British Academic Anaesthetists

1950 - 2000

Volume 2

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Preface

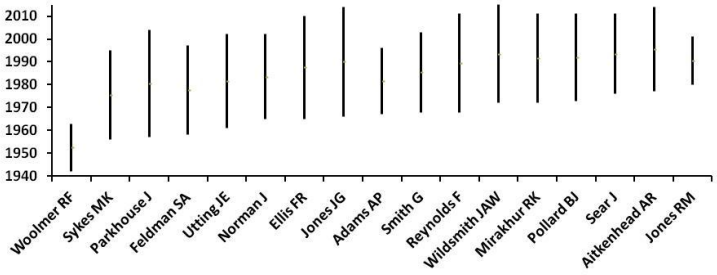
Research is the life-blood of medical practice. Without it we would still be following the edicts of Galen; a major investigator of his time. Since the renaissance medical knowledge has advanced because of the efforts of many investigators. Anaesthesia, a relative newcomer to medicine, got off to a slow start. The development of drugs and machines accelerated from about 1950 and, in the lifetime of many anaesthetists still working, changed from primitive to sophisticated.

This second volume highlights the work of some of the British workers in anaesthesia and it is not complete. A third volume would still not be complete, and to put it all into an international context would be a daunting proposition.

Below are the individuals whose work, and that of their colleagues, is covered. The dates 1950 -2000 have been transgressed but that's OK!

"It is the truth alone that we desire to know, and what a joy does it not give to have sought it out." Carl Wilhelm Scheele (1742 -86)

The Publishing Years



I would like to thank all those who have assisted me with various pieces of information and illustrations.

They include Douglas Russell (Society for Intra-Venous Anaesthesia, siva.ac.uk/ and http://www.docdr.co.uk/BAA.html), Sophie Lieven and Rose Sayce (Archives and Research Assistant, The Royal College of Anaesthetists), Matthew Whitaker (The Royal College of Surgeons (England)), Trish Willis (Anaesthesia Heritage Centre, The Association of Anaesthetists of Great Britain & Ireland), Fraser Faithfull (Archivist Australian & New Zealand College of Anaesthetists), Ewen Forrest (Honorary Secretary Liverpool Society of Anaesthetists), Peter Stanbury and Anna Gebels (Harry Daly Museum, Australian Society of Anaesthetists), Barry Hirst, Maureen Fortier, Jaideep Pandit, Vikram Jha, Arpan Guha, Chris Woollam, David Menon, Gareth Jones, Norma Woodhouse, David Rait, Pierre Foex, Philip Hopkins, Judith Hall, David Smith and the staff of the Medical Library, University of Otago (Wellington).

Michael Harrison 2015

Corrections, amendments or suggestions are welcome and should be sent to Michael.harrison@otago.ac.nz

Contents

Ronald F Woolmer

VRD BA BM BCh FFARCS

 [i]

Professor Woolmer qualified from St Thomas's Hospital in 1932 (BM BCh). He was awarded the Diploma in Anaesthetics in 1936. He became an anaesthetic registrar at the Westminster Hospital three months before joining the Royal Naval Volunteer Reserve in 1939. In 1941 he published a textbook 'Anaesthetics Afloat' [1].

At the end of the war, after a short time at the Woolwich memorial Hospital, he became Senior Lecturer in Anaesthetics in Bristol; later becoming Reader.

In 1957 he moved to the Research Department of the Faculty of Anaesthetists in the Royal College of Surgeons becoming the British Oxygen Company Professor in 1959. He studied research methods in the USA and returned to Britain with ideas and an interest in electronics. He died in December of 1962 year aged 54[ii].

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Ronald Woolmer was the first President of the Biological Engineering Society, a Vice-President of the International Federation for Medical Electronics and he was founder of the Anaesthetic Research Group (Society).

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[i] Photograph courtesy of Royal College of Surgeons of England..... The VRD (Voluntary Reserve Decoration) was awarded to commissioned officers in the United Kingdom's Royal Naval Volunteer Reserve (RNVR) for long service and good conduct.

[ii] Obituary - Annals of Royal College of Surgeons of England by GSWO. 1963;332(2):129-131

His first journal publication was in 1947, “Death from renal anoxia after Myanesin anaesthesia” [2] . Myanesin was a muscle relaxant [iii] that did not cause respiratory arrest...it had what was called a lissive effect – useful for conditions with increased muscle tone (it was also effective orally). The patient was given three doses. She died on the sixth postoperative day – she had had haematuria and at post-mortem the appearance of the kidneys was consistent with anoxia. Haemoglobinuria had recently been described by Pugh and Enderby (Lancet Sept 13,p387) following Myanesin and so this had stimulated Hewer and Woolmer to report this death.

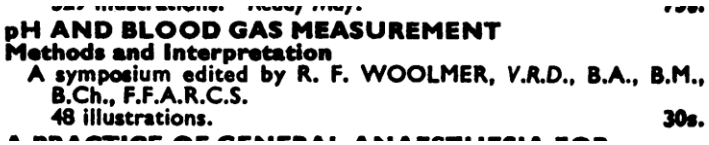
In 1951 he wrote about "Anaesthesia in Uruguay" [3], this was in the *British Journal of Anaesthesia*. He spent two or three months there following negotiations between Uruguay and The British Council; Uruguay wanted someone to teach modern methods of anaesthesia which would lead to a supply of trained anaesthetists for the future. He found the Uruguayans “the gayest and most hospitable people” - “The Uruguayans do not believe in revolution”.... and Uruguay “shines like a good deed in a naughty world.”

The larger hospitals were “old and decrepit in the extreme” but a new hospital was being built with fifteen operating theatres and “well placed spectators’ gallery”. Not all anaesthetists were medically qualified and many were medical students. Children’s tonsils were still removed without anaesthesia and obstetric anaesthesia was unknown. Because of the expense of anaesthetic agents closed circuit anaesthesia was common. In Uruguay there was no such thing as income tax and he suggested … “We in Britain would be the happier if we could adopt some of the many pleasant ideas which form part of the Uruguayan way of life.”

He was involved in several symposia … one in 1958 in Leeds on Pulmonary ventilation with a resulting publication edited by “Dr.R.P. Harbord

[iii] Berger FM. Brit. J. Pharmacol. (1947),2,241-50

and Professor R. Woolmer" in 1959[iv]. Another set of proceedings on "pH and Blood Gas Measurement – Methods and Interpretation" was edited by Woolmer alone. It had 48 illustrations and cost 30 shillings.


pH AND BLOOD GAS MEASUREMENT
Methods and Interpretation
A symposium edited by R. F. WOOLMER, *V.R.D.*, B.A., B.M., B.Ch., F.F.A.R.C.S.
48 illustrations. 30s.

