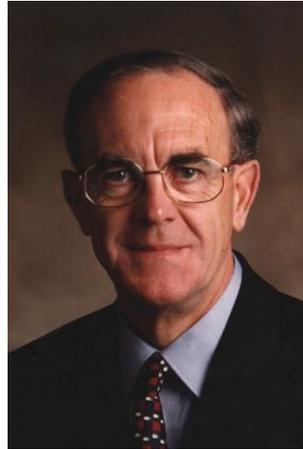


## **Graham Smith**

### **BSc MRCS LRCP MBBS FRCA MD**

Graham Smith studied medicine as an undergraduate at Guy's Hospital Medical School, in the University of London, where an intercalated Hons BSc course in physiology led to the early development of an interest in academic medicine. After qualifying in 1966, he commenced training in anaesthesia in Leeds where he fell under the influence of the Academic Department of Anaesthesia headed at that time by Professor John Nunn.



Whilst studying for the FFARCS examination, he found time to assist Alastair Spence in a study of post-operative thoracic epidural analgesia on pulmonary function[1]. Before the results of the final FFARCS examination were announced he secured the post of Research Fellow with Iain Ledingham in the Hyperbaric Oxygen Unit based in the University Department of Surgery headed by Sir Andrew Watt Kay at the Western Infirmary in Glasgow. Here, studies on pulmonary oxygen toxicity were accumulated to provide sufficient material to submit for an MD thesis.

After one year in this post he was appointed as Lecturer/Hon. Senior Registrar in the University Department of Anaesthesia headed by Alastair Spence at the Western Infirmary, Glasgow.

In 1971 he spent a year on an MRC Travelling Fellowship in the Department of Anesthesiology headed by John Bonica, at the University of Washington, Seattle. Studies on pulmonary oxygen toxicity with Peter Winter demonstrated that the speed of onset of toxicity in a model of lung damage was a function of both high  $\text{PaO}_2$  and  $\text{PAO}_2$ . In addition, he was a junior member of a team, which included Ted Eger and Tom Hornbein that was the first to demonstrate experimentally in volunteer divers that the MAC value of nitrous oxide was the same as that predicted theoretically from the Meyer-Overton theory.

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<sup>i</sup> This chapter was co-authored with David Rait, his friend and colleague.

At that time in the USA, it was generally regarded as essential to administer a small dose of d-tubocurarine prior to suxamethonium in patients at risk of aspiration because the raised intragastric pressure caused by fasciculations increased the tendency to regurgitation. As this seemed illogical, on returning to Glasgow in 1972, Graham Smith set about examining the effect of suxamethonium on lower oesophageal sphincter (LOS) pressure in healthy patients undergoing elective surgery. He demonstrated that barrier pressure was indeed raised during the period of fasciculations and was lowest during the period of flaccid paralysis in comparison with the baseline awake values. This led to a large series of studies on the effects of drugs used in the perioperative period on the LOS. Many NHS senior trainees seconded to the academic departments in both Glasgow and Leicester were involved, see section below on oesophageal studies.

In 1974, he was promoted to Senior Lecturer/Hon. Consultant at the Western Infirmary in Glasgow where he remained until 1979. During these five years he worked with Iain Ledingham, Jim Parrot (a pharmacologist from the University of Strathclyde) and two consultant anaesthetists, John Vance and John Thorburn on studies of experimentally induced myocardial ischaemia.

### **University of Leicester**

The medical school in Leicester opened for students in 1976 and Graham Smith was appointed as Foundation Chair of the Academic Department of Anaesthesia in 1979. In designing the new department, he recognised that in addition to the teaching and research responsibilities common to all medical school departments, anaesthesia could offer a unique opportunity to demonstrate some important aspects of applied physiology and pharmacology to the medical students. Their anaesthetic attachments concentrated on the perioperative management of surgical patients, including pain management and some practical skills. These proved to be very popular amongst the Leicester students.

### **Research**

During his years in the Glasgow Department and in Seattle, he had published numerous papers on basic physiology and pharmacology. Many of these dealt with the effects of oxygen and hyperoxia on the lung and cardiovascular system and these studies led to several editorials and seminal articles on oxygen toxicity.

