John W Sear
PhD MA (Oxon) BSc Dipl Obs RCOG MD FRCA FANZCA

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John Sear became an anaesthetic registrar at the Royal Devon Hospital (Exeter) in 1975, moved to Bristol and was the MRC Training Fellow at the University of Bristol becoming Lecturer in 1980. He became Clinical reader in Anaesthetics in the Nuffield Department of Anaesthetics, University of Oxford in 1982 and Professor in 2002. [1-192]

His first publication, in 1976, was a case report about tracheal stenosis associated with a low pressure cuffed endotracheal tube; he was one of five authors. This was followed in 1979 by six pharmacological studies, and so it continued for the next 35 years.

Sear is primarily a pharmacologist; the subjects of his writings being drugs, comparison of drugs, drug interactions, drug metabolism and elimination, complex pharmacokinetics and myocardial ischaemia. There is too much detail for a comprehensive description and so selective aspects of his work will be described.

"His academic achievements have been recognised world-wide; he was elected as an Academician in the European Academy of Anaesthesiology in 1984, was a 'Clause 18 Visitor' with Professorial status at the University of Cape Town, RSA in 1993 and was the inaugural 'Mary Burnell' Lecturer and appointed Honorary FANZCA in 1995[ii]. He was Honorary Secretary of the Anaesthetic Research Society from 1986 until 1991 and a member of Editorial Boards of Journal of Clinical Anesthesia (Boston, USA) and the British Journal of Anaesthesia (Member of Executive, 1996-2001)."[iii]

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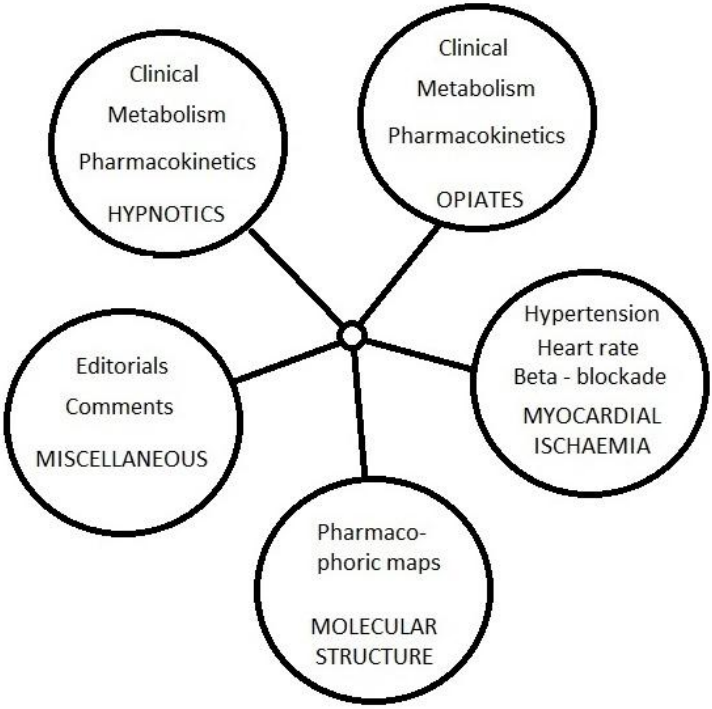
[i] Courtesy of Dr Douglas Russell

[ii] Mary Burnell, in 1950, facilitated the campaign for a Faculty of Anaesthesia in Australia.

[iii] Michael Ward – citation on JWS's receipt of the honour of the Featherstone Award from Council of the Association of Anaesthetists of Great Britain and Ireland.



Hypnotics:

His PhD thesis was 'The metabolism of steroid intravenous anaesthetic agents and their modification by liver disease' (Faculty of Medicine, University of Bristol, 1981)

His work covered aspects of methohexital, Althesin, Minaxolone, Etomidate and Propofol.

Methohexitone - [21, 24, 29, 35, 36]
Althesin - [2, 5-10, 12-22, 29, 30, 36, 37, 47]
Minaxolone - [2, 7, 12, 15, 18-20]
Etomidate - [21, 27, 35, 38, 43, 67]
Propofol - [32, 41, 42, 46, 49, 53, 68, 85, 88, 90, 93, 94, 98, 99, 102, 105, 106, 133]

Minaxolone:
Normotensive patients and patients with treated hypertension were studied during induction of anaesthesia. Arterial pressure, heart rate and cardiac output measurements were measured. Arterial pressure fell and heart rate increased; cardiac output decreased similarly in both groups. There was very little difference between Minaxolone and other induction agents (1979) [7].