Churchill, London 1959

The next publication was in 'Der *Anesthesist*' and was on the subject of carbon dioxide homeostasis during anaesthesia [4]. Did he speak German?

In 1960 he gave the Kelvin Lecture to the Institute of Electrical Engineers [Ref], the first physician to do so; it was on Medical Electronics.

He published "The Conquest of Pain" in 1961[v]; this was a compilation of articles that had been published in a Sunday newspaper. In the same year, what has been described as his thesis, was in print in the Proceedings of the Royal Society of Medicine [5], it was titled "Information Please". 'Information Please' was a presentation given on 2 December 1960, the "President's Address". "The desirability of anaesthetists being learned, in the academic sense, needs no arguing" by which he meant "of being well informed". He was of the firm belief that the pre-operative assessment of the patient should not "be skimped"; preoperative assessment clinics have only become the norm in the last ten years. Intra-operative knowledge was also of importance...and "the response to it which make up the science of anaesthesia, a science as yet in its

[iv] RP Harbord and RF Woolmer, Contributor British Journal of Anaesthesia, Publisher Sherratt 1959

[v] The Conquest of Pain RF Woolmer London Cassel 1961 171p (Nat Lib Australia)

infancy". However he was aware of the argument of others that "the more apparatus there is in use the more there is to go wrong." He dismissed this approach. Apparatus had to run on the principle of 'failure to safety'. A comment made a little later is of great interest to the author: "A properly designed instrument should present the appropriate information to the operator in a form in which it can be used immediately and without further computation....". This is describing the use of artificial intelligence to produce diagnostic information years before the concept existed[vi].

He goes on to describe transducers for pulse detection and the determination of heart rate ... this can be "caused to flash a light *and* emit a bleep on a loudspeaker." The sound signal was described as omnidirectional (cf. visual displays) and of use when the anaesthetist was otherwise engaged in "brow-mopping, light-adjusting or record-keeping." He went on to describe a variety of ways to automate other measurement devices. He also included measures of blood loss in this armamentarium of devices (a haemoporrhometer), something we still lack.

EEG analysis, anaesthetic blood gas concentrations, servo controlled devices for controlling the cooling of patients – he was certainly a futurist. He even puts forward the idea of simulation for teaching. "Clinical judgement and experience are indispensible, but by themselves are not enough"... "Information and control must go together, and we cannot fully exercise the control required for mastery of the situation unless we are supplied with the information which is a prerequisite for it."

In1962 he seemed to be gaining momentum with an article on "Principles of measurement in anaesthesia" in Acta Anaesthesiologica

[vi] Lowe A, Harrison MJ. Computer enhanced diagnosis of malignant hyperpyrexia. Anaesthesia and Intensive Care, 1999;27:41-44

Scandinavica [6]; one on anaesthesia by remote control [7] and a book review[vii].

The article in Acta Anaesthesia Scandinavica was a transcript of a talk he gave at a Postgraduate Course in Aarhus (Denmark). He covered measurement concepts such as - the measurement should not affect the measured variable, the random and systematic errors should be assessed, biological variation, and that the values are relative to some other measurement device – therefore requiring calibration. Response time also came under scrutiny as did analogue visual displays; he could see that digital displays were coming. He also saw the value in the recording of measurements, either on paper or magnetic tape, so that the data could be replayed. Even then, he voiced the "danger of being swamped by an inflow of information which is too great for us to handle."

Remote control of anaesthesia [7] – this paper with Fowler, Hill, Morgan, Nunn and Weaver was a description of an anaesthetic technique used to anaesthetise pigs whilst they were irradiated with neutrons or X-rays. The anaesthesia was conducted at a distance of 40ft (12.1m) and in a concrete 'bunker'. After a gaseous induction with Halothane the anaesthetic gas was passed through a 0.5cm bore pvc. tube to a Magill attachment. The door to the chamber weighed 32 tons and took five minutes to close/open. The only monitoring was a 'stethograph' as ECG and EEG monitoring was disrupted by the 50 KW of high frequency radio activity. These problems are so similar to those of the present age where radiotherapy treatment and CT and MRI scanning are done with using remote anaesthesia.

An interesting facet of this work is the death of several pigs in 1961 due to heat stroke. This was put down to the ambient temperature and humidity in the cyclotron chamber. Could it have been malignant

[vii] BJA 1962 4th April vol 34 Book review

hyperpyrexia? Malignant hyperpyrexia was first described in 'recent' times by Denborough (1960)[viii].

Professor Woolmer was obviously a farsighted academic anaesthetist.

References:

1. Woolmer, R.F., *Anaesthetics Afloat*. 1942.
2. Hewer, T.F. and R.F. Woolmer, *Death from renal anoxia after myanesin anaesthesia.* Lancet, 1947. **2**(6486): p. 909.
3. Woolmer, R.F., *Anaesthesia in Uruguay.* British Journal of Anaesthesia, 1951. **23**(1): p. 42-8.
4. Woolmer, R.F., *Carbon dioxide homeostasis during anesthesia.* Der Anaesthesist, 1960. **9**: p. 47-50. .
5. Woolmer, R.F., *Information please.* Proceedings of the Royal Society of Medicine, 1961. **54**: p. 114-9.
6. Woolmer, R.F., *Principles of measurement in anaesthesia.* Acta Anaesthesiologica Scandinavica. Supplementum, 1962. **11**: p. 17-21.
7. Fowler, J., et al., *Anaesthesia for the irradiated pig: A study in remote control* Br. J. Anaesth., 1962. **34**(5): p. 327-331.

[viii] Denborough M.A. Lovell R.R.H. Lancet 1960;2:45

Sir Keith Sykes
MA MB BChir (Cantab)
FFARCS FANZCA (Hon)
FFA (SA) (Hon) DA

 [i]

Keith Sykes became a full-time lecturer at the Postgraduate Medical School and Consultant Anaesthetist at Hammersmith Hospital in 1958. He was promoted to Reader in 1967 and was Professor of Clinical Anaesthesia at the Royal Post-graduate Medical School and Hammersmith Hospital between 1970 and 1980. He moved to Oxford in 1980 becoming the Nuffield Professor.[ii] He retired in 1991 and was knighted in the same year.

In 1956 Keith Sykes was Assistant Anaesthetics Registrar at University College Hospital, London, and he reported on a visit to the USA where he had tenure of a Fellowship in Anaesthesia at the Massachusetts General Hospital, Boston, 1954-5 [1, 2].

At that time, he thought that "the anaesthetist in America is still fighting an uphill battle for recognition. He has little to say in the clinical management of patients, and in some cases is not allowed to advise on the premedication or even the choice of anaesthetic which the surgeon orders him to deliver." The problem was that the demand for anaesthetic services had significantly outstripped the supply of suitably qualified anaesthetists. Some of the problem was due to a maldistribution of practitioners but it had been calculated that another 18000 were needed. The nurse anaesthetists carried the main load and were supervised by the surgeons who then treated anaesthetists as technicians.