At Leicester, his initial goals were three:

- i. Postoperative **pain control** was, and is, a fertile ground for anaesthetic research. Smith instigated many studies of analgesic drugs, their effects on physiology and patient outcomes and also various methods of administration.
- ii. Following on from his research on the cardiovascular system in Glasgow, he obtained a high-pressure gas chromatograph for the department. This allowed further studies to be made of the **sympatho-adrenal response to surgical stress** and the methods of reducing it.
- iii. Study of the **lower oesophageal sphincter** and the effects of various drugs upon it aimed to reduce morbidity caused by regurgitation, particularly in obstetric anaesthesia. Many studies were carried out using direct pressure measurements made simultaneously within the oesophagus and the stomach. This research led to studies on gastric emptying and the effect upon it of starvation and a variety of drugs used in anaesthesia. A generation of volunteer registrars became familiar with Campbells Consomme soup (the control 'stomach content') and improved their CVs in the process.

To support him in these endeavours, Smith was supported by several senior lecturers, four of whom went on to occupy chairs: Alan Aitkenhead became chair in Nottingham, David Rowbotham succeeded him at Leicester, David Lambert occupies the Chair of Anaesthetic Pharmacology at Leicester and Paul Watson is Professor of Pain Management and Rehabilitation at Leicester.

## **i. Analgesia/pain**

There are 73 publications relating to 'pain' or 'analgesia'; obviously a major interest.

### **Extradural / epidural**

The first publication [1] was an abstract of a presentation to the Anaesthetic Research Society (ARS) meeting in Newcastle-upon-Tyne July 13<sup>th</sup> 1968. The report was a 'work-in-progress' and the aim was to assess the part played by wound pain in post-operative hypoxaemia. Randomisation threw up an unexpected allocation of patients, all cholecystectomy patients were in one group and it became..."clear that the patients for cholecystectomy behaved differently

from the others and must be considered separately". The observations were that "The extradural patients, who had complete pain relief and freedom to cough in the first 48 hours after operation, were restored to their pre-operative level of arterial oxygenation by day five whereas their control group had significant residual hypoxaemia." They also felt that the improvement in postoperative vital capacity was a function of factors in addition to pain relief and that gas under the diaphragm may play a more important role than was realized at that time.

A full publication in 1971 [2] reported on twenty-one patients allocated randomly to postoperative analgesia with either morphine by injection or continuous extradural nerve block. It concluded that the conventional use of narcotics for postoperative analgesia increased the risk of lung morbidity.

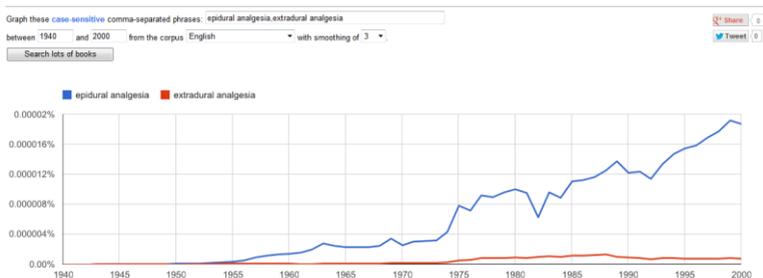
An overview by Buggy and Smith in 1999 [3] suggested that, with the balance of available evidence, epidural anaesthesia and postoperative analgesia may facilitate earlier recovery by reducing the incidence of thromboembolic, pulmonary, and gastrointestinal complications after major surgery. It did take meta-analysis to indicate these favourable outcomes.

### Slow release morphine [4-16]

There was a decade between this early work on postoperative analgesia with extradural (epidural) local anaesthesia and opiates and the work on controlled/slow release morphine. Smith's publications range from 1982 – 1989. There were three papers on the comparison of slow release morphine vs. intramuscular morphine [4, 10, 12] and a set of papers on slow-release morphine suppositories [5, 6, 8, 15].

[As an aside the terms extradural analgesia/epidural analgesia separate in frequency in use in, about, 1955; 'extradural analgesia' peaks in 1988.

[Google books Ngram Viewer](#)



In contrast, slow release morphine appeared in 1978 and peaked in 1994 but at a much lower frequency. Should the correct term be inter-, or intradural?]