Althesin:
Spontaneously breathing patients and patients ventilated artificially to normal $PaCO_2$ were studied during infusions of Althesin at various rates, during nitrous oxide anaesthesia. Increasing rates of Althesin infusion caused an increase in heart rate and cardiac output and a small decrease in arterial pressure, the result of a reduction in vascular resistance (1979) [5].

Minaxolone vs. Althesin:
Minaxolone, which was a new water-soluble steroid hypnotic (a distinct advantage – not requiring a solubilising agent in the formulation), was compared with Althesin as an induction agent. Recovery following Minaxolone was slower than after Althesin but an hour later there was no difference. Minaxolone, with nitrous oxide, did appear to provide adequate anaesthesia for short surgical procedures (1980) [12].

A new gas chromatography technique was assessed in 1980 [13]. This set the foundations for future pharmacokinetic studies. Interfering peaks and detector contamination by the silylation reagent made previous analytical techniques unsatisfactory. The new technique used nitrogen selective alkali flame ionization. The method had improved sensitivity and selectivity.

Methohexitone
1982 – This was a comparison of methohexitone, Althesin and Etomidate. They were used alone or with fentanyl and 66% nitrous oxide in oxygen. The time was recorded when patients recovered their ability to perform certain tasks. Etomidate was not adequate alone. Recovery from methohexitone alone was more rapid than Althesin alone; however, fentanyl with methohexitone reduced the required dose methohexitone and did not prolong the recovery time. Althesin had the least side effects [21].

Etomidate

Etomidate was considered an excellent agent in that its cardiovascular depressant effects were thought to be less than other agents and it was considered the drug of choice for those patients at risk of post-induction hypotension. It was found to have an Achilles heel; suppression of the normal adrenocortical response to stress (anaesthesia and surgery)[iv]. Etomidate was used for sedation in intensive care units and the indication that something was wrong was when a series of seriously injured patients developed adrenocortical insufficiency (the first report, according to Journal volume/page numbers was from the University Hospital, Queens's Medical Centre, Nottingham[v]). A letter from the Nuffield Departments of Anaesthetics and Clinical Biochemistry, headed by Sear, discussed whether the same problem existed with single induction doses of Etomidate; they provided their own data. The closing paragraph... "*...we do not know how long cortisol suppression lasts after anaesthetic doses of etomidate. Until we know this, and whether etomidate has other more general effects, it should be used with caution.*"

Five years later the effects of etomidate steroidogenesis were studied perioperatively; it was a comparison with thiopentone. In the thiopentone group serum concentrations of cortisol, aldosterone and 11-deoxycorticosterone were significantly elevated. In the etomidate patients the response was variably obtunded. It was suggested that steroidogenesis occurs at two sites. Low doses cause 11 beta-hydroxylase to be inhibited, lowering both cortisol and aldosterone secretion. Higher doses activate another pathway reducing the compensatory rise in deoxycorticosterone.

Neither Minaxolone nor Althesin have survived in clinical usage; etomidate is holding on by a whisker, as is methohexitone. The survivor of intravenous hypnotics is propofol. Althesin was very popular with clinicians and it came as a surprise when it was withdrawn from the market.

[iv] Fellows IW, Byrne AJ, Allison SP. Lancet 1983; ii: 54-55.
Allolio B, Stuttman R, et al. Lancet 1983; ii: 626.
Sebel PS, Verghese C, Makin HLJ. Lancet 1983; ii: 625.
Fragen RJ, Shanks CA, Molteni A. Lancet 1983; ii: 625-26.

[v] The present author worked in Nottingham at this time, in the intensive care unit at the City Hospital; we used opiate and benzodiazepam sedation and so did not see this problem.

Propofol

In 1984 the dose requirements of a new formulation of diisopropylphenol (ICI 35,868; propofol) was determined [32]. The new formulation was to avoid Cremophor which is solubilising agent and prone to producing anaphylactic reactions. It was found that 2.5 mg/kg was sufficient for 95% of patients; some cardiovascular and respiratory depression occurred. There was some pain on injection (3%) but the induction was considered good or adequate in 92% of patients.