[*Pask and Mushin responded with a letter strongly dissociating themselves from my criticisms!* – personal communication]

[i] Photograph courtesy of Andrew Farmery, Nuffield Department of Anaesthetics, Oxford.
[ii] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916

He describes in some detail the types of anaesthetic agents used; cyclopropane was used but there were worries about its explosive potential in the dry areas; ethyl chloride was banned because of cardiac arrests in children, at high altitude nitrous oxide was insufficiently potent to provide adequate analgesia and there were "grave doubts" about the safety of muscle relaxants[iii]. A paper in 1959 compares anaesthesia with ether with anaesthesia using thiopental, nitrous oxide and an infusion of succinylcholine [3]. It is a clear exposition of the methods of anaesthesia used at the time. The procedures were cholecystectomy, common duct exploration or gastrectomy; "Respirations were in almost all instances unassisted throughout surgery with ether." Of the 693 patients studied 50 died but there was no difference in the mortality rate, duration of surgery or duration of hospital stay between the two groups.. Hypotension was a problem during anaesthesia with ether and "the dangers of postoperative hypoventilation associated with the use of muscle relaxants are well recognised, but the observation of increased postoperative atelectasis came as a surprise." [!]

[Personal comment from MKS: *This paper resulted from discussions with Beecher who had just published his paper with DP Todd in Ann Surg 1954;140:2. I could not find any errors in the methodology of their study that showed that muscle relaxants produced a five-six fold increase in mortality when compared with ether and he challenged me to prove that relaxants were as safe as ether. I therefore set up the randomized controlled trial and ran it for the last six months of my time in Boston. I believe it was the first RCT in anaesthesia and was very proud of it. It clearly demonstrated that hypotension occurred more frequently during ether anaesthesia (because, as we learnt later, some very sick patients had a depressed adrenal response) and also that pulmonary complications were more common in the relaxant group. I had wanted to use curare in the trial but Beecher vetoed its use because his study showed a higher mortality with curare than scoline. We therefore had to use a scoline drip. Surgery was entirely done by residents with a couple of year's training and often took 6 hours and scoline doses approached 1500-2000mg so we attributed the pulmonary complications to prolonged hypoventilation from a type 2 block. In retrospect, John Bunker and I concluded*

[iii] Briggs, B.D. Anesthesiology 1954;15:323

that the high death rate in the B&T study was due to the failure of most American anaesthetists to use neostigmine after curare at that time.]

Following this description of his overseas experience, like many of his academic successors, he published a case report, an article on delayed spinal analgesia complicating epidural analgesia. The bottom line of this paper was that "the common practice of administering a test dose followed by a five minutes waiting period may be without value."[4]

Equipment, measurement and monitoring

Equipment:

1959 saw the first two papers (of about 20) on the subject of anaesthetic related equipment - they were both on the subject of non-rebreathing valves [5, 6]. The first described three valves with the goal of reducing rebreathing in the various breathing circuits in common use and the second was a review article on the subject.

This was followed by a letter to the BMJ in 1960 on the subject of resuscitation equipment [7]. He described the innovation of a resuscitation trolley for Wards (total cost £50). It had a typical floppy anaesthetic breathing bag which was provided with oxygen from a cylinder attached to the trolley – no self-inflating bag as we have today. However, in addition they did have a Porton bellows resuscitator[iv]. For airway management the trolley also contained a range of oropharyngeal airways and laryngoscopes. A mouth gag was also present and it was suggested that it could also be used as a rib spreader; sterile scalpels were included in the armamentarium and so it was expected that open-chest cardiac compression might be likely. The drugs contained in the trolley were calcium chloride, adrenaline, and methylamphetamine.

There was hardly one piece of equipment not examined (well, perhaps vaporisers). An air inlet valve for ventilation [8], equipment for tracheostomy care [9], rebreathing with Magill circuits[10, 11], accessories for humidifiers[12], a mixing device for expired air [13], plastic endotracheal tubes [14], a pressure-operated collect valve for respiratory studies [15]. All these before 1970; plastic endotracheal tubes were uncommon, carbon dioxide analysis was difficult and devices were very 'mechanical'.

[iv] Lucas, B. G. B., and Whitcher, H. W. (1958). Brit. Med. J., 2,887.

[Personal comment from MKS: *Rebreathing. My first paper on this problem was in 1959. At that time most anaesthetists simply squeezed the bag on the Magill attachment when doing short periods of controlled ventilation (e.g. an appendicectomy under thiopentone-N_20 trilene-gallamine) and it seemed obvious to me that different timing of expiratory valve opening would alter the CO_2 elimination. I used to provide topical anaesthesia for Hugh-Jones and John West to do regional bronchial sampling down a rigid bronchoscope and managed to persuade John to let me have a couple of runs with my model lung in the mass spectrometer room; it was the first machine to be built in the UK. I also managed to persuade a surgeon to do his minor ops session in this room so that I could study the patients. This was before the days of consent forms!*]

Keith Sykes was involved in the assessment of many diverse pieces of equipment. Between 1971 and 1980 a huge change took place and the equipment became more sophisticated. Evaluation of a lung ventilator performance analyser [16, 17], an evaluation of the IL-404 oxygen alarm monitor[18], a vortex-mixing membrane lung for open-heart surgery or for prolonged respiratory support [19-22], high frequency ventilation/ventilators [23-33], the classic Magill attachment [10, 11] and sterilization of ventilators [34].

High frequency ventilation: – In the 1980s a new form of lung ventilation emerged, high frequency ventilation (HFV), (respiratory rates of >150/min)[v]. Sykes and his team studied the technique in animals.

