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The James Young Simpson Legacy, 4–6 September 1997, Edinburgh. Abstracts of selected free papers

1. Chloroform abuse

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When James Y. Simpson [1] (1847) described the ease with which chloroform could be used to produce unconsciousness without specialized equipment these advantages were not lost on the criminal fraternity who were not slow to adopt the drug in pursuit of their nefarious practices. Unlike the use of the cudgel, the garrotte and the pistol, according to English law it was not a felony to administer chloroform to another unless the purpose of the act was murder! As early as 1851, it was widely known to the public that chloroform could be used to perpetrate various forms of crime such as rape and robbery as witnessed by a well-known cartoon in *Punch* magazine of that year.

Other problems were to arise. According to Dudley W. Buxton [2] (1888) 'many cases have now been reported in which the prosecutrix has affirmed that a dentist or a surgeon has violated her person while she was under the influence of anaesthetic. . . . But it is not only designing bad women who bring such charges. Modest, virtuous and refined gentlewomen have been prosecutrices in these cases. The cause for this remarkable and deplorable state of things is fortunately not far to seek. Chloroform, ether, nitrous oxide, gas, cocaine and possibly the other carbon compounds employed in producing anaesthesia possess the property of exciting sexual emotions and in many cases produce erotic hallucinations. It is undoubted that in certain persons sexual orgasm may occur during the induction of anaesthesia . . .'

As the aphrodisiac properties of anaesthetic agents became more widely known, chloroform came to be used to heighten sexual pleasure and to enhance performance in preference to other volatile agents because of the ease of administration and because it was relatively pleasant to breathe. Unfortunately, the dangers of the drug were less well known and inevitably tragedies occurred which are well documented in the world literature. However, the use of chloroform was not confined to consenting adults and in nearly 40 years' court experience as an expert witness, apart from the problems of addiction, I have encountered allegations that chloroform was used to facilitate rape, both heterosexual and homosexual, as well as paedophiliac abuse and murder. Predictably, none of these cases was straightforward and the issues were further complicated by the adversarial system inherent in English Law which sometimes tends to obscure rather than reveal the truth.

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2 Buxton, DW. *Anaesthetics, Uses and Administration.* London: H. K. Lewis, 1888; 149–150.

2. James Young Simpson and the South Australian connection

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The connection starts with George Albert Simpson who studied at Cambridge and graduated from the Society of Apothecaries of London in 1896.

He had three sons – George, killed in the Battle of the Somme, Robert and Stanley, the father of my patient David Simpson. His home in London was demolished by bombs in 1942, killing Dr George Simpson and Robert.

David left school and took up acting and then photography and joined Baron, the Royal Photographer.

David had two sons, John Patrick and Lewis James Young.

The MacBeth portrait of Sir James Young Simpson is reproduced with permission of the Royal College of Physicians of Edinburgh.

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Because of health reasons the family migrated to South Austraia in 1969.

The story of that family will be described in brief.

There is another South Australian connection in the form of ether anaesthesia, the Sesquicentenary of which is to be commemorated in a Seminar at Launceston, Tasmania, on 7 June 1997.

Following the first ether anaesthetic by William Morton in Boston on 16 October 1846, the news reached Hobart via London on 27 May 1847. The ether was rapidy produced and 11 days later the first anaesthetic was administered by William Pugh for the removal of a tumour of the jaw.

News of ether anaesthesia reached Adelaide on 3 May 1847 aboard the sailing ship, *The Lightning*, after a 100-day trip from London. However, the production of ether and the first anaesthetic in Adelaide was much slower than in Launceston. It was not until 30 September 1847 that the first anaesthetic in Adelaide was given by Dr Kent from England and Dr Bayer from Germany.

The events at the Pugh Sesquicentenary will be briefly presented.

3. Chloroform and ether anaesthesia in wartime Burma 1943–1945

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Anaesthesia, during active war campaign, for patients in the 2nd West African Field Ambulance (2WA Fd Amb) is described.

Patients, although mostly battle casualties, also involved general surgical and a few orthopaedic cases. No gynaecological, nor maternity, for obvious reasons.

As this particular unit was meant to operate in the jungles of the Arakan in particular and later in Burma in general, only equipment that could be carried by personnel was available, eliminating the use of anaesthetic machines, medical gas cylinders, etc. Thiopentone, glass syringes which had to be sterilized by boiling water, a Schimmelbusch mask, layers of gauze, airways and a bottle for dropping the anaesthetic on the mask were the main 'tools of trade'. The anaesthetic consisted of a mixture of Alcohol (1 part), Chloroform (2 parts) and Ether (3 parts) called the ACE mixture.

In spite of the primitive conditions (the whole Brigade was surrounded by the enemy, kept in a 'box' shelled and harassed for more than 3 months, details to be presented). Mortality rate attributable solely to anaesthesia was – mercifully – nil.

Elementary methods of general anaesthesia, given even under primitive conditions, although by no means ideal, may lead to acceptable results, provided judicious and meticulous care of the airway and respiration can be assured. As most battle casualties encountered here were due to exploding grenades and shells, the multiple wounds thus caused would not lend themselves easily to being managed with local anaesthesia. However, the latter was used wherever applicable.

NB Because – during active battle situations and conditions – the taking of photographs and keeping of records and notes were not allowed – exact figures cannot be given in this presentation.

4. Simpson: a woman-centred appraisal of his achievements

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The benefits of the introduction of chloroform in childbearing are well recognized. Similarly, Simpson's struggle against entrenched theological orthodoxy is comprehensively documented. However, the outcomes for the childbearing woman have been neglected in the research literature.

In this paper I present a systematic review of the literature, using databases such as MEDLINE, CINAHL and BIDS, as well as relevant indices and local archives. Contemporaneous and recent literature has been searched. I considered the implications of Simpson's work for childbearing women and for the midwives who attended them.

Certain themes emerge clearly from this systematic search of the literature. The concept of iatrogenesis emerges, and may be associated with the need for remedial intervention in the labour, birth and subsequently. These interventions have involved the use of medication as well as surgical instruments.

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Certain developments in obstetric practice followed Simpson's introduction of the use of chloroform in childbearing. It is possible to draw comparisons between Simpson's achievements and certain recent and current developments in maternity care.

5. The absolute-risk strategy for the management of raised blood pressure

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There is something of a ferment at present about how to get the best out of antihypertensive therapy. This is probably due to various factors, e.g. the accumulating knowledge of the natural history of raised blood pressure and cardiovascular disease, the evidence that even elderly hypertensives benefit from treatment, the improved but more expensive drugs and the drive to reduce costs.

Treatment has hitherto been based largely on relative risk of cardiovascular disease events, i.e. risk relative to that of a normotensive person. However, it has been pointed out that if absolute risk in a normotensive person with no other risk factors is extremely small, a small degree of relative risk will not lead to significant absolute risk in a hypertensive person of otherwise similar characteristics. It has therefore been proposed that the decision to use antihypertensive drugs should be based on absolute risk and that treatment is not needed unless the absolute risk of a stroke or heart attack is at least 10% in the next 5 years.

The absolute-risk strategy has some merit but also problems. The main problem is that the risk of cardiovascular events rises geometrically with age, so a given threshold of such events becomes easier and easier to reach as age advances. The strategy, in fact, incorporates the value judgement that a stroke or heart attack is of the same gravity in a person aged 70 as in a person aged 40. This does not seem right. The problem could be overcome by varying the timeframe of the 10% risk inversely with age, e.g. 20 years at age 40, 15 years at age 50, 10 years at 60, 5 years at age 70 and 3 years at age 80.

The absolute-risk strategy aims in particular to use antihypertensive drugs in people who, apart from having a high blood pressure, have risk factors such as cigarette smoking, diabetes, obesity, a high ratio of total/HDL-cholesterol and previous target organ damage. These risk factors vary greatly in their characteristics and in their relation to raised blood pressure. This raises practical and ethical questions that will be discussed.

6. The severity of systemic inflammatory response syndrome is reflected by the sedimentation properties of leucocytes in patients after major surgical intervention

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Erythrocyte sedimentation rate (ESR) is widely accepted as a non-specific test to assess the effect of some acute phase proteins on erythrocyte aggregation. The factors that determine the blood sedimentation have been thoroughly investigated; however, little is known about the behaviour of leucocytes during erythrocyte aggregation and sedimentation. Previously, it has been demonstrated that the leucocyte antisedimentation assay reflects some characteristics of leucocytes in an easy and reproducible way. The normal range of leucocyte antisedimentation rate (LAR) is between 0 and 20%. In our previous study we found a significant negative correlation between leucocyte adhesiveness and LAR as well as sigificant positive correlation between ESR and LAR [1]. *In vitro* pre-treatment of blood samples with water soluble prednisolone or lidocaine resulted in a concentration-dependent significant diminishment of LAR [1]. In another study, we demonstrated that LAR was superior to ESR in predicting progress of disease in outpatients suffering from chronic lymphocytic leukaemia or myeloma [2]. In the recent study our aim was to investigate LAR in patients with the risk of post-operative systemic inflammatory (septic) complication in a surgical intensive care unit.

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The original Westergren technique was modified to assess leucocyte sedimentation properties with a new, simple and reproducible method. LAR was measured as the increment of leucocyte concentration in the upper half section of blood column in a vertically positioned sedimentation tube after 1 h gravity sedimentation of the whole blood. The result was expressed as a percentage of the original, pre-sedimentation leucocyte concentration. In the recent study, LAR was measured in 15 patients after oesophageal or gastric tumour resective surgical intervention on the 1st, 3rd and 6th post-operative days. C-reactive protein (CRP), ESR and the severity score of systemic inflammatory response syndrome (SIRS) were also assessed simultaneously.

LAR was in positive correlation with SIRS scores ($r=0.493$, $P<0.01$), and LAR increased significantly at SIRS scores 3 and 4 compared with score zero ($P<0.05$ and $P<0.01$, respectively. The equation derived from the data: SIRS score $=0.05\times(\text{LAR\%})-0.77$. There was no significant correlation between SIRS scores and ESR ($r=0.346$) as well as between SIRS scores and CRP concentration ($r=0.017$).

The change in functional state of circulating leucocytes can be the earliest sign of systemic inflammatory response in patients treated at an intensive care unit after a major operation. This study demonstrated that LAR correlates significantly with the systemic inflammatory response syndrome in patients after thoracic and/or abdominal tumour resection. Furthermore, the leucocyte anti-sedimentation test does not require any cell isolation procedures. In this way it it highly probable that unwanted *in vitro* activation of leucocytes is avoided and the activation process during 1 h of sedimentation can only be due to the effect of inflammatory mediators already present in the patient's own blood sample. In conclusion, LAR is superior to ESR and CRP in monitoring systemic inflammation in patients after thoracic and abdominal tumour resection.

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7. Investigation of haemostatic parameters in relation to outcome in an intensive care population

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A pilot study to identify the relation of haemostatic factors to patient outcome in the intensive care population.

After ethics committee approval 50 admissions to the ICU were recruited consecutively subject to a maximum of two patients studied at any one time. After completing investigations in one patient the next admission was recruited.

On the first day of admission a peripheral blood sample was taken and sent for the following tests: full blood count, prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time (TT), plasma viscosity, fibrinogen, factor VII, factor VIII, von Willebrand factor antigen, tissue plasminogen activator antigen, plasminogen activator inhibitor activity, fibrinogen degradation products and thrombelastography (TEG) – where the reaction time R, clot formation time K, maximum amplitude MA and angle alpha were measured. APACHE II scoring, length of hospital and ICU stay and death in hospital were also recorded. Survival or death was used as the primary outcome measure. The differences in the above tests in the survivors and non-survivors were analysed using Mann–Whitney tests, and $P<0.05$ was taken to indicate significance.

Thirty patients survived and 20 patients died. There was a significant difference in the APACHE II ($P=0.003$), length of hospital stay ($P=0.01$), von Willebrand factor ($P=0.003$) and tissue plasminogen activator antigen activity ($P=0.05$) in the survivors and non-survivors. There was no significant difference in any of the other parameters.