The '82 paper with Fell and Chmielewski [4] reported on fifty patients in a trial of either intramuscular morphine or controlled-release morphine sulphate tablets orally. Both were acceptable to the patients. Interestingly, there was more sedation in those patients undergoing hysterectomy who received morphine sulphate tablets.

From this they moved on to rectal sustained release morphine [5] and there was a cluster of similar publications between 1982-1989; Derbyshire appears to be a consistent co-author [6-8, 10-13, 15-17].

In the 1985 paper by Derbyshire et al. there was a more conservative result. MST (a slow release formulation) and i.m. morphine provided satisfactory postoperative analgesia, but significantly greater amounts of supplementary i.m. morphine were required in the MST group. However, there were more adverse effects reported by the patients in the i.m. morphine group. The mean serum morphine concentration in 12 patients in the MST group was  $1.7 \text{ ng ml}^{-1}$  at 08.00 h and  $19.5 \text{ ng ml}^{-1}$  at 16.00 h on the 1st day after operation this suggested that gastric emptying was impaired. The authors thought that further work was necessary before any recommendations could be made regarding the routine use of MST.

The last paper authored by Lew [16] reported that of 12 patients three had delayed gastric emptying and impaired morphine absorption in the immediate postoperative period and later there was a significant reduction in eight patients. This effect on gastric emptying seemed to be the death knell for the use of oral sustained release morphine formulations for postoperative pain.

### **Local anaesthesia**

New methods of using local anaesthetic agents for the management of postoperative pain were also investigated; this was late in the publishing portfolio...1997-2004.

The first in 1997 (Williamson et al.) [18] was a preliminary randomized study where 50 ml of saline solution containing lignocaine 200 mg and adrenaline 1:500,000 were instilled into the peritoneal cavity after total abdominal hysterectomy. Pain scores at rest were significantly lower (otherwise there was no difference) at 24 and 48 h compared with the saline group. A year later Ali et al. made it clear, "Intraperitoneal bupivacaine or lidocaine does not provide analgesia after total abdominal hysterectomy" [19]. After a series of papers between 2002-

2004 [20-24] Ng et al. concluded that "Intraperitoneal administration of levobupivacaine with epinephrine is associated with modest analgesia following laparoscopic cholecystectomy"[24]; another technique that has not survived.

Tissue infiltration with local anaesthetic agents has a long history, two Leicester investigations added to the documentation - first "Effect of infiltration with ropivacaine on blood loss during reduction mammoplasty" [25], (there was greater blood loss with ropivacaine than bupivacaine) and the infiltration of the abdominal wall with local anaesthetic after total abdominal hysterectomy [26]. It had no opioid-sparing effect. Could any improved immediate postoperative analgesia be overwhelmed by the following 48h of data (when the local anaesthesia had worn off) - or was this an attempt to demonstrate a possible pre-emptive analgesic effect? Certainly, surgeons still infiltrate such wounds.

The same failure of efficacy was demonstrated with transcervical local anaesthesia for laparoscopic sterilizations [27, 28].

### **Palliators**

The use of the Cardiff Palliator was first described in 1976<sup>ii</sup>. The Leicester department started publishing on this topic in 1982 [29-33]. In 1985 the Leicester Micropalliator was described by Derbyshire et al. and in 1987 he and Vickers AP et al. reported on a comparison of it and the Cardiff Palliator. The Leicester Micropalliator delivered a mandatory background infusion in addition to the on demand bolus doses of morphine. The Cardiff Palliator gave only bolus doses of morphine. It was considered that the Leicester Micropalliator's provision of analgesia was equivalent or superior without an increase in side effects. The total dose of morphine did not differ significantly.

### **ii. Catecholamines**

In 1982 Fell et al [34] published "Plasma catecholamines in anaesthesia" and in 1984 Derbyshire and Smith [35] wrote a review on 'Sympathoadrenal responses to anaesthesia and surgery'. For five years (1986-1991), studies were carried measuring catecholamines. The high-pressure gas chromatograph had obviously arrived!

