 1959-1969.
Canadian Anaesthetists' Society Journal, **18**, 5-17.

Nunn, J.F. (1965) Influence of age and other factors on hypoxaemia in the postoperative period.
Lancet, **ii**, 466-468.

Nunn, J.F. & Payne, J.P. (1962) Hypoxaemia after general anaesthesia.
Lancet, **ii**, 631-632.

O'Brien, J.R. (1961) The adhesiveness of native platelets and its prevention.
Journal of Clinical Pathology, **14**, 140-149.

Ohman, U., Bjorkegren, N-A. & Fahlstrom G. (1969) Fracture of the femoral neck. A five year follow up.
Acta Chirurgica Scandinavica, **135**, 27-42.

Orr, J.E., Davidson, R.J.L., Russell, I.F. & Robertson, G.S. (1982) A haemorheological study of althesin.
British Journal of Anaesthesia, **54**, 1003-1006.

Owens, W.D. (1980) Anesthetic side effects and complications: seeking, finding and treating. In International Anesthesiology Clinics, Vol. 18 ed. Owens, W.D. Boston: Little Brown & Co.

Paskin, S., Rodman, T. & Smith, T.C. (1969) The effect of spinal anesthesia on the pulmonary function of patients with chronic obstructive pulmonary disease.
Annals of Surgery, **169**, 35-41.

Phillips, G. & Tomlin, P.J. (1977) Arterial oxygen tensions in elderly and in injured elderly patients.
British Journal of Anaesthesia, 49, 514.

Poigenfurst, J. & Schnabl, P. (1977) Multiple intramedullary nailing of pertrochanteric fractures with elastic nails: operative procedure and results.
Injury, 9, 102-113.

Quincke, H. (1891) Die lumbalpunction des hydrocephalus.
Berliner Klinische Wochenschrift, 28, 965-968.

Raine, J.M. & Bishop, J.M. (1963) A-a difference in O2 tension and physiological dead space in normal man.
Journal of Applied Physiology, 18, 284-288.

Rees, J.L. (1982) Accuracy of hospital activity analysis data in estimating the incidence of proximal femoral fracture.
British Medical Journal, i, 1856-1858.

Reid, H.L., Barnes, A.J., Lock, P.J., Dormandy, J.A. & Dormandy T.L. (1976) A simple method for measuring erythrocyte deformability.
Journal of Clinical Pathology, 29, 855-858.

Replogle, R.L., Meiselmand, H.J., & Merrill, E.W. (1967) Clinical implications of blood rheology studies.
Circulation, 36, 146-160.

Richard, L.C., Buller, H.R., Bovill, J. & ten Cate, J.W. (1983) Influence of anaesthesia on coagulation and fibrinolytic proteins.
British Journal of Anaesthesia, 55, 869-872.

Riska, E.B. (1970) Factors influencing the primary mortality in the treatment of hip fractures.
Injury, 2, 107-115.

Robertson, D.H. (1983) Subarachnoid spinal analgesia. Changing patterns of practice.
British Journal of Anaesthesia, 55, 1141-1146.

Robertson, D.H., Lewerentz, H., & Holmes, F. (1978) Subarachnoid spinal analgesia. A comparative survey of current practice in Scotland and Sweden.
Anaesthesia, **33**, 913-923.

Rosenberg, Per H. (1980) Synaptosomal studies of fluidity changes caused by anesthetics.
In: Molecular Mechanisms of Anesthesia, (Progress in Anesthesiology, Vol. 2), Ed. Fink, B.R. pp.325-335. New York: Raven Press

Ryall, C.E. (1911) The indications and contra-indications for the use of spinal anaesthesia.
Practitioner, **86**, 227-247.

Saldeen, T. (1970a) Fat embolism and signs of intravascular coagulation in a posttraumatic autopsy material.
Journal of Trauma, **10**, 273-286.

Saldeen, T. (1970b) The importance of intravascular coagulation and inhibition of the fibrinolytic system in experimental fat embolism.
Journal of Trauma, **10**, 287-298.

Scott, D.B. & Thorburn, J.T. (1975) Spinal anaesthesia (Editorial)
British Journal of Anaesthesia, **47**, 421-422.

Scottish Hospital Inpatient Statistics (1968 & 1978) Scottish Home and Health Department, Edinburgh: H.M.S.O.

Seeman, P. (1966) Erythrocyte membrane stabilization by local anaesthetics and tranquilizers.
Biochemical Pharmacology, **15**, 1753-1766.

Seeman, P. & Roth, S. (1972) General anesthetics expand cell membranes at surgical concentrations.
Biochimica et Biophysica Acta, **255**, 171-177.

Selman, B.J., & Tait, A.R. (1976) Towards blood-gas autoanalysis: an evaluation of the Radiometer ABL 1. British Journal of Anaesthesia, **48**, 487-494.

Severinghaus, J.W., Weiskopf, R.B., Nishimura, M. & Bradley, A.F. (1971) Oxygen electrode errors due to polarographic reduction of halothane.
Journal of Applied Physiology, **31**, 640-642.

Sevitt, S. & Gallagher, N.G. (1959) Prevention of venous thrombosis and pulmonary embolism in injured patients. A trial of anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractured necks of femur.
Lancet, **ii**, 981-989.

Sevitt, S., and Gallagher, N. (1961) Venous thrombosis and pulmonary embolism, a clinico-pathological study in injured and burned patients.
British Journal of Surgery, **48**, 475-489.