Von Willebrand factor and tissue plasminogen activator antigen levels are significantly higher in the non-survivors of an intensive care population. They probably reflect diffuse, endothelial disturbance, may be useful prognostic indices of severity of illness and merit further evaluation.

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8. Prognosis in obstetric-related ARDS

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Obstretic-related ARDS is a rare condition. In the reported triennium (1988–1990), it accounted for 44 maternal deaths in England and Wales. Our tertiary referral intensive care unit receives more than 50 patients per year with refractory acute respiratory failure from other intensive care units. Between 1989 and 1995, eight patients were referred with obstetric-related ARDS. Only one patient survived.

The aetiology of ARDS in these rare presentations proved difficult to identify. Presumptive diagnoses in these patients included 'silent' aspiration (2), anaphylaxis (1), pulmonary infection (1), eclampsia (2) and unknown (2). All patients exhibited a precipitous decline in respiratory function, necessitating immediate intervention in five, and within 24 h in the remaining three patients. Ventilation to referral time was generally long and ranged from 1 to 15 days (mean 10). The mean duration of respiratory support in non-survivors was 27 days (range 11–40 days). With the exception of the sole survivor, who received pressure-controlled inverse ratio ventilation (PC-IRV) with permissive hypercapnia from the outset, respiratory support to referral was of a conventional nature. Despite the application of novel therapies after referral, including PC-IRV, high-frequency ventilation, prone ventilation, aggressive permissive hypercapnia, IVOX, nitric oxide and nebulized prostacyclin, the mortality was extremely disappointing.

The outcome in this subgroup of ARDS patients is, in our experience, far worse than severe ARDS due to other aetiologies. By comparison, overall mortality from severe ARDS in our unit was 34% over the last 3 years.

Our experience suggests that the prognosis in obstetric patients who have progressed to severe pulmonary failure is extremely poor. Recognition of this expected mortality, and the rare and sporadic nature of these presentations, should encourage referral to a specialist respiratory support unit. Although novel respiratory support techniques are unproved, they must be applied early in combination with lung-protective ventilatory strategies if they are to influence outcome.

9. Does an inflatable obstetric belt assist in the second stage of labour?

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To test the hypothesis that an inflatable obstetric belt (The Labour Assister), which applies fundal pressure by inflating in synchrony with uterine contractions, facilitates spontaneous vaginal delivery, when used in the second stage of labour in nulliparous women using an epidural.

A randomized controlled trial of 800 women was

Table 1. (abstract 9) Influence of the obstetric belt (labour assister) on the progress of labour

	Belt ($n=107$)	Control ($n=93$)
Induced	35 (32.7%)	26 (27.9%)
Oxytocin	74 (69.1%)	59 (63.4%)
Spontaneous vertex delivery	**59 (55.1%)**	**33 (35.5%)** $P<0.01$
Total instrumental vaginals	**45 (42%)**	**56 (60.2%)** $P<0.025$
Liftout instrumental	38 (35.5%)	39 (41.9%)
Rotational instrumental	**7 (6.5%)**	**17 (18.2%)** $P<0.025$
Caesarean section	3 (2.8%)	4 (4.3%)
Required transfusion	**0**	**5 (5.4%)** $P<0.025$
3rd degree tear	1 (0.9%)	0
SCBU admissions	4 (3.7%)	3 (3.2%)

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undertaken. A power analysis has shown that this will demonstrate a 25% reduction in the primary outcome of instrumental vaginal delivery at the 5% significance level with a power of 90% in our population, where 45% of these women have previously undergone instrumental deliveries. Recruitment occurs in labour once the women is comfortable with her epidural, provided she has an uncomplicated singleton cephalic pregnancy at term. Informed written consent is gained. Randomization occurs at full dilatation, and the woman either receives standard care or standard care plus the belt.

We have recruited 200 women to date (16/2/97), 32 women declined to enter the trial. Nine belts were removed at the patient's request but analysis is by intention to treat. Preliminary analysis has shown both groups to be homologous for age and gestation (30 years and 40 weeks, respectively). The spontaneous vertex deliveries in the belt and control groups were 55% and 35%, respectively ($P<0.01$), and the instrumental vaginal deliveries were 42% and 60% ($P<0.025$). Induction of labour, use of oxytocin and Caesarean sections were similar in both groups.

The Labour Assister increases spontaneous vertex deliveries and reduces instrumental vaginal deliveries in nulliparous women with singleton cephalic pregnancies at term using an epidermal.

10. Antenatal diagnosis of trisomy 21 – the West of Scotland experience

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Trisomy 21 is the most common chromosomal anomaly (live birth incidence ≈1:600). Recent advances in antenatal serum screening and more widespread application of ultrasound markers have been responsible for a four-fold increase in the antenatal detection rate and reduction in live births. As yet it is unclear as to whether trisomy 21 detected by serum screening is a distinct group from those detected because of ultrasound markers. Many patients are reluctant to undergo invasive pre-natal diagnosis and request detailed anomaly screening in lieu of this.

To determine the mode of trisomy 21 diagnosis, the place of ultrasound in detection and the sensitivity of ultrasound in detecting markers.

Retrospective case note review of cases of trisomy 21 occurring in the West of Scotland 1991–1997.

One hundred and thirty cases were identified; 95 analysed at time of abstract, we anticipate that all cases will be analysed by 4/9/97.

Sixty-five per cent (62/95) of cases were detected antenatally. Of these 54% (51/95) of patients were at high risk from serum screening, 9% (9/95) of these high-risk patients decined invasive pre-natal diagnosis. An additional 11% (10/95) of patients were at high risk because the maternal age was >35 years. A recognized marker for trisomy 21 was found at post-mortum or post-natal assessment in 54% (51/95). Only in 20% (19/95) of patients was the marker identified antenatally. Therefore, the majority of the detailed ultrasound scans were false negative assessments. However, the use of ultrasound to look for markers is extremely variable.

The subset of foetuses picked up by serum screening appear to have fewer detectable structural anomalies. This may be related to the gestational age at the time of assessment.

11. Gonadotrophin-induced pregnancies in Belfast: 1979–1996

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This is an audit of all pregnancies resulting from ovulation induction using gonadotrophins in Belfast over a 17-year period.

A cohort descriptive study.

Regional fertlity centre at the Royal Victoria hospital, and the gynaecology unit at the Belfast City hospital.

One hundred and ninety-nine consecutive conceptions.

Patient characteristics and outcome of pregnancy.

All patients were aged between 20 and 40 years. The main causes of anovulation were: PCOS (66%), hypothalamic causes (19%) and hyperprolactinaemia (4%). Forty-six per cent of patients were nulliparous and 18% had previous spontaneous abortions only. Fifty-one per cent of the patients who had previous successful

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pregnancies had been treated with ovulation-inducing drugs at that time. Sixty per cent of pregnancies occurred within three treatment cycles. There were 38 spontaneous abortions in the first trimester, and 14 in the second trimester. There were two ectopic pregnancies. There were two intra-uterrine deaths and seven congenital defects in the 148 continuing pregnancies. There were 18 sets of twins, two sets of triplets and one set of quins.

The most common problems antenatally were: premature pre-labour rupture of membranes, premature labour, intra-uterine growth retardation, antepartum haemorrhage and pre-eclampsia. There was a 33% Caesarean section rate. There was a 1.23:1 male to female ratio (higher in multiple pregnancies). Fourteen per cent of singletons, and 52% of multiple births were admitted to an intensive special care baby unit (SCBU) facility.

This is the largest study to date to examine the outcome of pregnancies resulting from ovulation induction solely with gonadotrophins. The current policy of performing six treatment cycles before management reassessment may not be efficient. Four cycles followed by a single cycle of IVF would be expected to both improve the cumulative pregnancy rate and the cost efficiency. The data confirm the high incidence of multiple pregnancy and early pregnancy loss associated with assisted conception. There seems to be a definite trend towards increased male offspring, which although not statistically significant, is confirmed by studies of ovarian hyperstimulation programmes. The potential for increased cost of this fertility service in relation to an increase in perinatal morbidity is discussed.

12. Audit of the impact of magnesium sulphate on the management of severe pre-eclampsia in a London university hospital

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Hypertensive disorders of pregnancy remain a significant cause of maternal mortality and morbidity. We describe the impact of the introduction of a regional protocol (including the use of magnesium sulphate on the morbidity of women with severe pre-eclampsia attending an inner London university hospital.

A retrospective analysis was performed of all patients treated with magnesium sulphate ($MgSO_4$) from October 1995–September 1996. Thirty-five patients were identified from the labour ward and intensive care unit (ICU) records as having been potentially treated with $MgSO_4$. Of these, 30 sets of notes were available for analysis and 22 women were identified as having received $MgSO_4$. Treatment consisted of 4 g $MgSO_4$ given intravenously (i.v.) over 20 min followed by an infusion of 2 g per hour until 24 h post-delivery as per the protocol written by Robson *et al.* [1] Plasma levels were not monitored and the women were reiewed hourly to review respiratory rate and the presence of deep tendon reflexes. During this period 21 obstetric patients were admitted to the ICU (seven with hypertensive disease).

Twenty-two women were treated with $MgSO_4$ during this audit of which 50% were of African origin (21% in the maternity population). Their mean highest blood pressure was 175/111 (180/95–220/120) mmHg with 14 women having >three pluses of proteinuria. Nine women developed thrombocytopenia (100×10^9 L), the mean urate was 0.436 mmol L^{-1}. Five women were admitted to the ICU (two renal complications, two haematological and one for routine observations). Three women had to have their $MgSO_4$ stopped for side effects (one was flushed, one was drowsy and one had a decreased respiratory rate though her Mg level was in the therapeutic range). There were no eclamptic fits after starting treatment.

In comparison with a previous audit [2] (during which time Phenytoin was used) the total number of ICU admissions decreased (23 per annum in this study as compared with 29 per annum in the previous one); this reduction is almost entirely accounted for by the reduction in admissions for hypertensive disorders.

Best practice for the management of severe pre-eclampsia includes both the use of regionally agreed protocols and the use of $MgSO_4$ as anticonvulsant of choice, although its use prophylactically is still controversial. At this hospital we have shown that $MgSO_4$ is safe to use with side effects being minor or quickly reversed (without the need to measure magnesium levels). We have shown a reduction in ICU admissions for hypertensive

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disease which is due to a number of factors including greater use of regional anaesthesia and improved nursing care on the labour ward. We feel that $MgSO_4$ is safe to use for severe pre-eclampsia and the labour ward (or ideally an obstetric high-dependency unit) is a safe place to manage these patients.

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13. Maternal mortality in the Peninsula Maternal and Neonatal Service, Cape Town, South Africa

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Maternal mortality in Africa is some 500 times higher than in northern Europe. South Africa shows features of both a developing and a developed country in its patterns of health care provision. The Peninsula and Maternal and Neonatal Service (PMNS) in Cape Town is the only community-based perinatal service (CPS) in South Africa. The essential requirements for a CPS are regionalization, a tiered system of perinatal care facilities, continuing perinatal education, appropriate equipment, comprehensive referral criteria, adequate means of communication and transport, regular audit and community acceptance. A central feature of the PMNS is the Midwife Obstetric Unit (MOU) as the Level 1 perinatal facility.

Maternal mortality rates (MMRs) and the causes of all maternal deaths in the PMNS and its predecessor have been analysed since 1953.

Between 1953 and 1987–1989 the MMR dropped from 300 to $31/10^5$ deliveries. This decrease has been credited to the development of the PMNS system. Since then the MMR has risen, largely due the negative impact of the burgeoning informal settlements in the PMNS region.

In the PMNS, two-thirds of all maternal deaths are caused by hypertensive disorders of pregnancy, sepsis, haemorrhage, cardiac disease and pulmonary embolism. Other important maternal problems include age over 34, unbooked status, parity over 4 and emergency Caesarean section.

It is submitted that the high maternal (and perinatal) mortality and morbidity rates in developing countries could be substantially lowered by implementing the essential requirements for a CPS, as has been demonstrated in the PMNS region.