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<sup>ii</sup> Evans, J M, et al, Anaesthesia, 1976, 31, 847 and Evans, J M, et al, Lancet, 1976, 1, 17

The first paper [36] assessed the concentrations of adrenaline following infiltration of local anaesthetic with adrenaline 1:200,000 for rhinoplasty and brachial plexus block. There was a much greater increase in the adrenaline concentration in the rhinoplasty group. It was concluded that the 'safe dose of adrenaline' was meaningless unless the site of administration is specified. In 1987 "Sympathoadrenal responses to tracheal intubation after thiopentone or propofol" [37], "Effects of alfentanil on the pressor and catecholamine responses to tracheal intubation" [38], "Sympathoadrenal responses to tracheal intubation after thiopentone or propofol" [39] and "Cardiovascular and catecholamine responses to laryngoscopy with and without tracheal intubation"[40], a busy year. There were others on this topic...[41-43]...practolol did not ameliorate the response, halothane did.

It would appear that topical anaesthesia of the mucosa of the upper airway is ineffective in reducing the pressor and catecholamine responses to laryngoscopy. It does not seem to be current (2013) practice and has not been so for twenty years (personal observation).

Intravenous lignocaine prior to intubation was also studied [43]... 1.5 mg/kg, Mean arterial pressure did not increase in patients given lignocaine but in the placebo group it increased by 19.1%.

A variety of papers on the topic of catecholamine concentrations were subsequently published for a variety of situations [44-49], including respiratory therapy, naloxone and endovascular aortic aneurysm repair.

### **iii. Lower oesophageal sphincter studies**

There are seventeen studies from 1978 – 1991[50-66]. They systematically assess the effects of many agents used in anaesthesia on the lower oesophageal sphincter (LOS); atropine, metoclopramide, glycopyrrolate, diazepam, beta-blockers, pancuronium, atracurium, vecuronium, neostigmine, edrophonium, domperidone and finally, posture – the Trendelenburg<sup>iii</sup> position (steep head-down tilt).

As an example [61], the simultaneous administration of atropine and neostigmine were studied in healthy patients. Atropine 1.2 mg and neostigmine 2.5 mg were given together at the termination of surgery and for the following 15-20 minutes measurements of lower oesophageal sphincter pressure were made. This

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<sup>iii</sup> Friedrich Trendelenburg was a German surgeon (1844–1924).

combination of drugs resulted in transient but significant decrease in LOS pressure.

Studies of the Trendelenburg position, a position that would intuitively suggest an increased risk of regurgitation, were reported in 1990 and 1991 by Heijke et al. The 1991 paper [64] described how measurements were made of gastric, lower oesophageal and barrier pressures in the supine, moderate and steep Trendelenburg positions. The Trendelenburg position resulted in no significant changes and it was concluded that the steep Trendelenburg position did not increase the risk of regurgitation.

There are three general articles on the subject [67-69], the last, in 2003. It is about gastric reflux and pulmonary aspiration; the factors which contribute to the likelihood of aspiration and methods to minimise it.

### **Hyperbaric and oxygen studies**

There were three investigative papers from 1970-72, one on the haemodynamic and myocardial effects of hyperbaric oxygen in dogs subjected to haemorrhage (Cardiovasc. Res. [70]), one on the effects of hyperoxia on airways resistance (J. Appl. Physiol. [71]) and one on the effects on the cardiovascular system (Br. J. Anaes. [72]).

1. In the first, anaesthetized dogs were subjected to moderate and severe haemorrhage and the administration of oxygen at 2 Ata failed to modify the cardiac changes that result from blood loss; myocardial blood flow was decreased and myocardial oxygen availability was not improved.
2. After breathing 100% oxygen at 2 Ata for five hours there was a 30% increase in airways resistance and a 25% increase in thoracic gas volume. There were no significant changes with the air equivalent.
3. The hyperoxia/cardiovascular system paper showed that, in dogs, 100% oxygen at 2 atmospheres for 8 hours caused a fall in cardiac output of approximately 30% within 4 hours with a 70% increase in systemic vascular resistance and a rise in left ventricular end-diastolic pressure. There was a rapid restoration of all parameters towards the initial values when an air equivalent was given. It would appear myocardial oxygen toxicity is reversible in this time frame.

The effect of 100% oxygen during anaesthesia was also studied. Patients with a fracture of the neck of the femur were anaesthetized by three different techniques, (halothane in oxygen, halothane with 66% nitrous oxide breathing spontaneously, and artificial ventilation with 66% nitrous oxide in oxygen). There was a small decrease in PaO<sub>2</sub> 60 min after anaesthesia but there was no significant

difference between the groups. The main message from this study was that there was no significant absorption collapse in the 100% oxygen group [73].