[Personal comment from MKS: *High frequency ventilation. The paper that sparked off our interest was Jonson A, Oberg PA, Sedin G, Sjöstrand U. (1971) High frequency positive pressure ventilation by endotracheal insufflation. Act Anaesthesiologica Scand (Supple) XLIII.*]

Chakrabarti and Sykes published a paper on the cardiorespiratory effects of increasing respiratory frequency in dogs [23]. Increased respiratory frequency

[v] D. P. Schuster, M. Klain & J. V. Snyde. "Comparison of high frequency jet ventilation to conventional ventilation during severe acute respiratory failure in humans". Critical Care Medicine 1982; 10 (10): 625–630D.

with a reduction in tidal volume, was accompanied by a reduction in physiological deadspace, the proportions were such that the deadspace/tidal volume ratio increased. "The peak airway pressures were minimal at a frequency of 45 bpm" but, at frequencies of 60 bpm. and more, the lungs "failed to empty so that peak airway pressures were increased and cardiac output decreased." These frequencies are not really HFV. HFV was expected to solve all problems associated with high airway pressures and resulting lung damage; there were many varieties. In 1986 they (the Sykes team) studied "the effects of frequency, tidal volume and added deadspace on carbon dioxide clearance were measured during high frequency jet ventilation at 1, 3 and 5 Hz in dogs"; that is at 60/min,180/min and 300/min [26]; "for a given minute volume the clearance [of CO_2] decreased with increase in frequency." It was concluded that "at 1 Hz, carbon dioxide elimination is governed by bulk flow, but at 5 Hz other mechanisms are important." They were not very happy with CO2 elimination at higher frequencies (see [27]) ..."the clearance of carbon dioxide at 5 Hz was very inefficient compared with that at 1 Hz. It is concluded that, during HFJ [Jet] V, carbon dioxide is cleared most efficiently when the frequency is low enough for the delivered tidal volume to be greater than the volume of the morphological deadspace"; a conventional approach. Although frequency of ventilation is preset two parameters are dependent on anatomical and the physical nature of the chest, arterial CO_2 and tidal volume. Mortimer et al [28] highlighted a problem with HFV which was that the slow response of infra-red carbon dioxide analysers made it difficult to measure $EtCO_2$ and so the HFV was interrupted with normal ventilatory frequencies and thus enabled the assessment of arterial PCO_2 by measurement of the end-tidal CO_2.; a cunning approach to the problem! This was developed further in 1989 [31]; a flow controller in a computerized high frequency jet ventilator delivered either a single deep breath or a series of three deep breaths and thus enabled the end-tidal value to be measured. With an optimum deep breath "the P_ECO_2 during the first deep breath was found to be similar (±0.2 kPa) to the $PaCO_2$ immediately before the onset of deep breaths."

The second parameter, tidal volume, was addressed in Young's paper [29]. A pneumotachograph was positioned in the expiratory limb of the breathing circuit and enabled the gas volumes, true I:E ratios and mean driving pressures to be determined.

They not only addressed the problem of measuring ventilatory parameters but they also investigated whether HFV improved lung 'repair' in a

rabbit model of hyaline membrane disease [30]. Saline lavage of the lungs produced surfactant-depletion (a model of the neonatal respiratory distress syndrome). Animals treated with high frequency oscillation (HFO) at 15 Hz [900 resps/min] were compared with rabbits treated with controlled mechanical ventilation. HFO produced "significantly higher arterial oxygen tensions and end-expiratory lung volumes than those treated with CMV, but there was no significant difference between hyaline membrane scores". There was no significant difference in mean survival times but some showed signs of recovery of surfactant function. There had been two previous publications with this rabbit model and conventional ventilation [35, 36].

Later in the 1980s came the new form of computerised axial tomography (CAT) - the nuclear magnetic resonance (NMR) scanner with its peculiar requirements, and so a ventilator for use in nuclear magnetic resonance studies [37]; then the wonderful multigas monitors, the Datex Capnomac [38], and the wonders of pulse oximetry – "Pulse oximetry: a "which" hunt?" [39-41] followed by the full power of the computerised world – the new microprocessor-controlled anaesthetic machine[42] and an evaluation of the Bruel and Kjaer monitor 1304 [43].

The 1980s were wonderful years for technological developments in anaesthesia.

Measurement

Electronic monitoring in the 1960s was basic and in 1963 Sykes wrote an article on "Venous pressure as a clinical indication of adequacy of transfusion" [44].

[Personal comment from MKS: *John Nunn walked into the cardiac theatre one day and saw how we used venous pressure to guide transfusion after bypass and included me in the Faculty meeting at the RCS. Venous pressure monitoring took off after my paper was published and I think it is the only time that I feel to have changed clinical practice!*]

However, more technological work was to come.

The determination of the arterial pCO2 was not easy in 1960/63 and a rebreathing technique was used, the concept was to equilibrate gases in an expired 'air' collection bag with gases in the alveoli in equilibration with gases in the pulmonary vessels. The first paper on this measurement technique was

about use of the technique in apnoeic patients [45], this involved the study of patients with tetanus at the King Edward VIII Hospital in Durban. These patients were totally paralysed – the present author has difficulty understanding the methodology as, even though the patients were "treated by total paralysis", equilibration still appeared to occur – was this due to bulk movement of oxygen into the lungs with CO_2 being displaced upwards and outwards?

[Clarification from MKS - *We disconnected the ventilator and squeezed the O_2 containing reservoir bag manually until we had made a CO_2 rich mixture. We then returned the patient to the ventilator for a minute or so and repeated the rebreathing for about 6-10 breaths. The gas was then analysed on a simple Haldane* [apparatus].]

The second was a discussion of "Possible sources of error in the determination of arterial carbon dioxide tension by an interpolation technique"[46]. Calibration of blood samples was carried out using 3% and 7% carbon dioxide and Interpolation was used to determine patients' PCO2 value; in clinical use it was found that these values were lower than expected – the suggested reasons were a) the occurrence of metabolic acidosis during the storage of the blood and b) incomplete equilibration of the blood samples with the known concentrations of CO_2 / O_2 mixtures.

Other measurements commonly required, particularly for patients in intensive care units, were pH and blood gases. A review of their measurement and the sources of error using electrode systems was published in 1967 [47], the lead author being AP Adams.

[Personal comment from MKS: *Blood gas errors: When we first obtained an Astrup machine (the 1955 version with the mercury U tube to move blood to and from the equilibration chamber) I got Barbara Bird to measure the standard bicarbonate in a number of normal blood samples. To my surprise, the mean value was about 18 instead of 23. I did not believe our results and eventually learnt from Geoffrey Burton of Bristol that protein contamination of the electrode could cause low pH readings on blood. He showed that the electrode could be cleaned with pepsin and advocated using a standardized plasma preparation to check the electrode before use. When we followed his procedure we got the correct values for standard bicarbonate.*]

One of the aspects of pathophysiology associated with anaesthesia was alveolar collapse and subsequent hypoxaemia. Sykes and his team investigated the pulmonary vasoconstriction that accompanies alveolar hypoventilation (see below) and in 1977 (and also in 1981) evaluated new methods for measuring blood flow/ ventilation in the lungs. [48, 49]. The new technique involved the use of an isotope that allowed the distribution of blood flow between the two lungs to be measured continuously. In 1981 they compared regional ventilation using nitrogen-13 and krypton-81m in mechanically ventilated dogs

In 1980 oxygen measurement went under the 'microscope' [50]. It was found that even if the IMI oxygen analyser was properly set up the readings could be seriously affected by nitrous oxide. Ten years later it was pulse-oximetry [51, 52], first author Verhoeff; they used the computer simulator MacPuf to create three oxygen failure scenarios and compared the time of onset of hypoxia with the delays they detected between a fall in PO2 and its detection by pulse oximetry. They thought that oxygen saturation might reach dangerously low levels before a pulse oximeter alarm occurred. The second paper was a report on the inaccuracy of SpO2 readings in the presence of elevated concentrations of carboxyhaemoglobin and methaemoglobin. They describe the theory and an experimental in vitro test system using a blood circuit containing a model finger capable of pulsatile flow. The theoretical and experimental results were compared and "found to agree well" with carboxyhaemoglobin, but not so well with methemoglobin.