14. Obstetric complications probably contribute to schizophrenia: a Scottish case control study

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There have been many reports of a higher incidence of 'obstetric complications' in the histories of schizophrenics than of controls, but because of the methodological shortcomings of most of these comparisons the relation remains controversial.

The Information and Statistics Division of the Scottish Health Services possesses comprehensive records, on magnetic tape, covering all psychiatric hospital admissions and all hospital deliveries in Scotland since 1971. This database made it possible to identify the obstetric records of people born in 1971–1974 who were subsequently admitted to hospital with a diagnosis of schizophrenia, and then to compare their standardized obstetric records with those of controls matched for maternal age and parity, paternal occupation, sex and time and place of birth.

One hundred and fifteen schizophrenic/control pairs were compared. The former showed a highly significant ($P<0.001$) excess of complications of both pregnancy and delivery. In particular, there was a significant excess of pre-eclampsia (10 vs. 2) and of infants detained in hospital for neonatal care (18 vs. 6).

The raised incidence of obstetric complications often reported in schizophrenics is genuine and probably contributes to the aetiology of the condition. Brain damage secondary to foetal anoxia is the likely mechanism.

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15. Transmission of the news of chloroform anaesthesia from Edinburgh to Boston

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Professor James Young Simpson described the anaesthetic effects of chloroform, as an alternative to ether anaesthesia, in November 1847. While much has been written about how the news of ether anaesthesia was brought to Britain from Boston, little is known about the transmission of information on chloroform anaesthesia from Britain to the American continent.

Professor Simpson's first announcement of chloroform anaesthesia was given on 10 November 1847 and he published a report on 12 November. On 15 November he reissued the report with a postscript in which he described having given chloroform to 50 patients without complications. We set out to examine the likely distribution of the pamphlet in the United States. We found two copies of the report. One is in the Frances A. Countway Library, Boston and the other in the Norman Library of Medicine and the Life Sciences, San Francisco. These were presentation copies sent to Dr J. V. C. Smith, Editor of the Boston *Medical and Surgical Journal* and to Dr J. C. Warren, the surgeon who performed the first surgical operation under ether anaesthesia given by W. T. G. Morton at the Massachusetts General Hospital on 16 October 1846. Professor Simpson sent out these copies on 19 November from Edinburgh and judging from postmarks on the copies, they had reached Boston by the end of 1847.

16. Stress response to tracheal intubation vs. laryngeal mask in normotensive and hypertensive patients

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Among the advantages of the laryngeal mask airway (LMA) is that its insertion is associated with a smaller haemodynamic response compared with laryngoscopy and intubation. This study was designed to investigate stress responses to tracheal intubation and laryngeal mask insertion in normotensive and hypertensive patients.

Eighty adult patients of both sexes, aged between 50 and 75 years, and classified as ASA Class I or II, were scheduled for elective lower abdominal surgery. They were divided into two equal groups, respectively, of 40 normotensive and 40 hypertensive patients. They were then further subdivided according to the method of airway management to two equal subgroups of 20 patients each.

According to the patient's group either intubation or LMA insertion were performed after induction of anaesthesia with thiopentone and muscle relaxation with suxamethonium. The haemodynamic variables were recorded immediately, 1, 3 and 5 min after intubation or insertion of LMA. Blood samples were taken for determination of serum/plasma cortisol and plasma ACTH.

Haemodynamic variables were found to be significantly increased immediately after and for the subsequent 3 min following intubation and mask insertion in both groups. These increases showed the same pattern of rise in both groups, but were more marked following laryngoscopy and intubation. Significant increases were recorded in the rate-pressure-product (RPP) in both groups, but were not associated with any arrhythmias or myocardial ischaemia. Plasma cortisol and plasma ACTH showed increases which were not significant.

We conclude that, although laryngeal mask insertion is associated with attenuated circulatory responses compared with laryngoscopy and intubation, the use of additional pharmacological agents is essential to block adequately the stress response to such procedures.

17. The immune consequences of subarachnoid anaesthesia

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Surgical trauma and anaesthesia are known to cause immunosuppression [1]. Extradural and subarachnoid

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anaesthesia (SA) may protect against the immunosuppressant effects of surgery depending on the site and extent of surgery [2]. There is no evidence on the effects of SA or extradural anaesthesia alone on the immune mechanisms. The aim of this study was to determine the effects of SA alone on the immune system.

After institutional approval and informed consent patients undergoing elective inguinal hernia repair were studied. All the unpremedicated patients received standard SA with 3 mL 0.5% heavy bupivicaine via a 25-G Whitacre needle following fluid pre-load with 500 mL 0.9% saline to achieve a block >T10. Immune function was monitored by measuring natural killer (NK) cell and lymphokine-activated killer (LAK) cell function 1 day pre-operatively; before SA; 45 min after SA before surgery; 90 min after SA during surgery; and 1 day post-operatively. Mean NK and LAK cell function was compared with pre-operative values using lytic unit 30 cytotoxicity of K562 cells and Daudi cells, respectively. Interleukin 6 (Il 6) was measured at the above times and at 15 min intervals following SA up to 90 min. Demographic, anaesthetic, surgical and medical data were also obtained. One-way ANOVA was used when appropriate and $P<0.05$ was considered statistically significant.

Six patients were studied. There were no complications and the demographic data is shown in Table 2. NK and LAK cell function demonstrated no significant change from the pre-operative values. There was a small, but insignificant, rise in NK and LAK cell function before SA was commenced. There was a significant rise in Il 6.

This demonstrates that SA anaesthesia has no effect on the host defence as measured by NK and LAK cell function for 45 min. It would have been desirable to monitor the effects of SA without surgery but would have been ethically unjustifiable. The small rise in NK and LAK cell function could be explained by endogenous catecholamine release. The rise in Il 6 levels is consistent with other studies and was present before SA was commenced. We acknowledge being funded by a grant from Aberdeen Royal Hospitals Trust Endowment Fund.

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18. Co-induction with propofol and ketamine: effects on heart rate (HR), arterial pressure (AP) and other features

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During induction of anaesthesia propofol causes a decrease in AP, a transient increase in HR and attenuates airway reflexes. The aim of the study was to evaluate haemodynamic changes following co-induction of anaesthesia with propofol–ketamine.

Eighty ASA I–III abdominal surgery patients (two equal, randomized groups) were anaesthetized using propofol with ketamine in a ratio of 2:1.5. Every millilitre of induction agent was administered over 3 s until the end-point of hypnosis was reached. Leptosuccin was added for endotracheal intubation. AP and HR were measured before, during, after injection of the induction agents, after intubation and every minute for the first 12 min. Anaesthesia was then continued with 70% nitrous oxide in oxygen, fentanyl and atracurium. Student's *t*-test was used for statistical analysis.

Two groups were comparable according to age, sex,

Table 2. (abstract 17) Demographic data

Weight (kg)	ASA (no pts) I	ASA (no pts) II	Height (cm)	Age (years)	Duration of surgery (min)	Block after 15 min (range)
82 ± 14	5	1	177 ± 6	53 ± 6	67 ± 23	T8 (T10–T6)

Mean ± SD.

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body weight and height, type and duration of surgery, ASA state and Mallampati test for intubating conditions. We found no difference between groups in respect of: pain and spontaneous movement on injection, time to hypnosis (64.5 ± 13.6 s vs. 60.3 ± 12.1 s) and intubating conditions. Ketamine significantly reduced the dose of propofol at induction: 114.0 ± 20.4 mg in the propofol group to 98.6 ± 20.6 mg in the propofol–ketamine group ($P<0.05$). Mean ketamine dose added to propofol was 60.5 ± 11.2 mg (0.69 ± 1.46 mg kg^{-1}). We found a significant decrease in systolic AP after bolus injection in the propofol group and significant increase after intubation and 2 min later, with a decrease towards pre-induction levels 3 min after intubation. In the propofol–ketamine group systolic AP significantly decreased after induction but did not change significantly during and after intubation. Changes in diastolic AP were similar: a significant decrease after induction, increase during intubation and slow decrease 4 min after intubation in the propofol group; and a decrease after induction and significant increase only 1 min after intubation. HR in both groups significantly increased after injection. That increase lasted 5 min after intubation for propofol and 6 min for the propofol–ketamine group. There were no significant differences in HR between the two groups. Patients from the propofol group had a significantly higher systolic AP measured on 5, 7, 8 and 10 min after intubation compared with the propofol–ketamine group, and significantly higher diastolic AP on 4, 7, 8 and 10 min ($P<0.05$).

Induction with propofol and co-induction with ketamine and propofol decrease AP. Ketamine added to propofol for induction does not prevent a decrease in AP, but attenuate the hypertensive reaction to endotracheal intubation, without affecting the change in HR. In neither group did ketamine alter pain on injection, spontaneous movement after injection, hypnotic time or intubating conditions. Co-induction with ketamine reduced the propofol dose for induction.

19. Carboxyhaemoglobin and closed-circuit anaesthesia

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With a change in concept of the uptake of inhalation anaesthetics based on common physiological principles [1], we are able to provide simple, easily applicable closed-circuit anaesthesia with an existing anaesthesia machine. Following intubation, the anaesthesia circuit and FRC were primed with the desired O_2 and anaesthetic concentration with high flow anaesthetic/O_2/air mixture for several minutes. Following this, only the supply of calculated anaesthetic vapour, dependent on the desired inspired anaesthetic concentration, and 200–300 mL min^{-1} of O_2 are required for maintenance of anaesthesia. Recent pubications [2,3] indicate the possible production of carbon monoxide (CO) during closed-circuit anaesthesia with inhalational anaesthetics. We have examined the possibility of CO production in the circuit by determining blood carboxyhaemoglobin levels during closed-circuit anaesthesia.

With IRB approval, we administered general anaesthesia with inhalation anaesthetics using a closed circuit. After several minutes of high flow gas mixture to prime the anaesthesia circuit and FRC, we closed the circuit with a minimum total gas flow of less than 500 mL min^{-1}. We obtained arterial blood samples for measurement of carboxyhaemoglobin levels during the initial stages of anaesthesia and at the end of surgery. We recorded the length of closed-circuit, fresh gas flow rate and changes in the soda lime.

We studied 73 patients. During the mean duration of 3.74 ± 0.92 h of closed-circuit anaesthesia, very little change occurred in carboxyhaemoglobin level (from 0.88 + 0.57 to 0.90 + 0.59). Average fresh gas flow during closed-circuit anaesthesia was 322 + 99 mL min^{-1}. No correlation was found between the changes of soda lime canister and the level of carboxyhaemoglobin.

During 73 consecutive cases with closed-circuit anaesthesia, we failed to demonstrate an increase in blood carboxyhaemoglobin level. Possible explanations are: (1) the limited use of inhalation anaesthetic agents despite maintaining similar adequate inspired anaesthetic concentration; and (2) humidity (water content) of soda lime is much higher than in the conventional high fresh gas flow anaesthesia. We consider that closed-circuit anaesthesia is a simple, safe anaesthetic technique and able to provide a considerable reduction in environmental

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pollution as well as anaesthetic consumption. Closed-circuit anaesthesia is also able to maintain airway humidity and body temperature with good haemodynamic stability.

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2 *APSF Newsletter* 1994; **9**: 14.
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20. Closed-circuit anaesthesia with air

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On many occasions, we use O_2/air mixtures instead of $N_2/O/O_2/$ or O_2 alone as a carrier gas to limit the inspired O_2 concentration. Most anaesthetic machines currently available are equipped only with a high flow air rotameter. Because nitrogen is inert and less soluble than O_2 or N_2O we have developed a new simple and safe technique for closed-circuit anaesthesia with air using a conventional anaesthetic machine. With proper recognition of the existence of the FRC and the alveolar membrane, we are able to calculate the required anaesthetic vapour according to the desired inspired concentration and this enables us to practise simple and safe closed-circuit anaesthesia with a conventional anaesthetic machine [1]. Following intubation, the anaesthesia circuit and FRC were primed with the desired O_2 and anaesthetic concentrations with high flow anaesthetic/O_2/air mixture for several minutes. Thereafter, only the supply of calculated anaesthetic vapour and 200–300 mL min^{-1} of O_2 are required for maintenance of anaesthesia. Air is no longer required after the initial prime of the FRC and the circuit.