Three other, hyperbaric, papers are of interest - hyperbaric nitrous oxide anaesthesia in man: determination of anaesthetic potency (MAC) and cardiorespiratory effects [74, 75], the MAC of N<sub>2</sub>O was determined to be 1.04 atm ± 0.10 (SE) and "The performance of anaesthetic equipment under hyperbaric conditions. Performance Characteristics of Anaesthetic and Related Equipment", this was an overview article in International Anesthesiology Clinics [76].

### **Nitrous oxide.**

Apart from the hyperbaric work on nitrous oxide, Smith et al. also studied nitrous oxide during anaesthesia and its effect on postoperative pulmonary function. Arterial blood-gases and lung volumes were measured before and after upper abdominal surgery, they found no significant difference between patients ventilated with oxygen and nitrogen and a group receiving oxygen and nitrous oxide [93].

They also determined the threshold concentration of nitrous oxide that affected psychomotor performance using audiovisual reaction times. A positive effect was found at a concentration of between 8 and 12% nitrous oxide [94].

A study into the effect of nitrous oxide on the cardiovascular system and coronary circulation of the dog showed that there was a significant decrease in cardiac output, increases in right atrial and left ventricular end-diastolic pressure and systemic vascular resistance. However there was no significant change in mean coronary artery flow, coronary vascular resistance or myocardial oxygen consumption [95].

### **Ischaemia**

For ten years Smith was involved in investigations on myocardial blood flow in a canine model. The investigation started whilst he was in Glasgow (first publication in 1973) and the last publication (1982) when he was in Leicester. In chronological order, 'they' studied the effect of halothane, propanidid, hypocapnia, methohexitone, halothane-induced hypotension and hypocapnia, hypoxia, hypercapnia and hypoxaemia, ketamine, sodium nitroprusside-induced hypotension, enflurane and thiopentone; a huge array of work. For six Smith was the principal author, JP Vance for another six.

The halothane study [96] was presented at an Edinburgh ARS meeting. The dogs were exposed to 0.5%, 1% and 1.5% halothane for 30-min periods. Blood

flow was measured using using xenon-133. There was a dose-dependent reduction in myocardial blood flow in proportion to the decrease in cardiac output and myocardial oxygen consumption. Higher doses of halothane produced an increase in myocardial vascular resistance, myocardial oxygen extraction; causing a fall in coronary sinus PO<sub>2</sub>.

Propanidid [97] produced a large but transient increase in myocardial oxygen availability in the dog. Myocardial blood flow rose considerably independent of any change in perfusion pressure, cardiac output or myocardial oxygen consumption. The stabilizing agent Cremophor-EL was found to have no effect.

In the hypocapnia study [98] (PaCO<sub>2</sub> about 25mmHg) there was a highly significant reduction in myocardial blood flow and oxygen availability but myocardial oxygen extraction increased so that oxygen consumption was unaffected.

Methohexitone caused a reduction in myocardial blood flow, oxygen availability and consumption but no change in myocardial oxygen extraction [99]. Halothane and hypotension [100] - mean arterial pressure was reduced with 1-1.5% halothane, myocardial blood-flow and oxygen consumption decreased and myocardial vascular resistance increased. With added hypocapnia myocardial blood-flow was further decreased.

Ketamine [101] - caused a decrease in arterial pressure and an increase in cardiac output, coronary blood flow and myocardial oxygen consumption; there was no change in myocardial oxygen extraction.

All these investigations are of importance in the understanding of the effects of common occurrences during anaesthesia - however they are of greater importance to those patients with ischaemic heart disease. Three studies in the '80s addressed this situation.

In 1980 "Halothane improves the balance of oxygen supply to demand in acute experimental myocardial ischaemia" [102], and in 1982 myocardial ischaemia was induced in dogs by ligation of the anterior descending branch of the left main coronary artery and were given thiopentone [103]. The oxygen availability/consumption ratio did not change significantly.

A similar study using Enflurane [104] produced a significantly smaller reduction in blood flow in the ischaemic than in the non-ischaemic areas. It was suggested that the improvement in the oxygen availability/consumption ratio was due to a decrease in heart rate and, as they said, "the beneficial effects of

anaesthesia in acute myocardial ischaemia are probably secondary to changes in systemic and myocardial haemodynamics and not a result of specific mechanisms." There were other publications in this series [105-112].