Monitoring

Sykes had a major interest in equipment and measurement and therefore it is natural that he must have had views on monitoring. The first was in 1965. [53]on the monitoring of patients in respiratory failure, it is primarily a discussion about blood gas analysis in the situation where the hypoxic drive may be suppressed by moderately high concentrations of inspired oxygen. In 1988 he wrote a review article on 'Essential Monitoring' with many astute observations: "Studies of morbidity and mortality and critical incident analysis have revealed that the majority of complications associated with anaesthesia result from inadequate training or inadequate experience of the anaesthetist[vi].

[vi] Cooper, J. B., Newbower, R. S., and Kitz, R. J. (1984). Anesthesiology, 60, 34; Craig, J., and Wilson, M. E. (1981). Anaesthesia, 36, 933; Lunn, J. N., and Mushin, W. W. (1982).

Some are caused by tiredness or boredom, and others by lack of attention. Knowledge and experience are a function of the intensity and duration of training, but vigilance is, unfortunately, only generated by self-motivation." and: "Because of the limitations of the individual monitors outlined above, it is necessary to use a combination of monitoring devices which is capable of detecting the majority of hazard situations". This was an attempt to minimise false positives and false negatives. A letter followed in 1989 when a correspondent described a failure of a disconnection monitor. These were in the British Journal of Anaesthesia [54, 55]. Many of the comments still pertain today (2013).

A year later he wrote an introduction for the "Panel on practical alarms" (Fifth International Symposium on Computing in Anesthesia and Intensive Care) [56]. These were defining enterprises and probably structured monitoring for the coming decades.

Pulmonary vasoconstriction

For 14 years, pulmonary vasoconstriction was the subject of much investigation - [57-77]. Pulmonary vasoconstriction, as a result of poor alveolar oxygenation, attenuates the effect on the arterial oxygenation by reducing blood flow to the poorly ventilated (oxygenated) parts of the lung. It would appear that an animal model (in both cats and dogs) was used to investigate the phenomenon and the effect on it of about 20 drugs.

The complex experimental set up is described in the first paper in 1972 [57]. In this study greyhound dogs ...."were anaesthetized with nitrous oxide-oxygen-halothane, intubated and ventilated with air and 0.5-1.0 per cent halothane..... The respiratory frequency was 20 per minute and the tidal volume was adjusted to maintain the end-tidal CO_2 concentration between 4 and 5 per cent. A normal acid-base status was maintained … by the addition of 4.2 per cent sodium bicarbonate when required." End-expiratory pressure of 5—10 cm H_2O could be applied when the chest was open. "When the pulmonary and

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Mortality Associated with Anaesthesia. London: Nuffield Provincial Hospitals Trust;
Cooper, J.B., Long, C. D., and McPeek, B. (1978). Anesthesiology, 49,399.

femoral arteries had been cannulated, the halothane was turned off and anaesthesia maintained with intravenous injections of chloralose ... the animal inspired air either alone or with the inhalational anaesthetic agent under test." The description continues in great detail, all care being taken to avoid potential gas analysis pitfalls.

[Personal comment from MKS: *It took us four years to develop a satisfactory animal model. Initially we tried to keep the greyhounds asleep with electrical anaesthesia but they either convulsed or ran off down the corridor. We tried all sorts of complicated isolated lung perfusions but could not elicit HPV, probably because we used old greyhounds from White City dealers. Finally, I went to see a physiologist who introduced us to the standard model we later used.*]

The results showed that "alveolar hypoxia produced an increase in pulmonary vascular resistance in isolated cat and dog lungs or lobes perfused at constant flow. This response was abolished for varying periods of time by the administration of high concentrations of inhalational anaesthetic agents. In these preparations 5 per cent halothane caused pulmonary vasodilatation whereas 15 per cent ether, 1.5 per cent trichloroethylene and 79 per cent nitrous oxide caused vasoconstriction. Two per cent methoxyflurane did not cause a significant change in pulmonary vascular resistance. It is postulated that the abolition of the pulmonary vasoconstrictor response to hypoxia may increase the proportion of blood flowing through shunts or areas of lung with a low ventilation/perfusion ratio and so may contribute to a decrease in arterial oxygen tension during anaesthesia. The pulmonary vasodilatation or vasoconstriction produced by inhalational agents may augment this effect."
Sykes and his collaborators studied:

a) Protamine / heparin mixtures - they "produced a rise in pulmonary artery pressure ... the pulmonary vasoconstriction produced by protamine may be partly due to a direct action on the pulmonary vasculature or to the release of vasoactive substances from the lungs."[58]
b) Trichloroethylene – "It is concluded that trichloroethylene may increase arterial hypoxemia by reducing vasoconstriction in hypoxic areas of lung."[60]

c) Methoxyflurane – "Methoxyflurane decreased pulmonary vascular resistance and depressed the pulmonary vasoconstrictor response to hypoxia."[61]
d) Nitrous oxide – "Nitrous oxide, in concentrations of 50 per cent and 75 per cent, was found to produce a reversible depression of the hypoxic pulmonary pressor response."[62, 64]
e) Diethyl ether – "Two per cent diethyl ether markedly reduced hypoxic vasoconstriction under all acid-base conditions, the hypoxic pressor response returning after wash-out of diethyl ether."[63, 65]
f) Cyclopropane - "Cyclopropane was found to produce no significant changes in pulmonary vascular resistance or the pulmonary vasoconstrictor response..."[67]
g) Dopamine/isoprenaline – "Dose rates of dopamine 25 micro-grams kg^{-1} min^{-1} and isoprenaline 0.25 micrograms kg^{-1} min^{-1} (which produced equal increments in the contractile force of the heart in dogs) produced a similar degree of depression of the hypoxic vasoconstrictor response"[68]
h) Orciprenaline – "The hypoxic vasoconstrictor response was significantly depressed by an infusion of 1.0 micro-grams/kg/min of orciprenaline but not by a dose of 0.1 micrograms/kg/min."[69]
i) "Infusions of nitroglycerine and sodium nitroprusside which produced the same decrease in mean aortic pressure produced similar decreases in hypoxic pulmonary vasoconstriction."[70]

After these drug aligned studies the team now investigated the effects of FiO_2, CO_2 and mechanical factors on the reflex [71, 72, 74]. "Repeated hypoxic stimuli produced a progressively greater reduction in the blood flow to the hypoxic lung and a progressive increase in PaO_2." "It is suggested that the effects of CO_2 on h.p.v. and PaO_2 may be explained largely by the changes in alveolar oxygen pressure (P_AO_2) which are secondary to changes in P_ACO_2." and "We concluded that the reduction in blood flow during lobar collapse is due predominantly to hypoxic vasoconstriction, but that this mechanism is augmented by the raised PCO_2 and mechanical factors present during collapse." and "It is concluded that changes in local pCO_2 during collapse may account for the greater diversion of blood flow from the lobe when compared with ventilation hypoxia."