With IRB approval, 50 patients undergoing various operations requiring general anaesthesia were studied. Inspiratory–expiratory gases were sampled near the ET tube via a gas analyser. Fresh O_2 flow rate and change of nitrogen concentration were recorded.

Average $235 + 24$ mL min^{-1} of O_2 is required during closed-circuit anaesthesia. The average change in nitrogen concentration in the circuit was $2.4 + 0.9\%$ over the $3.2 + 0.9$ h duration of closed-circuit anaesthesia.

Combined use of O_2/air as a carrier gas during anaesthesia provide advantages by avoiding O_2 toxicity, and also provides alveolar splinting of the lung and prevents collapse of marginally ventilated alveoli. Because high concentrations and high flow rates of nitrous oxide are not used, environmental pollution is reduced. Following an initial prime of the FRC and the anaesthesia circuit with the desired oxygen–nitrogen mixture, we were able to maintain steady oxygen concentration in the circuit with anaesthetic and a minimal O_2 supply. An average 2% drop in O_2 concentration over 3 h of surgery indicates minimal outflow of stored body nitrogen along a concentration gradient. This simple closed-circuit anaesthesia technique provides safe anaesthesia with the maintenance of near physiological gas concentrations in the lung.

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1 *Anaesth Intensive Care* 1992; **22**: 363.

21. Closed-circuit anaesthesia with desflurane

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With proper recognition of the existence of the functional residual capacity and alveolar membrane, a new concept of uptake of inhalation anaesthetics has been developed [1]. This physiological and common-sense approach to understanding the process of uptake of inhalation anaesthestics greatly facilitates the practice of closed-circuit anaesthesia. This new approach not only provides a simple calculation of the minute-to-minute requirement of anaesthetic vapour depending on the desired inspired anaesthetic concentration but also makes it possible

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to practise closed-circuit anaesthesia safely with conventional anaesthetic equipment. Because desflurane has the unique characteristics of a low blood–gas solubility coefficient, limited uptake at a given anaesthetic concentration (low fraction of uptake), and the requirement of a relatively high inspired concentration for anaesthesia, a large portion of desflurane will be wasted when a high fresh gas flow is utilized. Our aim in this study was to compare the the economic impact associated with closed-circuit anaesthesia with two inhalation anaesthetics, isoflurane and desflurane.

Forty-six patients undergoing abdominal surgery under general anaesthesia were randomly assigned to two groups. One group was anaesthetized with isoflurane. The other group was anaesthetized with desflurane. Both groups used simplified closed-circuit anaesthesia with the application of a new concept of uptake, and application of the EBC, a new index of the depth of anaesthesia obtainable after each respiratory cycle. Following intubation, the anaesthesia circuit and FRC were primed with the desired O_2, and anaesthetic concentration with high flow anaesthetic-O_2/air mixture for 10 min (normal dialled anaesthetic concentration at 2% with isoflurane and 8% with desflurane at total gas flow of 3000 mL min^{-1}). Thereafter, only 200–300 mL min^{-1} of 100% O_2 was provided for the maintenance of closed-circuit anaesthesia. A calculated supply of anaesthetic vapour was also provided through the vaporizer to maintain at least 0.3% of isoflurane or 2.5% of desflurane in mixed-venous blood. The following parameters were compared between the two groups: (1) total anaesthetic consumption per hour; (2) the patient condition on arrival in the recovery room; and (3) PCA (morphine) dose required during the 12 h post-operative period.

Significantly higher anaesthetic vapour consumption and costs were demonstrated in the group anaesthetized with desflurane during the first hour of anaesthesia compared with the isoflurane group. However, during the subsequent hour, the average cost per hour with desflurane dropped significantly to the level of isoflurane.

In contrast with what was previously believed, with the application of a new theory of uptake of inhalation anaesthetics, closed-circuit anaesthesia can be practised with ease, simplicity and maximum safety. This quantitative approach provides optimal airway humidity, haemodynamic stability and predictable wake-up. In addition, with the use of desflurane, closed-circuit anaesthesia provides a significant cost saving.

Reference

1 *Anaesth Intensive Care* 1994; **22**: 363.

22. Cardiorespiratory stability during transport of the critically ill

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Inadequate secondary transport of the critically ill can result in systemic insults, most commonly hypotension and hypoxia [1–3]. We prospectively measured mean arterial blood pressure and oxygenation prior to and immediately post-transfer on 50 critically ill patients. We aimed to show that specialist transport using invasive monitoring, dedicated equipment and personnel results in cardiorespiratory stability during transport of the critically ill.

Fifty consecutive patients were transferred according to our normal clinical practice. They were monitored with the portable Propak monitor and ventilated with an Oxylog 2000 ventilator. After appropriate resuscitation and stabilization they were established onto our ventilator and a mean arterial pressure was recorded from the Propak and a set of blood gases analysed using the Hewlett-Packard 'I-Stat' portable blood gas analyser. A second set of readings were taken on arrival at the destination unit but before transferring onto their monitors and ventilator. The MAP values were compared using a paired Student's *t*-test and (FiO_2–PaO_2) values using Mann–Whitney analysis.

Transportation of the critically ill is increasing. All patients should be delivered to their destination in at least as good a condition as they left. This requires careful preparation, monitoring and continued support. Specialist regional teams dedicated to and trained for transport of the critically ill will best achieve these goals.

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Table 3. (abstract 22) Mean arterial pressure (M) and FiO_2–PaO_2 measured after resuscitation and after arrival at destination

	MAP (1)	MAP (2)		(FiO_2 1–(PaO_2) (1)	(FiO_2–(PaO_2) (2)
Observations	26	26	Observations	26	26
Mean	**77.8**	**82.7**	**Median**	**38.7**	**45.6**
			Point estimate	−2.6 (95% CI–15, 8.8)	
P-value	0.16		*P*-value	0.55	

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23. Analysis of hypoxic changes in traumatic shock patients

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The purpose of the study was to investigate the dynamics of post-traumatic hypoxia in traumatic shock patients. Thirty multiple-injured (excluding severe head injury) adult patients were studied. From day 1 to day 5 the following tests were performed: PaO_2/FiO_2 and SaO_2 in arterial blood (ABL-2 'Radiometer'), lactate dehydrogenase (LDG) in arterial blood (enzyme assay, FP900), lactate and pyruvate in arterial blood (blood samples from femoral artery). In order to determine lung blood flow and alveolar ventilation, a lung rheogram was performed on 19 patients at the same time [1]. Patients were divided into two groups. In Group 1 patients ($n=10$) PaO_2/FiO_2 <33·3 KPa on day 2, in Group 2 patients ($n=20$) PaO_2/FiO_2 >33·3 KPa on day 2.

Details of the PaO_2/FiO_2, lung blood volume, alveolar ventilation SaO_2, lactate/pyruvate and LDG levels will be given for each of the 5 days for both groups.

In the first group four patients died on the 3rd–4th day after the injury; in the second group five patients died and only one during the investigation period. In the first group five patients had thoracic damage (multiple broken ribs), in the second group only two patients had that kind of trauma.

In conclusion: (1) thoracic damage leads to serious aggravation of post-traumatic hypoxia; (2) LDG is a good indicator of traumatic shock severity; and (3) the most probable cause of prolonged post-traumatic hypoxia is a decrease in LBF and a corresponding increase of ventilation/perfusion inequality.

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24. Patient-controlled epidural analgesia with morphine or morphine plus ketamine for post-operative pain relief

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Epidural morphine has been shown to produce effective analgesia with side effects of nausea, vomiting, pruritis and sedation. Ketamine, an N-methyl-D-aspartic acid receptor antagonist, has been reported to provide pain relief for acute pain by epidural administration. The aim of this study was to compare the analgesic and side effects of patient-controlled epidural analgesia (PCEA) with morphine alone and morphine plus ketamine during the first 24 h after elective lower abdominal surgery.

Sixty patients were randomly assigned into two equal groups. Group I received 1 mg epidural morphine after surgery and using the patient-controlled analgesia device proceeded to deliver morphine

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0.2 mg h^{-1}, 0.2 mg $bolus^{-1}$. Group II received an epidural loading dose of 1 mg morphine plus 5 mg ketamine and using the patient-controlled analgesia device to deliver 0.2 mg morphine + 0.5 mg ketamine h^{-1}, 0.2 mg morphine + 0.5 mg ketamine $bolus^{-1}$. All patients were observed for pain relief and adverse effects for 24 h. Pain was assessed using visual analogue scales and sedation was graded on a four-point rank drowsiness score. Cardiovascular and respiratory parameters were also recorded.

Mean morphine consumption was 8.6 ± 0.7 mg for Group I and 6.2 ± 0.2 mg for Group II. Although Group II utilized significantly less morphine ($P<0.05$), pain relief was better in Group II than in Group I ($P<0.05$) in the first 3 h. Vomiting occurred more frequently in Group I (25%) than in Group II (12%). The frequency and severity of pruritis and sedative level were similar in the two groups.

PCEA with morphine plus ketamine decreases morphine consumption and with better pain relief and less adverse effects than PCEA with morphine alone. PCEA with morphine plus ketamine is an acceptable alternative to PCEA with morphine alone after low abdominal surgery.

25. Lymphotropic injections of morphine for postoperative analgesia

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Despite advances in knowledge of pharmacology of analgesics and more effective techniques for postoperative pain control, many patients continue to experience discomfort. Intramuscular (i.m.) bolus administration of opioids is used widely, especially morphine, but has disadvantages: excessive sedation, respiratory depression and short duration of action.

To minimize adverse effects and to prolong the analgesia we have used indirect intralymphatic injections [1]. Drugs are injected in the upper lateral area of the leg, rich in lymphatic vessels, and a blood pressure cuff (60 mmHg) is applied to the ipsilateral thigh for 2 h immediately after injection. The drug is absorbed in the lymphatic system. We administered morphine hydrochloride 10 mg to 120 patients of both sexes (age range 17 to 72 y) after various types of trauma, orthopaedic, urological and vascular surgery. For a control we used i.m. bolus morphine with 10 mg in another group of 80 patients after similar operations. The study was randomized. Subjective and objective tests were used to assess the adequacy of analgesia. Subjective sensation was assessed on a four-point scale and 100 mm visual analogue scale. Sensory testing was by nerve stimulation of the ring finger. Pulse oximetry and spirometry were used and the respiratory rate and haemoglobin saturation with oxygen noted. Heart rate, blood pressure, ECG, peripheral pulse wave were monitored, and central haemodynamic responses were studied by transthoracic impedance. Assessments were made before operation, at 30 min and 1 h intervals.

Subjective assessment in controls showed good analgesia in 64 patients and moderate analgesia in 16. After injection these figures were 102 and 18, respectively. The onset of analgesia and time to peak effect were the same in both groups. Marked sedation was noted after all injections. The duration of analgesia after i.m. injection was 2.5–3 h and 7.5–8 h after lymphotropic injection. Indices of respiratory depression were more obvious after i.m. injection. The haemodynamic variables were similar in both groups.

The rationale for lymphotropic administration of morphine will be discussed.