### **Anxiety**

Two publications are of particular interest. "Measurement of plasma catecholamine concentrations. An assessment of anxiety" and Anxiety levels in junior anaesthetists during early training [113, 114].

The first study assessed plasma catecholamine concentrations following venous cannulation, there were no changes in the following two hours, In a second study surgical patients were asked to rate their anxiety on a linear analogue scale immediately before premedication and immediately before induction of anaesthesia. No significant changes in anxiety or plasma noradrenaline concentrations followed premedication but there was a mean 40% percent increase in plasma adrenaline concentration before induction of anaesthesia. A correlation ( $r=0.32$ ) was demonstrated between the Linear Analogue Anxiety Score and mean percentage change in plasma adrenaline concentrations.

A year later the predisposition to anxiety and personality profiles were recorded in four novice anaesthetists before training started and at the transition to solo practice. There was no difference in anxiety scores as a result of 'going solo' in any subject. This, in the author's opinion, is either due to the excellent preparation of the novice anaesthetists or the possibility that the novices didn't know what they didn't know (!); probably the former.

### **Teaching**

Whilst supporting and guiding the many individuals who passed through his department during his 27 years in Leicester, Graham Smith also developed many overseas links. He was External Examination Advisor to the Universities of West Indies, Calgary, Hong Kong, Singapore and Seattle and was Visiting Professor at the Universities of Sydney and Hirosaki, Japan.

In 1996 he was elected to the Senate of the European Academy. He became a Member of the Council of the Association of Anaesthetists of Great Britain and Ireland from 1983-1987 and of the Council of the Royal College of Anaesthetists from 1991-2003. He was Senior Vice-President from 2000–2002. He examined for the FRCA and at home and abroad examined in MB ChB, MD, PhD, and MMed degree examinations.

### **The British Journal of Anaesthesia**

Graham Smith enjoyed a long association with the British Journal of Anaesthesia (BJA). In 1973, the Journal Office moved from Liverpool to Glasgow when Alastair Spence assumed the Editorship after J Edmund Riding. Graham Smith became an Assistant to the Editor and from 1979 to 1987 he was ~~slow~~ Postgraduate Editor responsible for producing two issues per year of review articles devoted to a single theme.

In 1987 he was appointed Editor and the Journal Office transferred from Glasgow to Leicester. Significant changes occurred during his tenure as Editor from 1987-1997, including a transition in 1991 from manual handling of manuscript data on index cards to computerised tracking on a computer database. This paved the way for electronic editing and subsequent submission and printing. In 1992 the BJA became the official journal of the Royal College of Anaesthetists, and over the period 1987-1997, the number of manuscripts submitted to the journal increased threefold and the circulation doubled in size.

By 1997, the editorial workload was such that it was no longer possible for a sole Editor to oversee every manuscript, as all previous eight editors had since the founding of the journal in 1923. Consequently, Graham Smith's successor, Jennie Hunter, was appointed in 1997 as an Editor-in-Chief with a team of four full editors. In 1998, he became the chairman of the Board of the BJA, a post he occupied until 2004. During this period, there was progressive expansion in the international membership of the Board. In addition, the commercial success of the Journal (the foundation of which could be traced back to the change of publishers originated by Alastair Spence in 1973) allowed it to become a significant financial supporter of research in anaesthesia, intensive care and pain medicine.

### **Publications**

Graham Smith's name appears on over 300 peer reviewed publications and he produced two major anaesthetic textbooks. With Alan Aitkenhead, he produced the 'Textbook of Anaesthesia' (Churchill Livingstone) now in its 5th edition and the most popular textbook for trainees in their first two years. With Walter Nimmo he produced 'Anaesthesia', a two volume comprehensive text used widely.

Reflecting on his career in the specialty, he said that the most enjoyable part of it was the association with the British Journal of Anaesthesia. The biggest challenge was to found and develop an academic department in Leicester from

scratch. The department became one of the largest in the country and contributed more ARS (Anaesthetic Research Society) presentations than most others.

Graham Smith, and his department, has produced a large body of research work on important topics...there are more publications listed below than have been reviewed for this overview.

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