In 1985 Sear et al. moved on to investigating the effects of propofol as a maintenance agent supplementing nitrous oxide and oxygen [49]. Small doses of propofol (10-20 mg) were given intermittently during body surface surgery. The average rate was 73.4 micrograms/kg/min. Recovery was faster in patients receiving propo-fol than other agents. In this study 9 out of 20 patients experienced pain on injection.

From single dose, to intermittent doses, to infusions [68] 1988. Propofol infusions were compared with halothane, again for body surface surgery. Propofol was initially infused at 12 mg/kg/hour but then at a variable rate. The median infusion rate was 149.4 micro-grams/kg/minute. The cardiovascular effects were similar in the two groups but recovery was significantly faster in the propofol group.

The use of infusions of propofol became more sophisticated and a variety of regimens were devised to provide satisfactory hypnosis. This next study compared two techniques – one where body weight was a determinant of the dosage and the other where 70kg was used as standard [105]; it was a three-step infusion method. Cardiovascular effects and recovery times and the apparent steady state blood propofol concentrations were similar. Although i*t* was suggested that for the 60-90 kg weight range a standard dose infusion regimen may be a suitable starting point, titration of the infusion rate according to clinical response may reduce the need for the supplementary volatile agent. Retrospective comparison indicated that *"The variables described by Tackley and colleagues provided a more accurate prediction of the measured blood propofol concentration than did the variable set reported by Gepts and colleagues."* [vi]

[vi] Tackley RM, Lewis GTR, Prys-Roberts C, Boaden RW, Dixon J, Harvey JT. British Journal of Anaesthesia 1989; 62: 46-53

Opiates

Buprenorphine [3, 26, 48, 78, 130, 135, 149, 161]

The first two reports are clinical; reports of its postoperative role as an analgesic and as a premedicant, the remainder are pharmacokinetic studies.

The first was a letter in response to studies by other authors – Sear, Cartwright and Alexander agreed that buprenorphine was a better analgesic but they believed that it had an unacceptable frequency of unwanted effects [3]. The second studied buprenorphine and papavaretum, both with hyoscine, as premedicants. Apart from greater drowsiness and tranquility with buprenorphine the analgesic effects seemed to be similar [26].

Morphine [34, 39, 40, 45, 54, 55, 63, 74-76, 130]

All these studies are pharmacokinetic...see below.

Alfentanil [35, 56, 60, 69, 72, 86]

References [35], [60] and [69] are clinical

Alfentanil was considered suitable for short procedures and so was compared with the well established volatile agent halothane as supplements to nitrous oxide-oxygen anaesthesia. The etomidate/ halothane/nitrous oxide recipe was unsatisfactory. Anaesthesia with alfentanil resulted in a faster recovery [35].

Sedation in intensive care units was changing; narcotics and hypnotics, or a combination, became routine. Alfentanil is a potent depressant of ventilation and does not adversely affect cardiovascular stability. Its short half-life was also advantageous as it enabled greater control of dosage; it was used in combination with midazolam [60]. Their work was reported further a year later – some patients still needed muscle relaxants. After stopping the infusion spontaneous ventilation rapidly returned; there were no major cardiovascular effects and importantly, unlike etomidate, alfentanil did not obtund the plasma cortisol response. However the plasma concentrations were very variable [69].

Nalbuphine [61] **Sufentanil** [64, 73]

Non-opiates
Meptazinol [40]
Ketorolac [101]

……

And now for the complicated stuff! **Pharmacokinetics:**

Pharmacokinetics includes speed of onset, distribution of the drug in the body, metabolism, elimination, and hence duration of action.

The synopsis below is a small, in fact tiny, fraction of the work done.

Onset (induction) [42, 117]
1997: This was a study of the relative potency of eltanolone as an induction agent in young and elderly patients. They received between 0.05 and 0.75 mg/kg given over 30s. The goal was loss of verbal contact within 120s and duration of more than 4 minutes. This was achieved in 12/40 of the elderly and 7/40 of the young patients. Effective drug doses showed a relative potency of 0.28 (95% CI 0.12-0.52) but the drug safety profile was similar [117].