Simpson, P.J., Radford, S.G., Forster, S.J., Cooper, G.M. & Hughes, A.O. (1982) The fibrinolytic effects of anaesthesia. Anaesthesia, **37**, 3-8.

Skacel, P.O., Hewlett, A.M., Lewis, J.D., Lumb, M., Nunn, J.F. & Chanarin, I. (1983) Studies on the haemopoietic toxicity of nitrous oxide in man.
British Journal of Haematology, **53**, 189-200.

Slogoff, S., Allen, G.W., Wessels, J.V. & Cheney, D.H. (1974) Clinical experience with subanesthetic ketamine.
Anesthesia and Analgesia (Cleveland), **53**, 354-358.

Smith, J.A.R. & McLauchlan, J. (1975) A survey of fractures of the proximal femur.
Injury, **6**, 196-201.

Snook, G.A., Chrisman, O.D. & Wilson, T.C. (1981) Thromboembolism after surgical treatment of hip fractures.
Clinical Orthopaedics and Related Research, **155**, 21-24.

Soumalainen, O., Kettunen, K., Rissanen, V., Karjalainen, P., Lansimies, E. & Tanska, S. (1983) Postoperative thromboembolism and risk factors in elective hip surgery.
Annals Chirurgiae et Gynaecologiae, 72, 207-213.

Spence, A.A. & Alexander, J.I. (1972) Mechanisms of postoperative hypoxaemia.
Proceedings of the Royal Society of Medicine, 65, 12-14.

Spreadbury, T.H. (1980) Anaesthetic techniques for surgical correction of fractured neck of femur. A comparative study of ketamine and relaxant anaesthesia in elderly women.
Anaesthesia, 35, 208-214.

Stamatakis, J.D., Kakkar, V.V., Sagar, S., Lawrence, D., Nairn, D. & Bentley, P.G. (1977) Femoral vein thrombosis and total hip replacement.
British Medical Journal, ii, 223-225.

Tachakra, S.S. & Sevitt, S. (1975) Hypoxaemia after fractures.
Journal of Bone and Joint Surgery, 57, 197-203.

Thomas, D.J., Marshall, J., Ross Russell, R.W., Wetherley-Mein, G., Du Boulay, G.H., Pearson, T.C., Symon, L. & Zilkha, E. (1977) Effect of haematocrit on cerebral blood-flow in man.
Lancet, ii, 941-943.

Thomas, M.L., (1971) Radiology of deep vein thrombosis.
British Journal of Hospital Medicine, 6, 735-740.

Thorburn, J., Louden, J.R. & Vallance, R. (1980) Spinal and general anaesthesia in total hip replacement: frequency of deep vein thrombosis.
British Journal of Anaesthesia, 52, 1117-1121.

Tocantins, L.M., Carroll, R.T. & Holburn, R.H. (1951) The clot accelerating effect of dilution on blood and plasma. Relation to the mechanism of coagulation of normal and hemophilic blood.
Blood, 6, 720-739.

Tuffier, T. (1901) L'analgesie chirurgicale par voie rachidienne.
Oeuvre Medicale et Chirurgicale, **24**, 855-898.

Urbach, K.F., Lee.W.R., Sheely, LL., Lang, F.L. & Sharp, R.P. (1964) Spinal or general anaesthesia for inguinial hernia repair? A comparison of certain complications in a controlled sense.
Journal of the American Medical Association, **190**, 25-29.

Wallace, W.A. (1983) The increasing incidence of fractures of the proximal femur: an orthopaedic epidemic.
Lancet, i, 1413-1414.

Ward, R.J., Bonica, J.J., Freund, F.G., Akamatsu, T., Danziger, F. & Englesson, S. (1965) Epidural and subarachnoid anesthesia. Cardiovascular and respiratory effects.
Journal of the American Medical Association, **191**, 275-278.

Ward, R.J., Tolas, A.G., Benveniste, R.J., Hansen, J.M., & Bonica, J.J. (1966) Effect of posture on normal arterial blood gas tensions in the aged.
Geriatrics, **21**, 139-143.

Watkins, J. (1979) Anaphylactoid reactions to i.v. substances.
British Journal of Anaesthesia, **51**, 51-60.

Wickstrom, I., Holmberg, I. & Stefansson T. (1982) Survival of female geriatric patients after hip fracture surgery. A comparison of 5 anesthetic methods.
Acta Anaesthiologica Scandinavica, **26**, 607-614.

Wishart, H.Y., Williams, T.I.R. & Smith, G. (1977) A comparison of the effect of three anaesthetic techniques on postoperative arterial oxygenation in the elderly.
British Journal of Anaesthesia, **49**, 1259-1263.

Wright, H.P. (1942) Changes in the adhesiveness of blood platelets following parturition and surgical operations.
Journal of Pathology and Bacteriology, **54**, 461-468.

Xabegras, A., Gray, L. & Ham, J.M. (1978) Heparin prophylaxis of deep vein thrombosis in patients with a fractured neck of the femur.
Medical Journal of Australia, 1, 620-622.

Yates, C.J.P., Andrews, V., Berent, A. & Dormandy, J.A. (1979) Increase in leg blood-flow by normovolaemic haemodilution in intermittent claudication.
Lancet, ii, 166-168.

Zahavi, J., Price, A.J. & Kakkar, V.V. (1980) Enhanced platelet release reaction associated with general anaesthesia (letter).
Lancet, i, 1132-1133.

Zetterberg, C. & Andersson, G.B.J. (1982) Fractures of the proximal end of the femur in Goteborg, Sweden, 1940-1979.
Acta Orthopaedica Scandinavica, 53, 419-426.