Two papers in 1986 [75, 76] described the effect of lignocaine on the hypoxic pulmonary vasoconstriction reflex: "It is concluded that lignocaine reverses the depression of hypoxic pulmonary vasoconstriction produced by lobar ventilation with nitrous oxide…" and "… the subsequent infusion of lignocaine during 7% oxygen in nitrous oxide increased the response to a value which was not significantly different from that produced by 7% oxygen in nitrogen alone."

The mechanism by which dopamine alters blood flow distribution during lobar collapse was determined [77] – " It is concluded that the [the effect] produced by dopamine was due to a decrease in hypoxic vasoconstriction in the lobe secondary to an increase in mixed venous PO_2 and to vasoconstriction in the oxygenated lung".

Many other articles on this important pulmonary reflex were published [78-86]

This was a large body of work addressing the problem of hypoxaemia associated with anaesthesia and commonly seen in intensive care patients. There were many collaborators.

Lung ventilation

Over a thirty-year period the unravelling of pulmonary physiology took place as it pertained to anaesthesia and intensive care. Some publications to do with oxygenation [87-89], two about differential lung ventilation [90, 91] (this was an investigation into the V/Q mismatch associated with IPPV with the patient (dog) in the lateral position using the equivalent of a double lumen tube); the first a presentation to the ARS and the second a full paper. If each lung was ventilated so that the $EtCO_2$% in each was the same then the V/Q was as if the patient was supine. Six investigated the effect of the pattern of respiration on oxygenation [92-97] and later on the possibility of ventilation causing lung damage [98-100], one a comparative study, another a review; all these investigations of great importance to clinical practice.

Resuscitation

His first publication on resuscitation has been described above [7] in the Medical Electronics section of the BMJ, "New Appliances". This described a resuscitation trolley with all the equipment required for lung ventilation and CPR. The second was about the organization of a resuscitation service [101].

The article was divided into "**Organization**" – a sub-committee of the Medical committee, convened by the Resuscitation Officer who is in charge of the day-to-day running of the service. **Aims**: management of cardiac arrest, collapse in the outpatient or casualty department, all postoperative patients, patients having myocardial infarct or Stokes-Adams attack, and other patients at special risk. **Treatment**: "Treatment is based on the principle that the person on the spot is responsible for diagnosing the arrest and for establishing artificial ventilation and an effective circulation: this is then maintained until more definitive treatment, aimed at restarting the heart, can be carried out by the duty surgeon and anaesthetist." **Training:** "It is obvious that both medical and nursing staff must be trained in the recognition and emergency treatment of cardiac arrest." At the Hammersmith these lectures were given twice yearly at the new intake of residents. **Procedure:** The on-the-spot clinicians start the resuscitation, 'phone the switch board, and if no responses in a short time a general cardiac arrest call is to be made over the hospital Tannoy! Life was simple then. The **results** of this service were then described – a seven year period from 1956-1963. Of 251 patients 34 survived. The three top categories were either during procedures, in the postoperative period or during induction of anaesthesia. It is interesting to note that between 1956-1961 there were 21 patients per year who received internal cardiac massage (13 survived); in the years 1962-3 no patients had internal cardiac massage from the start. However, there were 24 patients who started out having external cardiac massage and then proceeded to internal cardiac massage - only one survived. "One rather startling complication of external cardiac compression has been the rapid return of consciousness resulting from effective treatment. For this reason we have now added a supply of anaesthetic drugs to the cardiac arrest trolleys." **Conclusion**: "Every hospital should make its own arrangements for the emergency treatment of cardiac arrest."

Internal cardiac massage was obviously on the way out. The article that followed this in the journal was "Automatic External Cardiac Massage Machine" by V Keating.

A further report in 1966 covered the years 1963-1965 [102], the survival rate was almost identical – 13.1%. A year later a paper entitled "Resuscitation of the apparently dead" was published in International Anesthesiology Clinics [103]; an interesting title. This is a comprehensive (39 pages, 131 references) review of the causes, effects treatment and sequelae of cardiac arrest, including descriptions of the equipment that can be used.

Cardiopulmonary bypass

Keith Sykes' was a cardiac anaesthetist at Hammersmith but not in Oxford[vii], he published sixteen research projects on factors around cardiopulmonary bypass and cardiac surgery over 26 years.

1963 "Intermittent positive pressure respiration after open-heart surgery" [104].
1965, in the Lancet, two articles on post-perfusion lung syndrome [105, 106].
1966 "The elimination of carbon dioxide after total body perfusion" and "Pulmonary changes after extracorporeal circulation in dogs" [107, 108].
1967 "The effect of low molecular weight dextran and haemodilution on acid-base balance and lactate and pyruvate levels during cardiopulmonary bypass" [109]
1969 "The effect of varying inspiratory: expiratory ratios on gas exchange during anaesthesia for open-heart surgery" [110] and "The effect of varying inspiratory: expiratory ratios on gas exchange during anaesthesia for open-heart surgery" [111]
1970 "The effect of variations in end-expiratory inflation pressure on cardiorespiratory function before and after open-heart surgery" [95] and "The effect of mechanical ventilation after open-heart surgery"[112]
1974 "Cardiorespiratory effects of protamine after cardiopulmonary bypass in man." [113]
1978 "Cardiorespiratory effects of increased airway pressure during controlled and spontaneous breathing after cardiac surgery." [114]
1982 "Changes in colloid osmotic pressure with plasma albumin concentration associated with extracorporeal circulation. [115]
1983 "A vortex-mixing membrane lung for open-heart surgery or for prolonged respiratory support" [19] and "Initial in vitro evaluation of a pediatric vortex-mixing membrane lung" [20]
1985 and 1986 "Oxygen and CO_2 transfer of a polypropylene dimpled membrane lung with variable secondary flows" [21, 22].