Metabolism
Specific studies on metabolic mechanisms were centred on alphaxalone [14, 17] and Althesin (alphaxalone and alphadolone) [16]. There was one other on alfentanil with different hepatic pathologies [86].

In 1980 rabbit liver cells were prepared and incubated in suspension with the addition of the appropriate concentration of alphaxalone. It was considered that isolated hepatocytes were a useful model for the study of the metabolism of alphaxalone. The reproducibility of results was high but it was uncertain whether the results reflected activity in the whole animal. It was suggested that this method might be used to study the metabolism of alphaxalone during liver disease [14].

A year later degradation of alphaxalone was studied using hepatocyte and microsome preparations. It was shown that alphaxalone was metabolized by the hepatic mixed function oxygenase system which might determine the duration of anaesthetic effect [17].

An in vivo study in the same year used Althesin (alphaxalone and alphadolone acetate). Two metabolites were detected in the plasma and the

urinary metabolites were excreted as glucuronide conjugates. No parent steroids or metabolites were found in bile [16].

The last study [86] was about the effect of liver disease (alcoholic dysfunction, non-alcohol related disease and healthy con-trols) on the disposition of alfentanil. Plasma clearance of alfentanil was less in the presence of non-alcoholic liver disease than the alcoholic group or controls. Overall drug clearance was reduced in liver dysfunction compared with controls.

Elimination (renal)

Sear carried out numerous studies in situations of renal dysfunction, during and after renal transplantation, renal ischaemia, and end-stage renal failure [34, 39, 45, 72, 73, 75, 78].

1984: "*Morphine kinetics during and after renal transplantation*"

Morphine concentrations fell in the first 10 minutes, no further in the transplant patients until recovery of renal function after transplantation.

1985: "*Renal failure and the use of morphine in intensive care*"

"D*ose-related plasma morphine concentrations rose as renal function deteriorated"* The elimination half-life increased and it was warned that if unrecognised, the effects of high concentrations of morphine could cause misdiagnosis.

1985: "*Morphine kinetics and kidney transplantation: morphine removal is influenced by renal ischemia*"

During renal transplantation the donated kidney is cooled; about two hours for living-related donors and 14 hours from cadavers. The plasma concentration falls to a plateau (as above) and then when elimination resumes it decreases. Cold ischemic time determines the postoperative day creatinine clearance and morphine elimination; it was therefore concluded that morphine elimination is dependent upon intact renal function.

1989: "*Disposition of alfentanil in patients receiving a renal transplant*"

Patients undergoing kidney transplantation were compared with normal anaesthetized patients to understand the pharmacodynamics of alfentanil. The concentration decayed in a curvilinear manner but restoration of function did not influence it. The clearance and apparent

volume of distribution at steady state for the unbound drug was similar in the two groups.

1989: "*Sufentanil disposition in patients undergoing renal transplantation: influence of choice of kinetic model*"
Sufentanil was studied similarly but this is primarily a comparison of analytic techniques. Pharmacokinetic parameters were calculated from drug concentration-time profiles by two methods (ELSFIT) and a (MI) approach using AUC and its first moment. MI results showed no differences for the elimination half-life, clearance and apparent volume of distribution at steady state. The complex pharmacokinetic mathematics / statistics are beyond the author to paraphrase, the original needs to be read by the reader.

1989: "*Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites*"
This is another study of morphine in normal and transplant patients. Apart from morphine's volume of distribution at steady state there were no differences between the two groups. However the peak concentrations of morphine glucuronides (MG3 and MG6) were greater in the transplant patients and as MG6 has analgesic properties it could be responsible for the prolonged effect in patients with renal failure.

1990: "*Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites*"
Buprenorphine was studied in a similar manner There were no differences in buprenorphine kinetics between normal patients and those with renal impairment. However, the concentrations of NorB and B3G (metabolites) were increased, fourfold and 15 times respectively, in patients with renal failure.