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26. Haemodynamic monitoring during diagnostic gynaecological laparoscopy

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Haemodynamic changes during laparoscopy result from the effects of pneumoperitoneum and patient position. There is a decrease in cardiac output with an increase in arterial pressure and systemic and pulmonary vascular resistance. This work described an endo-oesophageal probe equipped with ultrasonic transducers, a Doppler ultrasound velocimeter and an 'M' mode ultrasound scanner imaging system to

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measure aortic blood flow (ABF), the systolic, diastolic and mean arterial pressures (SAP, DAP, MAP) and heart rate (HR), stroke volume (SV), total vascular resistance (TSVRa). The patients studied were undergoing gynaecological laparoscopy. We noted haemodynamic changes, first at the beginning of anaesthesia, after Trendeleburg positioning, and at the end of peritoneal insufflation of 4 L of CO_2. We compared the measurements in two groups of 30 females under general anaesthesia: (a) induction with propofol 2.5 mg, atracurium 0.06 mg kg^{-1}, with propofol 6 mg $kg\ h^{-1}$ and fentanyl 0.002 mg kg^{-1} and atracurium 0.04 mg kg^{-1} for maintenance; (b) induction with thiopentone 4 mg kg^{-1}, Myorelaxin and maintenance with O_2/N_2O (1:1) and halothane 0.6 vol.%, fentanyl 0.002 mg kg^{-1} and pancuronium 0.04 mg kg^{-1}. ABF in the second group decreased from 3.8 to 2.75 L min^{-1}. TSVRa increased from 1846 to 2050. In the first group ABF decreased from 3.69 to 2.53 L min^{-1} and TSVRa increased from 1504 to 1730.

We conclude that this technique is useful during laparoscopy for dynamic monitoring and also offers a sensitive and early method for detecting gas embolism.

27. Combined spinal/epidural bupivacaine/ sufentanil for labour analgesia

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Sixty parturients in active labour, aged 17–34 years, ASA class I, were divided in two groups. In the first group we used bupivacaine 1 mg sufentanil 0.005 mg into 2 mL, in the second group bupivacaine 1 mg in 2 mL, administered intrathcally. Additional doses of bupivacaine 10 mL 0.25% were administered epidurally when needed. The epidural space was located in lateral decubitus position with loss of resistance technique. We used Tuohy G-16 and spinal needle G-26. We followed the changes HR, SBP, DBP, of the parturients, the level of sensory block and motor block (Bromage), pain score (PLS, PVA), duration of effective analgesia, foetal heart rate. Apgar score, the influence of analgesia in the course of labour.

Duration of analgesia with intrathecal bupivacaine/ sufentanil was between 90 and 160 min. Sixty-two per cent of patients (95% – multipara) had delivered with the intrathecal dose alone. The analgesia was excellent on the 5th min in 90% of the patients and in 95% of the patients at the 10th min. The only side effect was pruritus. Hypotension and paresis were of no concern.

In our opinion intrathecal bupivacaine/sufentanil provides very good analgesia with rapid onset and duration for $\approx$2 h and it may be used for analgesia during labour.

28. Analysis of obstetric patients treated in general intensive care units

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The critically ill obstetric patients who require intensive care are few and a multidisciplinary intensive care unit (ICU) is often used to care for these patients. This study reports characteristics of obstetric patients treated in general ICUs of our hospital from 1985 to 1996.

A retrospective review of all obstetric patients who were cared for in the general ICU of our hospital from 1985 to 1996 was undertaken. The reasons of admission to an ICU, morbidity, duration of ICU stay and outcome were examined.

Forty cases, one peripartum and 30 post-partum, were identified; 18 of the latter (46%) were referred from other hospitals and seven of them were associated with intrauterine death of the foetus. One patient with severe asthma was admitted to the ICU for peripartum respiratory care. The primary obstetric complication was abruptio placantae in five, pre-eclampsia/eclampsia in 15, postpartum haemorrhage in eight, puerperal sepsis in one and amniotic fluid embolism in one. There were 10 patients with non-obstetric conditions including cardiac disease in four, haematological disorders in three, hyperthyroidism, asthma and pulmonary thromboembolism in one, respectively.

Severe morbidity was found in 17 patients (43%); pulmonary embolism in two, pulmonary oedema in two, acute renal failure in eight, HELLP syndrome in

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two, pneumonia in one and disseminated intracoagulopathy in 10. A patient with pulmonary embolism secondary to amniotic fluid embolism did not respond to cardiopulmonary resuscitation. Another patient with post-partum pulmonary thromboembolism was successfully treated with pulmonary thrombectomy. Only one of the patients with acute renal failure required haemodialysis. In three of eight patients with post-partum haemorrhage, a massive blood transfusion over 10 mL was given peri-operatively.

Twenty-four of 40 patients (60%) including all the patients with post-partum haemorrhage and eight with non-obstetric disorders had a smooth course and were discharged from the ICU within 24 h. Five patients stayed in the ICU over 1 week, and nine patients stayed for 2–4 days. Most of them were related to pre-eclampsia/eclampsia.

This study reconfirmed that proper pre-natal care is essential for reducing post-partum morbidity and that pre-eclampsia/eclampsia remains a significant complication with high morbidity. Considering the number of critically ill obstetric patients who require intensive care, it appears that the general ICU is the most practical and economic facility to care for these patients.

29. Quality of life in children after emergency surgical operations, resuscitation and intensive therapy in the neonatal perod

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Improvement in surgical, anaesthetic and intensive care provision together with developmet of medical science and technology has decreased mortality in children and raised a new problem for long-term management–assessment and the improvement in the quality of the survivors.

We studied the biopsychosocial development of 606 children, 180 of whom underwent emergency surgical operations, resuscitation and intensive therapy in the neonatal period, compared with 426 as a control group. We analysed the hospital records, discharge letters from the maternity units, pregnancy charts, outpatient development charts for children, as well as the results of biopsychosocial development in children in age groups 0–14 years. Statistical analysis was carried out with the assistance of a software package (Statgraphics).

Following neonatal surgery, resuscitation and intensive therapy the quality of life of the survivors was lower than for those in the control group according to all parameters of biopsychosocial development, based on self-estimation (the mean difference 11%) as well as expert estimation (the mean difference 24%). The expert estimation of quality of life was lower than that by self-estimation (the mean difference 13%). The quality of life was especially affected in early life and during the primary school period until 10 years old. Other factors which tend to worsen outcome are female sex, severity of initial condition, hypoxia and malnutrition.

Survivors of neonatal surgery, resuscitation and intensive therapy demonstrate deranged biopsychosocial development which lowers their quality of life compared with the general population. Biopsychosocial rehabilitation may only be successful if it is early, persistent and considers the above stated factors contributing to the outcome.

30. Anaesthesia for videoarthroscopy of the knee. A comparison between desflurane and sevoflurane

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Sevoflurane and desflurane have a low blood:gas partition coefficient and consequently recovery from these anaesthetics is known to be rapid. The aim of this study was to compare recovery characteristics of the newer inhalational anaesthetics, desflurane and sevoflurane, following diagnostic and minimally invasive arthroscopic knee surgery in 50 ASA I–II patients.

Base-line values were obtained for the following psychomotor tests: digit symbol substitution test (DSST), perceptive accuracy test (PAT) and simple reaction time (SRT). The patients were then randomly allocated to one of two groups according to an open

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Table 4. (abstract 30) Demographic and recovery data

	Sevoflurane	Desflurane
Age (years)	31.0 (8.5)	27.4 (6.5)
Weight (kg)	81.6 (13.0)	80.2 (14.4)
Duration of anaesthesia (min)	47.3 (25.7)	41.6 (23.1)
Induction dose of propofol (mg)	241 (50)	251 (61)
Time to eye opening (s)	744 (210)*	504 (218)
Time to give name (s)	808 (225)*	517 (249)
Time to sit (min)	25.2 (13.8)	24.3 (15.3)
Time to 'home ready' (min)	209 (60)¶	188 (43)

* $P<0.01$; ¶ results of one patient who was discharged the following day have been excluded.

(unblinded) study design: Group D (Desflurane) were maintained with 2–6% desflurane while Group S (Sevoflurane) were maintained with 1–3% sevoflurane. Glycopyrrolate 0.2 mg was given to all patients prior to induction of anaesthesia. Propofol was used as the induction agent and the laryngeal mask was used to maintain a free airway. Oxygen and air (FiO_2 0.33) were used as the carrier gases. The concentration of desflurane or sevoflurane was adjusted in order to maintain adequate anaesthesia and stable haemodynamic responses. In both groups, alfentanil was given at induction and every 15 min. At the end of the operation the gases were turned off abruptly and 100% oxygen was delivered at 6 L min^{-1} until eye-opening. Early recovery was measured by the time to eye-opening, giving name and date of birth. Intermediate recovery was measured by psychomotor testing every 30 min after the end of anaesthesia, and the time to sit up in bed, drink fluids and discharge home, by a nurse who was blinded to the anaesthetic technique.

Early recovery was quicker in the desflurane compared with the sevoflurane group ($P<0.001$) (Table 4). Psychomotor recovery, as measured by the PAT, occurred significantly earlier in the desflurane compared with the sevoflurane group at 15 and 45 min ($P<0.001$) and as measured by the DSST at 30 min ($P<0.05$). The number of patients who could not perform the SRT test at 15 min was greater in the sevoflurane compared with the desflurane group (13 vs. 0) ($P<0.01$). No differences were found in other recovery parameters including home discharge between the groups. The incidence of pain and other minor post-operative complications was similar between the groups except for sore throat which was higher in the desflurane group.

Early and intermediate (psychomotor) recovery was quicker in the desflurane compared with the sevoflurane group but no differences were seen in discharge times.

31. Validating an ultrasound scanner in surgical patients and in volunteers

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Peri-operative urinary retention can lead to bladder distension and bladder dysfunction and can cause severe and lifelong complications. Thus, peri-operative information on the urine volume is of great importance. The aim of this study was to validate an ultrasonic device to determine urine volume. To evaluate a broad volume range, measured volumes were compared with true volumes in two groups. The first group consisted of surgical patients. Higher volume ranges were studied in healthy volunteers with a full bladder (maximum capacity).

After informed consent and institutional approval, 50 surgical patients with no pathology of the urinary tract were included. They were scheduled for operations requiring bladder catheterization. After induction of general anaesthesia the mean of three ultrasound measurements (BladderScan BVI 2500, Diagnostic Ultrasound, Redmond, WA, USA) was recorded, followed by urinary catheterization and measurement of the actual volume. In the other group 60 healthy volunteers were asked not to void for as long as possible. After three ultrasound measurements they voided in a validated bowl and the actual urine volume was measured. After collection of the urine, residual volumes were measured by scanning in both groups. The level of agreement between both methods was compared using linear regression and a modified bias analysis. Data are expressed as mean $\pm$ SD.

There were no residual volumes in patients and volunteers. In patients ultrasound volumes ranged

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from 14 to 698 mL (median 297 mL) and in volunteers 150 to 990 mL (median 573 mL). Urine volumes and ultrasound measurements did not differ significantly in both groups. Maximum voided volumes in males (660 ± 195 mL) and females (506 ± 186 mL) differed. Linear regression analysis showed a correlation coefficient between the ultrasound measurement and the actual urine volume of 0.95 in patients and 0.92 in volunteers ($P<0.001$). The bias in volume between the two methods (=mean difference) was 19 mL in patients and 31 mL in volunteers, while the limits of agreement ($= \pm 2 \times$ SD) ranged from 154 to -51 mL for patients and from 251 to -84 for volunteers.

Ultrasound bladder scanning is a reliable non-invasive method for measuring bladder volumes over a wide volume range. Post-operatively, urine volumes exceeding 500 mL probably necessitate catherization. Therefore, it seems that ultrasound scanning can be used peri-operatively to establish bladder distension and to prevent complications.

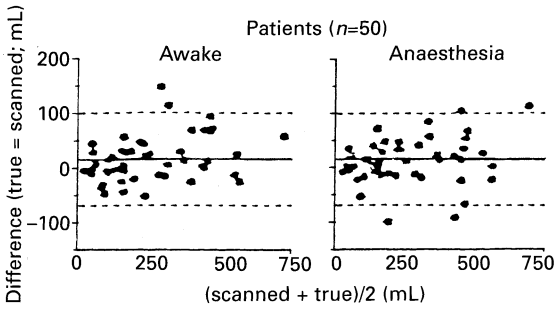

Fig. 1. **(abstract 31)** Bland Altman plot of surgical patients showing the mean of scanned and true urine volume on the X-axis against their difference on the Y-axis.