[vii] Personal communication – Pierre Foex

1989 "A randomized comparison of total extracorporeal CO_2 removal with conventional mechanical ventilation in experimental hyaline membrane disease" [116]

This body of work alone is worthy of respect – a thorough analysis of all of Sykes' work with critical appraisal (with an explanatory subset of chapters on the complex physiology involved) would entail a textbook all of its own. One book of his own (as co-author) was Principles of Clinical Measurement and Monitoring in Anaesthesia and Intensive Care with M D Vickers and CJ Hull.

Some final words:

In 1995, the last year he published, he wrote two articles, one on quality assurance in research [117] and the other titled "Recognition of the anaesthetist" [118]. In addition there was the re printing of a 1960 paper on Intermittent Positive Pressure in tetanus neonatorum; reprinted as a classic paper[119].

The quality of research article covered the fact that there were about 80 journals pertaining to anaesthesia, a high proportion of the papers being of "doubtful validity" and an estimated 1% being scientifically sound. The quality assurance issue starts with study design and continues through ethics committees, execution of the project and the analysis. Of projects signed off by the Central Oxford Research Ethics Committee only 59% had been published three years later. It was thought that 30% had not been published because of insignificant results, negative results or had been rejected by the journal's editor. Sykes thought that pilot studies were of importance because they highlighted the difficulties of the study and allowed the opportunity to modify the protocol, data collection and analysis. He was particularly concerned about bias, both overt and subtle, and the dangers involved in studies for the benefit of pharmaceutical companies.

The "*Recognition of anaesthetists*" editorial in Anaesthesia was about the fact that even in 1995 the anaesthetist still seemed to be a 'backroom' service provider and was losing out with regard to funding in the 'purchaser-provider' split in the UK. Anaesthetists were performing many important clinical and administrative roles but were still not recognised by patients as not only being doctors but being specialists. He advocated preoperative assessment visits and postoperative checks as a start to greater recognition by the public. He was of the view that patient education was an anaesthetist's role

and that duplication of information was important to get information to the patient – interviews, booklets and videos would all reinforce in the importance, and potential hazards, of anaesthesia. He considered post-operative audits of patients' experiences important, not only for them but as feedback for the service.

A finale: ...the reprinting of the 1960 paper on the management of tetanus neonatorum is good in that it does give us an inkling of Keith Sykes himself. A brief description of the encounter leading up to his work in 1958 in the King Edward VIII Hospital in Durban is interesting. He had £1000 to buy ventilators and analytical equipment; he had to sell his car to buy boat tickets to get his family there, let his home etc... and whilst there his asthma was a problem because of the humidity.

The intended work on adult tetanus did not succeed because the number of patients presenting with tetanus fell so they transferred their attention to the neonates. There were many physical problems to overcome with ventilators, humidification and tracheostomy tubes but the mortality fell from 84% to 44% and later 11%. Unfortunately, Pat Smythe and Arthur Bull pre-empted the publication of his results[viii] with a similar small study.

[Personal comment from MKS: *On the way back from Durban our Union Castle boat stopped in Capetown for a week and I gave a talk to the University department about the setting up of the Durban tetanus unit. Arthur Bull and Pat Smythe came up quietly after the talk and showed me the copy of the BMJ that had just been published containing their article announcing their 9/10 survivors! We were good friends for many years and they kindly stated that my rebreathing PCO_2 technique had helped improve their results.*]

Overall, a huge body of varied work is attributable to Keith Sykes and to the team around him.

He continues to write, notably in the History of Anaesthesia Society Proceedings, and has written a book, with John P. Bunker, called "Anaesthesia and the practice of medicine: historical perspectives" that was published in 2007. I enjoyed reading it.

[viii] Smythe P and Bull A. British Medical Journal 1959;2:107

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[Further comments MKS...*I think your comments about my motivation are correct. I have always been a keen clinician, gave anaesthesia for 5-6 sessions a week at both Hammersmith and Oxford and took my share of a 1 in 5-7 on call rota at both places. At Hammersmith we had plenty of SRs to deputise when I was travelling but at Oxford the other Consultants always insisted on my doing a swap if I was away so I ended up with a lot of on call when at home. I started using mechanical ventilation on post-op open heart and tetanus cases in 1960 and ran one of the first intensive care units at Hammersmith from 1961 to 69.*

In Boston there was always a surgeon scrubbed to do internal cardiac massage before anaesthesia was started. The cardiac arrest service at Hammersmith (which I think was the first in the country) was started because one of the physicians who was doing bronchoscopies under topical anaesthesia biopsied the left atrium with fatal results and asked me to create an emergency team. I ran

this service with lecture-demos to all departments every three months until about 1965. It is interesting that our survival rates approximated to those currently reported.

When running 12 operating rooms in the charity block in the Massachusetts General Hospital I had to supervise year 1 and 2 junior residents and nurse anaesthetists. I gained an amazing experience of anaesthetic complications and thereafter I took great interest in safety, chairing the AAGBI committee and working on British and International standards committees for over 30 years.

I was extremely fortunate in having good labs and an unending supply of potential researchers at both Hammersmith and Oxford. At Hammersmith I usually spent a day a week on animal work, ably assisted by Mr Chakrabarti, a highly intelligent émigré Indian Electrical engineer who could never be persuaded to service equipment but who nearly always managed to get it going again when pressed! He became interested in high frequency ventilation and transferred this interest to Joe Whitwam when I went to Oxford. Unfortunately, I did not have time to work in the labs myself at Oxford but I kept a close eye on the experiments downstairs and reviewed the data with the researcher at least every week. Within a year of going to Oxford, Clive Hahn, Pierre Foëx and I had 21 research fellows working on MRC, SERC and other studentships. About half were medical and the others mathematicians, engineers, and biochemists who divided their time between our labs and theirs. We continued to have 20-25 research students until I left in 1991.

I think most of my publications would come pretty low on the citation index as they rarely produced the ground-breaking results that others claimed and the only piece of apparatus named after me was the four-in-line reservoir bags filled with nylon pot scourers expired gas mixing unit that was known as Sykes's double-ended bra! However, the paper on venous pressure (which resulted from an invitation from John Nunn to speak at the RCS) did change clinical practice and was quoted quite widely at the time.

I think that teaching trainees to think and assess evidence was probably of more use to the profession than the research. The grilling that I gave the better FFA candidates was designed to identify those who would get a 9+ instead of awarding marks on the old school tie principle that was common at the time. The

books Respiratory Failure and Principles of Measurement were among the first in the field and sold well both here and abroad. Just before I retired an anaesthetist in Ireland presented me with a newly bound, dog-eared copy of the measurement book that he had used for the primary. The new title that was inscribed in Gold leaf was "The SHO's Bible"!]

James Parkhouse

MD MA Oxon FFARCS DA

 [i]

Born in 1927, James Parkhouse graduated in 1950, obtained the DA in 1952 and MD in 1955.