Disposition [54, 62, 73-77, 79, 89, 102, 133, 153]

'Disposition' is "the way in which something is placed or arranged, especially in relation to other things". It fits the study of pharmaco-kinetics/pharmacodynamics perfectly, the main interest was with opiates, particularly morphine [74-76], all in 1989, and alfentanil [72, 86].
An example:

In 1989 Sear, Hand and Moore studied the effects of aging on the disposition of morphine and its metabolites in middle-aged and elderly patients. The elimination half-life, mean residence time and apparent volume of distribution at steady state were similar. Clearance, however, was greater in the middle-aged group. The metabolite concentrations (M3G and M6G) were similar. The reduced clearance of morphine, presumably due to the reduced glomerular filtration rate in the elderly patient, may result in enhanced analgesic efficacy in the elderly patient [74].

These pharmacokinetic studies are time consuming, requiring great laboratory expertise and skill in interpretation; a large amount of work spanning 20 years. He helped develop the concept of total intravenous anaesthesia in various animal species; studies in 2013/5 involved tigers, leopards and horses.

Since 2002, of the publications presented here, eight were related to molecular structure.

2002: The molecular shape and electrostatic potential of intravenous general anaesthetics was examined using computational chemistry techniques. Eltanolone was the most potent agent and all the other agents were compared with it using Carbo indices[vii]. It was found that the similarity model they used was more effective at predicting potencies than that based on octanol/water partition coefficients. Alphaxalone was an outlier but this may have been due to difficulties with determining the in vivo potency. The determination of the mechanism of anaesthesia is one of several 'Holy Grails' for anaesthesiology – this study suggested that there may be a common molecular basis, that molecular shape and electrostatic potential are important determinants of potency and that a 'pharmacophore'[viii] may be constructed. [134].

2003: A similar study was done with nonhalogenated volatile anaesthetics using comparative molecular field analysis (CoMFA). The anaesthetics were compared with the most active agent - hexanol. After

[vii] "The Carbo Index (Carbo and Arnau, 1980) is probably the most common similarity descriptor and uses the overlap of the electron densities of the two molecules" Carbo,R.,L. and, Arnau M. (1980) Int. J. Quantum Chem., 17, 1185–1189. (http://peds.oxfordjournals.org/content/17/5/425.full)

[viii] A pharmacophore is an abstract description of molecular features which are necessary for molecular recognition of a ligand by a biological macromolecule (Wikipedia).

complex computations (involving Carbo indices) *"the final CoMFA model explained 95.5% of the variance in the observed activities of the training-set anesthetics".* They derived pharmacophoric maps (see Figure 3 in the paper) and they believed that the study supported the view that steric and electrostatic interactions do determine anaesthetic activity (minimal alveolar concentration) [137].

2004: This is very similar to the 2002 paper but it uses CoMFA and it does have brilliant illustrations of the pharmacophore maps in Figs. 1 and 4 [146].

2006: This was an investigation of the halogenated volatile anesthetics using CoMFA; similar to the 2003 study [158].

2009: After all this work, a review of the subject: *"What makes a molecule an anaesthetic? Studies on the mechanisms of anaesthesia using a physicochemical approach".* It describes all the above work and pointed out that it was difficult to separate anaesthetic activity and cardiovascular depression within a single molecule [168].

2009: N-methyl-d-aspartate (NMDA) receptors are variable affected by anaesthetic agents and the study was to characterize the molecules using CoMFA. *"The anesthetic structures were geometry optimized using ab initio quantum mechanics and aligned by field-fit minimization to provide the best correlation between the steric and electrostatic fields of the molecules and one or more lead structures."* [I hope you, the reader, understood that][ix]. It would appear that NMDA receptors do contribute to the immobilizing activity of volatile anaesthetics [169].

2010: Following on from the comment about cardiovascular depression (2009) this study investigated the molecular basis of the cardiovascular effects of intravenous anaesthetic agents, using CoMFA. Changes in mean arterial pressure (compared with awake values) during infusions of intravenous anaesthetics were compared and drug concentrations causing a 20% decrease in MAP were used for the CoMFA model. There was commonality between immobilizing and cardiovascular depressant activity which meant that separation of the the molecular features might not be possible [173].

[ix] Being a fan of the history of science, including quantum physics, I have always wondered if quantum mechanics could be applied to anaesthesia – and here it is.

2011: And finally, perhaps, a study examining the molecular basis hypnotic agents using CoMFA. The induction activity and the immobilizing activity was different suggesting that different molecular features may be responsible [176].