32. Cocaine-induced hyperkalaemia after suxamethonium?

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Life-threatening cocaine-related cardiac effects may occur when suxamethonium is used (Sch). Normally the serum potassium (K^+) concentration will increase by 0.3–0.5 mmol L^{-1}. The mechanism of Sch-induced hyperkalaemia is not known, but numerous factors including the reduction in the pseudocholinesterase (Pche) activity are considered. Pche activity is reduced in cocaine abusers.

In nine patients undergoing emergency surgery and who abuse cocaine, serum K was determined before and after Sch administration. Pche activity and liver function were assessed before induction of anaesthesia. The ECG was monitored throughout.

Sch was associated with an increase in serum K of 2.1 ± 0.7 mmol L^{-1} (median, SD). Serum K increased within the range 1.0–3.3 mmol L^{-1}. Pche activity was 30–70% less than normal. In five patients liver enzymes were abnormal, two exhibited cardiac arrhythmia, three patients were hyperthermic and one was delirious. Two patients had neurological seizures. There was a statistical relation between reduction in Pche activity and increase in K^+ after suxamethonium. Hyperkalaemic changes in the ECG occurred in one patient who had a serum value of 7.2 mmol L^{-1}.

It is recommended that in cocaine users succinylcholine should be avoided whenever possible.

33. Nocturnal desaturation and ECG ST-T abnormalities in the peri-operative period in patients undergoing infrarenal aortic reconstructon, preliminary report

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Peri-operative myocardial ischaemia is strongly associated with increased morbidity and mortality of patients who are the subject of major abdominal, vascular surgery. This group of patients also commonly suffer from post-operative hypoxaemia, even although there is little information regarding correlation between ECG ST-T abnormalities and nocturnal hypoxaemia [1]. Furthermore, little is known

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about how these changes affect the outcome of major vascular surgery.

The purpose of this prospective study was to assess peri-operative arterial blood haemoglobin saturation and evaluate the correlation between night desaturation and myocardial ischaemia manifested by the ECG ST-T abnormalities.

We examined 47 consecutive patients (42 male, five female) of mean age 60 ± 8.9 years, presenting for repair of an abdominal aortic aneurysm (20 patients) or aortoiliac occlusion (27 patients) with a vascular graft. Twelve patients suffered from pre-operative angina, eight had previous myocardial infarction. No patient suffered from chronic respiratory disease. All patients received standard general anaesthesia combined with epidural analgesia. Patients who had signs of uncorrected hypovolaemia and anaemia after surgery were excluded from the study. During 1 pre-operative and 4 post-operative nights (from 21.00 to 07.00 hours) patients were continuously monitored with the Athena monitoring system (S&W Medico Teknik). The following were recorded and analysed: SPO_2, heart rate (HR) and antero-lateral and inferior ST-T. We considered desaturation below 91% and ST-T depression below 2 mm or elevation above 3 mm to be significant.

In 23 (48.9%) patients nocturnal desaturation and in 14 (29.8%) patients ST-T abnormalities were recorded during the nights following surgery. In five (10.6%) patients myocardial ischaemic changes temporarily correlated with nocturnal hypoxaemia. However, none of these patients developed myocardial infarction. Analysis with Fisher's Exact Test revealed statistical significance between nocturnal SPO_2 changes and ST-T abnormalities in the 3rd post-operative night.

Nocturnal hypoxaemia and myocardial ischaemia are common complications of major vascular surgery. SPO_2 and ST-T changes in the ECG may be an important risk factor for post-operative cardiac morbidity. Although a correlation between these two parameters has been found, further investigation embracing more patients is necessary to confirm the relation between them and the incidence of life-threatening post-operative cardiac complications.

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34. A meta-analysis of epidural fentanyl as an adjuvant to local anaesthetics for surgical analgesia

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The efficacy of adding fentanyl to epidural local anaesthetics for decreasing the incidence of pain during surgery is controversial [1,2]. Moreover, epidural opioids can cause side effects [3]. Thus, the risk/benefit ratio of this practice is unclear. In order to define the role of fentanyl as an adjuvant to local anaesthetics for surgical analgesia, we have performed a meta-analysis on analgesia and side effects.

The search was conducted on Medline, Excerpta Medica, Science Citation Index, authors' data base, abstracts from anaesthesia meetings, textbooks and reference lists of articles retrieved. Trials were considered if they were prospective, controlled and at least one of the following outcome variables were studied: inadequate analgesia, respiratory depression, nausea, vomiting, pruritus, urinary retention, hypotension, sedation, Apgar score and respiratory depression of the newborn. The papers were independently evaluated by two assessors, according to a quality score. If a value of at least 50% of the maximum score possible was given by both assessors the paper entered the meta-analysis. Pooled odds ratios (OR) and confidence intervals (CI) were computed using the method of Yusuf [4]. A P-value <0.05 was considered as significant.

Of the 414 trials retrieved, 17 were included in the meta-analyses (11 on Caesarean section). Fentanyl dose was 25–200 μg. The results of meta-analyses are shown in Table 5. No case of respiratory depression was reported ($n = 120/119$ fentanyl/control). However, four cases of early respiratory depression were described in trials not included in the meta-analysis. Urinary retention and respiratory depression of newborn were outcome variables in only one selected paper. One case of respiratory depresssion of the newborn was observed. One case of severe pruritus and no case of severe sedation was reported.

Epidural fentanyl decreases the incidence of pain during surgery. The effect magnitude is clinically relevant (OR = 0.20, 95% CI 0.14–0.30). Mild pruritus and

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Table 5. (abstract 34) Meta-analysis applied to side effects

Variable	No. trials	*n* Fentanyl/control	OR (95% CI)	*P*
Inadequate analgesia	12	377/371	0.20 (0.14–0.30)	0.000
Nausea and/or vomiting	12	316/283	1.29 (0.85–1.95)	NS
Pruritus	11	301/268	5.59 (3.12–10.05)	0.000
Hypotension	10	285/248	1.21 (0.82–1.79)	NS
Sedation	7	243/205	1.88 (1.19–2.98)	0.003
Shivering	4	136/90	0.72 (0.38–1.34)	NS
Apgar score (1–5 min)	8	154/143	—	NS

mild sedation may be associated with its use. Rare occurrence of early respiratory depression cannot be ruled out. The results indicate that the addition of epidural fentanyl to local anaesthetics for surgical analgesia is advantageous and safe. Surveillance during 3 h after injection is recommended.

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35. Mutation findings in Danish MH families

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The mutation C1840T in the ryanodine receptor gene is responsible for MH in all pigs susceptible to MH. In humans, 16 mutations until now have been discovered in this gene and heterogeneity seems to be a problem. The purpose of this study was to assess mutation data in Danish MH families.

Members of 48 MH families who have undergone contracture testing for diagnosis of MH susceptibility were in addition tested for the eight published mutations in the ryanodine receptor gene on chromosome 19 by standard methods following isolation of DNA from blood samples.

In six families (12.5%), a mutation was found. The observed mutations were: C487T (one family), G1021A (one family), C1840T (one family [1]), G1840A (one family) and C6484T (two families). In five of these families complete concordance between the IVCT result and the presence or absence of the mutation was observed. In these five families, a total of 28 MHS individuals did have a mutation, whereas 12 MHN individuals did not have the mutation found in their susceptible family members. In addition, one MHEh and one MHEc individual, and five family members presumed to be normal did not have the mutation.

In the sixth family in which the C1840T mutation was found, discordance between the IVCT result and the presence or absence of the mutation was observed. In this family the mutation was present in five MHS individuals and absent in one MHN individual, one MHEh individual and two individuals presumed to be normal. However, the mutation was not found in three MHS individuals.

Physiological studies of membranes with incorporated mutated proteins have indicated that the C1840T mutation does lead to altered function of the membrane compatible with MH. For the other mutations such studies have not yet been performed. However, the C1840T mutation has also been questioned as the sole explanation for MH in some pigs.

Our finding of three MHS individuals without the mutation may be explained by either false positive muscle biopsy diagnosis, false negative mutation diagnosis or additional factors causing MH in this family. The three individuals had variable contractures in the IVCT, which for two of them made a false positive diagnosis likely. However, in the third individual, the

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contractures were more pronounced. The diagnostic test is 93% specific [2] and we would thus expect 5–10% false positive results. In this family we observed a false positive rate of 3/10, i.e. 30%. However, pooling all our data the false positive rate is 3/52 (5.8%). The mutation screening was repeated on independent blood samples so a false negative mutation result is not probable.

Both the hypothesis that factors other than the C1840T mutation may contribute to MH susceptibility in this family and the hypothesis, that a high false positive rate in the muscle biopsy result was obtained in this family, remain to be tested.

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36. Physostigmine pre-treatment increases the dose of propofol required to produce loss of consciousness

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The effect of physostigmine on propofol anaesthesia has not been investigated. This study investigates whether physostigmine affects the dose of propofol required to produce loss of consciousness.

Forty female patients, ASA physical status I and II, scheduled for breast surgery, were randomly assigned to receive 2 mg physostigmine (P group) or an equal volume of normal saline (C group) in a blind manner 5 min before induction of anaesthesia. Two 16 g venous catheters were inserted, one in each antecubital fossa, propofol was administered at a constant rate of 200 mL h^{-1} (33.3 mg min^{-1}) by means of two infusion pumps (DSP, Jonson and Johnson). A 20 mL plastic syringe filled with water was placed between the patient's forefinger and thumb of the right hand. The dose of propofol required to produce loss of the ability to grasp this syringe was recorded as the end-point of consciousness. For analysis of data, we applied unpaired Student's *t*-tests.

Results are shown in Table 6.

Table 6. **(abstract 36)** Patient details and the dose of propofol required to produce loss of consciousness in each group. Values are mean ± SD, $t=2.566$, $P_{\alpha-\beta}=0.014$

	P group ($n=20$)	C group ($n=20$)
Age	41 + 10.5	37 + 9.6
Body weight (kg)	60 + 9.8	60 + 8.2
Height (cm)	164 + 6.2	162 + 6.7
Dose of propofol (mg kg^{-1}) to produce loss of consciousness	$2.40 + 0.60^{\alpha}$	$1.97 + 0.43^{\beta}$

Physostigmine increases the propofol requirements for loss of consciousness by 20%. The increase is statistically significant.

37. Propofol is a potent noradrenaline uptake blocker in human vascular sympathetic nerves

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Anaesthesia with propofol is accompanied by a reduction in blood pressure. Possible mechanisms include a central inhibition of the sympathetic outflow [1] as well as local effects on the heart and the blood vessels [2]. We have previously demonstrated (unpublished observation) that sympathetic neurotransmission is enhanced by low concentrations of propofol (10^{-6} M) in human omental arteries but not veins *in vitro*. In the present study we investigated the effect of propofol on pre-synaptic uptake of [^{3}H]-noradrenaline in isolated human omental arteries and veins.

Omental arteries and veins were obtained from six patients undergoing abdominal surgery. Segments about 1 cm in length were pre-incubated for 15 min in 3 mL vials containing aerated Krebs–Ringer solution with normetanephrine (10^{-5} M) to prevent extraneuronal uptake and propofol at 0, 10^{-6}, 10^{-5} or 10^{-4} M or the neuronal uptake blocker desipramine (6×10^{-7} M). The segments were then transferred to

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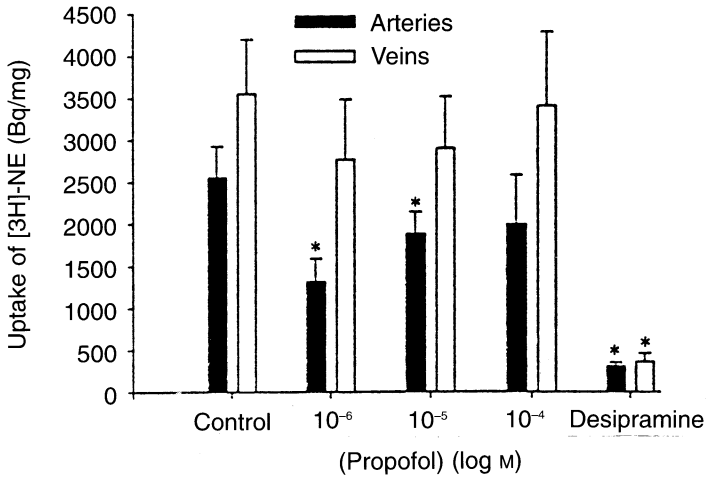

Fig. 2. (abstract 37) [^{3}H]-noradrenaline uptake in isolated human omental arteries and veins. Mean + SE; $n=6$. * Significantly different from control. Wilcoxon's signed rank test ($P<0.05$).

new vials containing the same media plus [^{3}H]-noradrenaline (10^{-7} M). After 15 min incubation the segments were washed, blotted, weighed and dissolved and the increase in radioactivity was measured in a scintillation counter.

The uptake is shown in Fig. 2.

Propofol at 10^{-6}–10^{-5} M blocks the uptake of the sympathetic transmitter noradrenaline in human omental arteries but not in veins. This may explain the propofol-induced facilitation in sympathetic neurotransmission previously reported.

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38. Leucocyte and lymphocyte behaviour in peripheral microcirculation under propofol and halothane anaesthesia

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Propofol sedation is often used in intensive care patients. Many functions of the immune system are depressed after anaesthesia and severe trauma. Propofol has been found to reduce the proliferative response of lymphocytes in intensive care patients and cause hyperlipidaemia, hypertriglyceridaemia, neurological complications and metabolic acidosis. The mechanism of these adverse effects is not well known. The aim of this study was to investigate the extent, if any, to which propofol anaesthesia can compromise the immune response in the peripheral microcirculation and the final outcome of surgical procedures.

The cremaster muscle flap model for intravital microscopic studies was used. Fourteen male Sprague–Dawley rats were studied. Group I halothane anaesthesia ($n=6$). Following induction with pentobarbitone 40 mg kg^{-1} i.p., the trachea was intubated and the lungs were ventilated with halothane (2 MAC) and oxygen ($FiO_2=0.35$) at a respiratory rate and tidal volume sufficient to maintain $PaCO_2$ at 5·2 + 0·5 KPa. Group II propofol anaesthesia ($n=8$). Following induction with pentobarbitone, the femoral vein was cannulated and propofol anaesthesia (2.5 mg kg^{-1} h^{-1}) was maintained via a continuous infusion pump. The following vital signs were monitored: MAP, CVP, ECG, pH, $PaCO_2$ and PaO_2. The cremaster muscle flap was isolated on a neurovascular pedicle, and prepared for 4 h of intravital microscopic measurements of vessel diameters, RBC velocities (optical Doppler velocimeter), leucocyte and lymphocyte activation (rollers,

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stickers and transmigrating WBC), endothelial oedema index and capillary perfusion.

When compared with halothane, during the first hour of propofol anaesthesia, rolling leucocytes increased by 57.2% ($P<0.05$). However, after 4 h, a significant drop (96.6%) in the number of circulating leucocytes was found in the propofol group ($P<0.05$). This was accompanied by 122.8% increase in transmigrating leucocytes, 6.5% rise in endothelial oedema index and a significant (34.1%) decrease in capillary perfusion ($P<0.05$). The most striking finding was the over 20-fold 'increase' in the lymphocytic activation during propofol anaesthesia.

In this study propofol anaesthesia proved to significantly alter leucocyte function by decreasing the total number of PMNs and by increasing the adhesive properties of the leucocytes. The unexpected surge of lymphocytic activation may further suggest immunosuppressive effect of this agent and should be considered when propofol is used in immunocompromised patients and in patients exposed to severe trauma.

39. Relation between systemic adhesion molecule concentrations and injury type, severity and outcome after acute brain injury

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The leucocyte adhesion molecules control adhesion of leucocytes to the cerebrovascular endothelium and their subsequent migration into brain tissue. We have shown that concentrations of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble L-selectin (sL-selectin) are increased and decreased, respectively, after acute injury to the brain [1]. We hypothesized that these changes would be related to injury type, severity and neurological outcome.

We studied 32 patients (22 with traumatic brain injury (TBI) and 10 with spontaneous subarachnoid haemorrhage) admitted to the intensive care unit. Data collected on admission included the Glasgow Coma Score (GCS) and Injury Severity Score (ISS – in TBI). Injury type was classified as focal or diffuse in patients with TBI from the initial CT scan by a single neuroradiologist. Arterial blood samples were taken at designated times after brain injury: on admission, at 24 h, 48 h and 96 h. Analysis of serum for sL-selectin and sICAM-1 was performed by ELISA. A total of 110 samples were analysed in duplicate for each adhesion molecule. Glasgow Outcome Scores (GOS) at 6 months after injury were obtained from information supplied by the patients' general practitioners. The GOS refer to the following: 1 – dead, 2 – vegetative, 3 – severely disabled, 4 – moderate recovery, 5 – good recovery [2].

Median time from primary insult to admission sample was 8 h 30 min (range 2–14 h). Controlling for time (two-way ANOVA with interaction factor), in all patients, there was no significant relation between sL-selectin concentrations and outcome ($P=0.053$). However, there was a highly significant relation between sICAM-1 and outcome when the maximum number of time points were considered ($P<0.001$). sICAM-1 concentrations were significantly related to outcome in the traumatic brain injury group, but not in the smaller subarachnoid haemorrhage group ($P=0.001$ and $P=0.272$, respectively). When only the concentrations on admission and at 24 h were considered in the traumatic brain injury group, there remained a significant relation with outcome ($P=0.014$). There was a significant negative correlation between sICAM-1 and GCS ($r=-0.382$, $P<0.001$), but no correlation between sICAM-1 and ISS in the TBI group. There was no relation between either sICAM-1 or sL-selectin and injury type, and no relation between sL-selectin and either GCS or ISS. The relation between sICAM-1 and outcome could not be explained by the additional presence of extracranial injuries.

This is the first study to examine serial changes in adhesion molecule concentrations and their relation to outcome after acute brain injury. We have shown that there is a highly significant relation between arterial concentrations of sICAM-1 and neurological outcome, and between sICAM-1 and severity of brain injury. These are new and important findings, as rather than merely being a marker of injury, ICAM-1 is an active mediator in the ongoing inflammaory process which results in secondary brain injury. By antagonizing the actions of ICAM-1, it may be possible to limit inflammatory secondary damage and improve outcome in this patient population.

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40. Immunoreactive (ir)-galanin release in the spinal cord of the neuropathic rat

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After peripheral nerve injury, galanin synthesis is significantly increased in dorsal root ganglia, with a corresponding increase in galanin levels in the superficial dorsal horn [1,2]. Galanin has an increased inhibitory action after nerve injury and may therefore act as an endogenous analgesic during nerve regeneration [3]. Previously, extensive basal ir-galanin release has been found in normal rats, which is not affected by peripheral stimulation [4].

The aim of this study was to investigate the effects of peripheral stimulation on ir-galanin release after peripheral nerve injury. The persistence of stimulus-released ir-galanin was also studied.

A chronic constriction injury was produced in male Wistar rats ($n=42$), by placing four 4/0 chromic gut ligatures loosely around one sciatic nerve [5]. The guidelines for the care of experimental animals of the International Association for the Study of Pain were followed [6]. At 10–14 days after ligature placement, the lumber spinal cords of urethane-anaesthetized rats were exposed. Microprobes bearing immobilized antibodies to galanin (Peninsula Labs) were inserted 2.25 mm into the dorsal spinal cord. Following removal from the spinal cord and incubation in ^{125}I-labelled galanin (Peninsula Labs), autoradiographic images of each microprobe tip were analysed and compared using a computerized image analysis system. Binding of endogenous galanin to the microprobes resulted in deficits in binding of ^{125}I-labelled galanin. Differences between specified groups of microprobes were assigned statistical significance using Student's unpaired *t*-test.

There was a new peak of ir-Gal release in the superficial dorsal horn, ipsilateral to nerve injury, when compared with the contralateral side. This area of spontaneous release was increased further by electrical stimulation of the injured nerve at a strength sufficient to activate A and C fibres, but not by stimulation of A fibres alone. Unlike other neuropeptides, such as neurokinin A, there was no evidence of persistence of the new areas of galanin release after the stimulation had finished.

These studies showed that ir-galanin was continuously released in the superficial dorsal horn ipsilateral to nerve injury. This release was increased further by stimulation of small primary afferent fibres. Although functional studies are required to elucidate the role of galanin after nerve injury, these studies of release suggest an important role in the modulation of nociceptive transmission. Its lack of persistence after stimulation would indicate that its main site of action is close to its site of release.

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41. Inhibition of hyperalgesia through peripheral and central alpha2-adrenoceptor activation in the inflamed knee joint model of the rat

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Recently, the location of peripherally distributed alpha2-adrenoceptors was demonstrated in a model of inflammatory pain [1]. The inflamed knee joint model of the rat presents a well-established pre-clinical model of thermal hyperalgesia. Inhibition of hyperalgesia could be achieved by either peripheral (intra-articular (IA) or central (intrathecal (IT)) delivery of clonidine. However, until now no data have existed,

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about the superiority of central or peripheral administration of clonidine for the inhibition of thermal hyperalgesia. As it was shown for peripheral opioid receptors the analgesic efficacy of peripherally acting clonidine could depend on the state of inflammation. Thus, in this present study we sought to evaluate the antinociceptive action of intra-articular and intrathecal administered clonidine with regard to time effect and dose–effect relation for two distinct routes of alpha2-agonist application.

After IAR approval, male Sprague–Dawley rats received a chronic intrathecal catheter (i.c.). Inflammation was induced once by IA injection of 3% carrageenan-caolin (CC; 100 μL) into the right knee joint. Thermal hyperalgesia (TH) was tested using a modified Hargreaves device every 30 min up to 4 h on day 1 and day 2 (6–8 rats/group): 1 = IT saline/IA saline; 2 = sham-operated rats/IA saline; 3 = IT clonidine/IA saline; 4 = IT saline/IA clonidine. Drug delivery was 30 min after induction of inflammation.

Thermal hyperalgesia of the hind paw was stable during the 28 h observation period ($P<0.05$). IT and IA clonidine resulted in a dose-dependent inhibition of TH, revealing similar ED_{50} on both days. All effects were reversible by IT or IA yohimbine.

This study suggests a similar efficacy for inhibition of thermal hyperalgesia by peripheral and central administration of an alpha2-adreno-agonist such as clonidine for inflammatory pain. Unlike the response to opioids, this analgesic activity does not appear to depend on the duration of inflammation.

Reference

1 *Neuroscience* 1995; **66**: 427–432.

42. A perinatal survey and its relevance to anaesthetic care. The Perinatal Survey (RPE) at the Chamber of Physicians of NorthRhine 1988–1995, Düsseldorf, Germany

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Measurement of clinical performance is of utmost importance in health care at a time when government agencies as well as third party payers scrutinize health care and its cost carefully. The Perinatal Survey at the Chamber of Physicians of NorthRhine was established in 1982. It was a joint endeavour of the Public Health Insurers, the Hospital Association and the Chamber of Physicians.

It is the goal of this project to encourage the physicians and the hospitals to make use of the statistics provided, to stimulate quality assurance and improvement. Confidentiality is assured and maintained in the interest of both the patients and the physicians taking care of these patients.

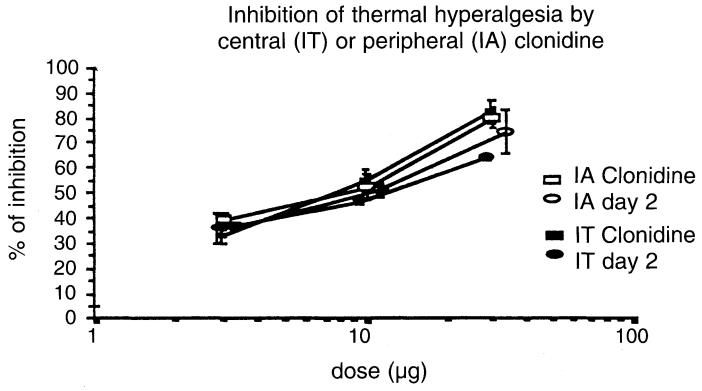

Fig. 3. (abstract 41)

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The main problems are the validity of the collected data, the measurement of process and outcome quality and the evaluation of the effectiveness of the programme. It took some time to overcome the logistic and computer problems considering the size of the sample taken.