These studies were detailed and complex, JC Sewell was a common co-author.

And now for something different...

Myocardial ischaemia

The first two, in 1988, were on the risks of myocardial ischaemia in hypertensive patients and the possible protection afforded by beta-blocker therapy [70, 71]. In the first, patients with hypertension were monitored for myocardial ischaemia during surgery. Ischaemia occurred in about 30% of the untreated hypertensive patients but in no patients receiving a beta-blocker. Ischaemia was associated with noxious stimulation and tachycardia. It was thought that pretreatment with atenolol provides prophylaxis. The second was a prospective, randomized study, mildly hypertensive patients were studied. Eighty nine (out of 128) patients received a small dose of a beta-blocker. Tracheal intubation and emergence from anaesthesia were associated with "... *a brief, self-limited episode of myocardial ischemia* ..." in about 30% of untreated control patients (same patients as in previous publication) and in 2% of patients who received a beta-blocker. It was concluded that a single dose of a beta-blocker given preoperatively can reduce that risk.

In 1991 Sear et al. determined the incidence of silent myocardial ischaemia in the general surgical population, and the predictors. They used ambulatory ECG monitoring and the prevalence of silent myocardial ischaemia was 18.2% in the vascular group of patients and 7.6% in the non-vascular group. A history of ischaemic heart disease or an abnormal ECG suggestive of an old myocardial infarction predicted a high risk of silent ischaemia but a third of silent ischaemia occurred without risk factors. There was a strong association between silent ischaemia and a low ventricular ejection fraction; less than 40% [81].

In 1994 a study of over 300 patients who had preoperative ambulatory ECG monitoring showed that 20% had at least one episode of myocardial ischaemia and the one consistent variable was elevated arterial

pressure, despite therapy and silent ischaemia occurred in over 35% of these patients. It was suggested that arterial pressure on hospital admission may identify patients at risk [97][x].

The next thirty-five publications continue the examination of this topic; (1996 [110, 113], 1997 [115], 1998 [119], 1999 [122, 123], 2000 [124-126], 2001 [127-129], 2003 [138], 2004 [139, 141-144], 2005 [147, 148, 151], 2006 [154-157], 2007 [159, 162], 2008 [163-166], 2009 [170], 2010 [171, 174] and 2011 [175].

I will attempt a summary:

1. *"There was no association between systolic or diastolic pressure at admission for operation and perioperative cardiovascular death."* [110]
2. *"Merely the presence of short duration silent myocardial ischaemia* [in TURP patients] *probably has little predictive value for postoperative adverse outcome*." [113]
3. *"Pre-operative silent myocardial ischaemia was found to be strongly associated with postoperative silent myocardial ischaemia"* [for patients undergoing vascular surgery] [115]
4. *"Three risk factors* [for cardiovascular deaths after elective surgery]: *previous myocardial infarction, history of hypertension and renal failure*." [119]
5. [Major lower limb joint replacement surgery] "*...cardiac risk factors do not predict the occurrence of silent myocardial ischaemia or adverse outcome. Peri-operative silent myocardial ischaemia was associated with increased postoperative fatigue."* [122]
6. *"...patients who died from a cardiovascular cause within 30 days of emergency or urgent surgery under general anaesthesia... Only one significant risk factor was identified in the final model: a history of cardiac failure."* [123]
7. *"We found troponin T to be the only prospective marker for both major and minor cardiovascular complications..."* [in patients undergoing vascular or major orthopaedic surgery.][125]
8. A complex re-analysis of four published studies investigating the incidence of postoperative silent myocardial ischaemia for the effects

[x] Author's note: There is some evidence that blood pressure on admission is a stressed blood pressure that may not reflect every-day blood pressure.

of intercurrent therapy with beta-blockers or calcium channel blockers. [126]