From 1988 to 1995, 792 218 deliveries were monitored. In 1995, for instance, 41.5% of all parturients received no anaesthetic pain relief, 11.65% received general anaesthesia, 6.8% a pudendal nerve block, 12.4% infiltration anaesthesia and 24.0% epidural anaesthesia (a total count of 95 787 deliveries). The Perinatal Survey is primarily obstetrics oriented and the RPE steering group is sending the individual results of the survey to the heads of the obstetric units concerned. The steering group organizes regional audit meetings on a regular basis and encourages participation of the hospital staff in that region.

Anaesthetists can use the data of pre-existing maternal disease, foetal and maternal outcome as well as anaesthetic techniques used in association with spontaneous delivery, instrumental delivery and Caesarean section for the care they are providing.

Quality assurance in perinatology is a process that allows for effective identification of potential problems. Perinatology demands interdisciplinary collaboration, particularly during labour and delivery. Anaesthetists are members of the team.

43. Does epidural injection of isoprenaline with local anaesthetics induce haemodynamic changes in the parturient?

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Inadvertent intravascular cannulation with an epidural catheter is a frequent complication of epidural anaesthesia in obstetrics. Several authors have proposed isoprenaline 5 μg as a safer and a more effective test dose than adrenaline in patients in labour [1]. However, isoprenaline, because of its β2-agonistic action, when injected simultaneously with local anaesthetics, could have, as adrenaline, negative effects on UBF and UMB. The present study was undertaken to determine the effects of epidural isoprenaline in contrast with adrenaline added to local anaesthetics on UBF and UMB in parturients.

Following IRB approval, written informed consent was obtained from 40 healthy labouring, pregnant patients at term (ASA physical status I and II) carrying a single foetus in the vertex presentation, where an epidural catheter was inserted in the epidural space. The women were randomly divided into two groups, receiving either 0.125% bupivacaine with 0.75 μg sufentanil and 12.5 μg adrenaline (E) or 0.125% bupivacaine with 0.75 μg sufentanil and 5 μg isoprenaline (I). A main branch of the uterine artery was identified in 30 women. In another 10 women a foetal umbilical artery was identified by a colour Doppler technique. Blood velocity waveforms were recorded by the pulsed Doppler method (Hewlett Packard Sonos 2500) using a 3.75 MHz sector probe, as well as MHR, mean maternal arterial pressure (MMAP), foetal heart rate (FHR) before (base-line), and at 5, 10 and 15 min following the injection of both E and I. Statistical analyses were performed using repeated measures ANOVA followed by Dunnett *t*-testing.

UBF after local anaesthetics with isoprenaline did not change. However, after local anaesthetics with adrenaline the UBF decreased significantly for the whole study period (Table 7). UMB, MMAP, MHR and FHR did not change in both groups.

In conclusion, this study indicates that epidural injection of local anaesthetics with isoprenaline has no significant effect on maternal and foetal haemodynamics, UBF and UMB. However, after local anaesthetics with adrenaline, the UBF decreased.

Reference

1 *Anesthesiology* 1989; **71**: 206–209.

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Table 7. (abstract 43) UBF ($m\,s^{-1}$) after epinephrine 12.5 μg or isoproterenol 5 μg with local anaesthetics

	n	0 min	5 min	10 min	15 min
Adrenaline	15	133 ± 12	116 ± 9.2*	113 ± 10*	114 ± 9.1*
Isoprenaline	15	129 ± 8.4	126 ± 7.9	131 ± 9.8	131 ± 12

n = number of patients; values are mean ± SEM; * $P<0.05$.

44. Does epidural isprenaline change the quality and duration of analgesia in parturients?

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It is known that the addition of adrenaline to local anaesthetics, the usual test dose for detecting inadvertent intravascular cannulation of an epidural catheter, decreases vascular absorption of local anaesthetics and improves the quality, intensity and duration of anaesthesia. Several authors have proposed isoprenaline 5 μg as a safer and a more effective dose than adrenaline in patients in labour. The addition of isoprenaline, due to its β_2-mimetic action without α-mimetic action, could shorten the quality and duration of anaesthesia. The present study was undertaken to determine the effects of isoprenaline added to local anaesthetics on the quality and duration of anaesthesia.

Following IRB approval, written informed consent was obtained from 80 healthy labouring, pregnant patients at term (ASA physical status I and II) carrying a single foetus in the vertex presentation, where an epidural catheter was inserted in the epidural space. The 80 women were randomly divided into two groups, receiving either 0.125% bupivacaine with 0.75 μg sufentanil and 12.5 μg adrenaline (E) or 0.125% bupivacaine with 0.75 μg sufentanil and 5 μg isoprenaline (I). For each women a set of three coded ampoules containing 10 mL was prepared. If, after the use of the three coded ampoules, further analgesia was requested, the women, in either group, received 10 mL injections of 0.125% bupivacaine with adrenaline (1:800.000). Contraction pain was measured before epidural analgesia and at 5 min intervals for 15 min after each epidural administration of 10 mL of the study solution, and for every hour after the beginning of the study using a 100 mm visual analogue scale (VAS) ranging from 0 (no pain) to 100 (worst pain imaging). The time when the parturients developed further analgesia was noted. Statistical analysis was performed using Student's *t*-test and repeated measures analysis of variance.

The total study population consisted of 80 patients, of which 78 patients were analysed. Demographic data did not differ between the two groups. The VAS scores were better for the first 15 min after each injection with isoprenaline. The VAS scores did not differ every hour thereafter, with delivery, suturing and episiotomy. However, the analgesia after each administration lasted significantly longer in patients who received adrenaline in their epidural administration (Table 8). This difference led to more patients who received a fourth epidural administration in group I. The incidence of instrumental deliveries and Apgar scores were not different between the groups.

The duration of analgesia when isoprenaline was added to a mixture of local anaesthetics and sufentanil was not affected but the quality of analgesia was shorter than when adrenaline was used in its place.

45. Anaesthesia for Caesarean section in pregnancy-induced hypertension – spinal anaesthesia is the best choice

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Pregnancy-induced hypertension affects 5–8% of pregnancies and appears to invoke abnormal microvascular pathology, resulting in systemic

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Table 8. (abstract 44) Time after previous administration (min) of bupivacaine 12.5 mg, and sufentanil 7.5 μg with adrenaline 12.5 μg or isoprenaline 5 μg in 10 mL

	First adm.	Second adm.	Third adm.	Fourth adm.
Adrenaline	0 ($n=39$)	103±6.5 ($n=35$)*	186±17 ($n=17$)*	260±29.6 ($n=6$)*
Isoprenaline	0 ($n=39$)	67±4.5 ($n=28$)	140±8.9 ($n=29$)	196±14.0 ($n=13$)

n=number of patients; values are mean±SEM; adm.=administration; * $P<0.05$.

vasoconstriction. Epidural anaesthesia has become popular in recent years. Spinal anaesthesia has theoretically more risk of rapid hypotension. No prospective study has compared the two techniques so this investigation was undertaken to assess their effects, particularly looking at cardiovascular stability, maternal and neonatal morbidity.

The study was approved by the local ethics committee. Twenty-eight women with pregnancy-induced hypertension severe enough to warrant oral antihypertensive therapy were consented to receive either spinal or epidural anaesthesia by a standardized tecnhique. Spinal anaesthesia was achieved with 2.75 mL of 0.5% heavy bupivacaine and epidural anaesthesia with 4 mL 2% lignocaine test dose followed by 16 mL of 0.5% plain bupivacaine with 50–75 μg fentanyl. Supplementary epidural bupivacaine was given as necessary. Anaesthesia was considered adequate when a sensory block to T5 was achieved. Hypotension was defined as a fall of 30% below baseline systolic values or if the patient was symptomatic with nausea, vomiting or light-headedness. Hypotension was treated with incremental ephedrine. Intravenous fluids consisted of a pre-load of 250 mL Ringer's solution followed by replacement of intraoperative losses only. Neonatal outcomes were obtained from the paediatric notes.

There were 28 women initially included in the study. Six were excluded because of protocol violations. Twelve women had spinal and 10 women had epidural analgesia. There were no differences in ephedrine requirements between the two groups. Mean ephedrine usage in the spinal group was 6.25 mg (range 0–24 mg) and 6.3 mg (range 0–27 mg) in the epidural group. Five of the 10 women who had epidurals and six of the 12 who had spinals required no vasopressor at all. Neonatal outcomes were similar between the two groups. Analgesia was much better in the spinal group. No patient in this group had intra-operative pain. In contrast, in the epidural group, three patients had mild pain, four other patients required intra-operative analgesia; two had Entonox and two had parenteral opiate. Because of this it became unethical to continue the study which was originally scheduled to include 40 women.

Epidural anaesthesia has been advocated as the method of choice for Caesarean section in women with pregnancy-induced hypertension because theoretically hypotension is less abrupt than with spinal anaesthesia. Our study shows this not to occur in clinical practice, ephedrine requirements being similar during both regional techniques. As maternal and neonatal outcomes in the two groups were also similar and as spinals result in more rapid onset and better anaesthesia for Caesarean section, it has become the preferred method of regional blockade for women with pregnancy-induced hypertension in our unit.

46. Reduction in the minimum local analgesic concentration (MLAC) of bupivacaine by epidural sufentanil is dose dependent

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To determine the relative analgesic potencies of epidural local anaesthetic agents and to assess the local anaesthetic sparing efficacy of epidural opioids, a clinical model was first devised to estimate the median effective concentration of local anaesthetics in the first

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Table 9. (abstract 46) Minimum local analgesic concentration (MLAC) following sequential allocation

Group	MLAC (95% CI)	*P* corrected*
Bupivacaine control	0.107 (0.101–0.112)	
Sufentanil 0.5 μg mL^{-1}	0.049 (0.030–0.065)	<0.001
Sufentanil 1.0 μg mL^{-1}	0.010 (0–0.024)	<0.001
Sufentanil 1.5 μg mL^{-1}	0.003 (0–0.008)	<0.001

ANOVA $P<0.0001$, $F=65.6$, SD residuals = 0.021; linear trend $P<0.0001$, slope = −0.019;
* Bonferroni correction against control; Kruskal–Wallis ANOVA $P<0.0001$, KW = 79.1.

stage of labour. This was defined as the minimum local analgesic concentration (MLAC) [1,2]. The aim of this study was to determine the effect of the addition of epidural sufentanil on the MLAC of bupivacaine in the first stage of labour.

After institutional ethics approval, 120 women who requested epidural analgesia at less than 7 cm cervical dilatation were enrolled. Thirty women were allocated to each of four groups in this double-blinded, randomized prospective study. In the first phase of the study, the control group received bupivacaine alone and the experimental group received bupivacaine with sufentanil 1.5 μg mL^{-1} (30 mg). In the second phase, two further experimental groups received bupivacaine with either sufentanil 0.5 μg mL^{-1} (10 μg) or 1 μg mL^{-1} (20 μg). After placing a lumbar epidural catheter, 20 mL of the study solution was given over 10 min. The test dose was omitted for the purposes of the study. The concentration of bupivacaine was determined by the response of the previous patient to a higher or lower concentration using up–down sequential allocation. Efficacy of analgesia was assessed using 100 mm visual analogue pain scores (VAPS) at 0. 15 and 30 min with VAPS 10 mm or less defining efficacy. MLAC (95% CI) was estimated using the method of Dixon and Massey and by probit regression as a back-up or sensitivity test [3].

There were no significant obstetric or demographic differences in the groups. The results of the sequential allocations are shown in Table 9.

This research demonstrates a significant dose-dependent reduction in the MLAC of bupivacaine by epidural sufentanil in labour. Sufentanil 1.5 μg mL^{-1} (30 μg) resulted in a significant 35.7 (95% CI 28.7–42.7) fold reduction in the MLAC of bupivacaine.

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