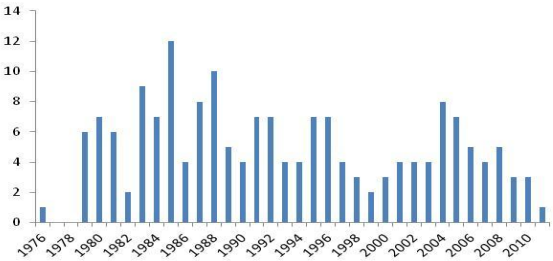
9. [The results were] "*...at variance with other published data, but* [they concluded] *that monitoring for peri-operative silent myocardial ischaemia does not aid the prediction of long-term [1 year] cardiovascular complications."* [127]
10. [It was concluded] "*...that, with the possible exception of the use of nitrates* [preoperatively] *in elective surgical patients, chronic intercurrent drug treatment alone does not significantly affect the odds of cardiac death within 30 days of surgery*." [129]
11. *"QT dispersion is prolonged in those at risk of early adverse cardiovascular events but is a poor screening tool*." [139]
12. *"...increases in troponin I and both a single elevated creatine kinase-MB and two successively elevated creatine kinase-MB concentrations were associated with an increased incidence of major cardiac outcomes, including cardiac death, to 1 year..."* [142]
13. *"The anaesthetist should be aware of the potential errors in arterial pressure measurements and the impact of white coat hypertension on them."* [144][xi]
14. *"This analysis suggests that peri-operative statin therapy for patients undergoing vascular surgery may present the most cost-effective use of statin therapy yet described, with a number-needed-to-treat of 15...*" [148]
15. [There is an*]"...increased incidence of major cardiac events in critically ill, cardiac high-risk patients with a prolonged elevated heart rate during their ICU stay*." [151]
16. *"This meta-analysis cannot confirm that heart rate control with beta-adrenergic blockade is cardioprotective*." [163]
17. *"Beta-blockers: must we throw the baby out with the bath water*?" [170]
18. [22 authors] An increased troponin measurement after surgery is an independent predictor of mortality, particularly within the first year; limited data suggest an increased creatine kinase muscle and brain isoenzyme measurement also predicts subsequent mortality. [175]

[xi] Remember what I wrote earlier?

Those observant readers will note that some of the 33 references are missing; they are, by and large, reviews, editorials or comments[xii].

So what is the bottom line? Preoperative blood pressure is not a good indicator of risk; preoperative silent myocardial ischaemia is associated with postoperative silent myocardial ischaemia which is associated with patient fatigue. A history of preoperative cardiac failure is a major risk factor, troponin T is a prospective marker for adverse events, prediction is difficult[xiii], increases in troponin I and creatine kinase-MB may help, statins are cheap compared with intensive care and having a high heart rate is not good (beta-blockers may help).

Number of publications per year



It is an understatement to say that this is a massive body of work and the output was maintained over 30 years. It included the highly practical and important studies of myocardial ischaemia to the equally important but more basic science of molecular properties which may lead to a greater understanding of how anaesthetic agents work.

In addition he was involved in the writing or editing of eight books, 47 chapters, two Cochrane reviews, was invited to give many lectures (>40), and filed one patent, in 2004 with MNJ Lim, SW Benham and AW Fitzgibbons for the Oxford Simulation Apparatus for Flexible Endoscopy (OxSAFE). "In 1997 Sear was a founding committee member and Honorary Treasurer of the Society for Intravenous Anaesthesia in the UK. He was President from 1999 – 2002 and in view of his enormous contribution to clinical research in Intravenous Anaesthesia, and to the Society, was awarded Honorary Membership in 2012"

[xii] There are more as there were some very late additions to the references in the production process.

[xiii] "Prediction is difficult, especially the future" has been attributed to Niels Bohr but this is incorrect - it was a Danish humourist by the name of Robert Storm Petersen (source - Preben G. Berthelsen – Editor Acta Anaesthesiologica Scandinavica).

[xiv]. He was awarded the Featherstone Medal, Association of Anaesthetists of GB and Ireland, in 2006; gave the WG Smith Memorial Lectureship at the Sir Charles Gairdner Hospital in Perth in 2007; was the Cecil H and Ida Green Visiting Professor, Green College, University of British Columbia in 2011; was elected to Hon. Membership of the Association of Veterinary Anaesthetists and the First 'Leslie Hall' Memorial Lecturer and elected to Hon. Fellowship of the College of Medicine of South Africa in 2013; and was awarded the ISAP (International Society of Anaesthetic Pharmacology) Lifetime Achievement Award in 2014. He has been on the Editorial Board of Anesthesia and Analgesia since 2006.

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