He became a consultant anaesthetist at the United Oxford Hospitals in 1958 and professor of anaesthetics at the University of Manitoba, Winnipeg, and chief anaesthetist at Winnipeg General Hospital in 1967. In 1969 he returned to the UK and became Postgraduate Dean at Sheffield University; in 1970 he became professor of anaesthesia in Manchester, then professor of postgraduate medical education in Newcastle and was later appointed director of the Medical Careers Research group (1984-89).

James Parkhouse became an adviser to the WHO on medical education and president of the medical education section of the Royal Society of Medicine.

He wrote several books - Anaesthetics (New Look) 1965, Medical Manpower in Britain 1979, Specialized Medical Education in the European Region (EURO Reports and Studies) with J-P Menu 1989 and Doctors' Careers: Aims and Experiences of Medical Graduates 1991.

Although trained as an anaesthetist, 45% of James Parkhouse's publications are on the subject of medical education, career choices and medical administration.

His publishing career spanned 47 years (1957–2004), the early subjects of a distinctly clinical nature; his educational expedition started in 1971.

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[i] Newcastle School of Medicine 1834-1984" A Sesquicentennial Scrapbook, by Gordon Dale and F.J.W. Miller. (ISBN 0 947678 00 X) 85655729

Anaesthetic studies

There are over 50 publications that are clinically orientated - four describing clinical cases, many reports on analgesics, pain assessment and management, and a further set of papers on a wide variety of clinical topics.

1957-1959

The first three publications were in 1957. At this time, he was still a trainee. Bronchography under ether anaesthesia is, obviously, the description of a procedure that is no longer necessary using a drug no longer used [1]. The second [2], an article in the British Medical Journal, was about general anaesthesia as an aid to therapeutic hypothermia. To have a publication in the BMJ is quite an achievement for a trainee. The patient described had a head injury and high temperature of 101˚F (38.3˚C). To maintain hypothermia they used N_2O, ice bags, chlorpromazine and levorphanol. When the patient awoke they shivered and were re-anaesthetised for 24hrs and kept at 30.8˚C-32.8˚C. Again, on awakening the patient shivered but was kept cool for 12 days. A good outcome occurred eventually.

The third publication [3], and a very thoughtful one, was an essay for a registrar's prize, published in the British Journal of Anaesthesia (another accomplishment for a trainee). It discussed the problem of choice of anaesthetic, about the transition from single drug anaesthesia to the use of multiple agents with specific effects. Waxing philosophical he said "There is no single answer to any anaesthetic problem..." and quoted Proust, "*Medicine is not an exact science*".

He describes the ritual surrounding the start of an anaesthetic as being like a bullfighter about to subdue a bull. [I like that]

The 'record card' he says is better than 'mere clinical impression' and a series of record cards becomes the literature. The literature then provides probabilities of events taking place but he says this is different to 'likelihood' in clinical practice. To make it clear he describes how the condition of an individual patient may make the likelihood of an adverse event greater or lesser than the 'probability'.

He believed that "...there is much to be said for settling down to a broadly acceptable and fairly conservative set of standards for routine anaesthetic practice." He continued to suggest that if "...he should wish to do something more exciting, a central organising body should supply him with a practicable and useful project for investigation..." - an essay worth reading.

In 1958 he became a consultant, publications were restarted in 1959. Of interest is the one entitled "A restatement of anaesthetic principles", this was co-authored with B R Simpson[6]. Again, he looks critically at changing anaesthetic practice and makes some suggestions for simplification. The bottom line is perhaps a little too simple and the views are now very dated.

In brief, there had been a move from single agent anaesthesia to multiple agent anaesthesia with drugs with specific effects, and the dosages of the drugs were now "*virtually innocuous*". He considered that with this great progress "*it was time to assess how much of our inheritance is superfluous, outdated, and needlessly unscientific.*" He decries the lack of quantitative knowledge about tidal volumes with various breathing circuits, levels of carbon dioxide – "*There is much glib talk of hyperventilation and hypoventilation, and much discussion of blood CO_2 levels, but little reliable data from which cause and effect can be correlated.*" He reinforces the idea of using being conversant with a single technique so that changes in patient's condition are then far more readily appreciated. He then moved on to choice of drugs (nitrous oxide being nontoxic, ether having an evil reputation – because of high dosage used). He says that "*When muscle relaxants are available, so that the quantities of general anaesthetic can be kept to a minimum, it is probably of rather small significance which agent is chosen.*" He went on to describe the hazards of using compressed gases and suggested that air was easily available, "*containing enough oxygen for our requirements*." Gas cylinders caused all sorts of problems!

The final section is entitled "Advantages of air" and goes into detail about the occurrence of cyanosis and high CO_2 levels (twice normal levels "*will not result in serious harm*"). Cyanosis is suggested as the indicator for increasing ventilation.

The bottom line was..."*It would seem that the quantitative administration of volatile liquid anaesthetic agents in air, through a non-return system, is the logical method of anaesthesia for the present day.*"

These are meta-papers...an overview...thinking through problems in a logical, hopefully well-informed, way. Unfortunately, to quote Sherlock Holmes "*I had come to an entirely erroneous conclusion, which shows, my dear Watson, how dangerous it always is to reason from insufficient data.*"[ii]

[ii] The Speckled Band, Sir Arthur Conan Doyle

1960 – 1970

Publications of interest include those on the place of nurses in anaesthesia, the effects of nitrous oxide, thermal vasomotor responses, polymers, placebos, and the assessment of pain and analgesics; a wide spectrum of subjects.

Nurses in anaesthesia [7, 8]:
it is interesting that both of these papers are in non-UK publications (South African and Canadian); even in the 21st century the concept of non-medical anaesthetists is a hot topic in many countries – UK, Australia, New Zealand to name three.

The studies of nitrous oxide are of interest...around this time the 'Liverpool technique' of anaesthesia (the result of the work of Cecil Gray) was common but was often 'just' a mixture of nitrous oxide, oxygen, hyperventilation and some opiate (often quite small doses – personal recollection as a novice under tuition) [9-11].

Thermoregulation - [12]: Polymers – a seemingly odd topic – but at that time the routine tracheal tube was made of red rubber; it was satisfactory for the relatively short exposure during surgery but was a real problem for prolonged intubation such as required in intensive care units [13].

Placebos and their place in research, another 'hot' topic; it would now be very unusual for an ethics committee to allow the use of a placebo in a clinical trial [14, 15].

And finally, in this clinically orientated period of his academic pursuits, – pain and the assessment of analgesics [16-24], the last few papers taking us up to 1975.

Associated with these publications are articles on recording data, analysing data and methodology [21, 25, 26].

Medical training, education and careers.

The first paper on this type of topic was in 1965 [27], "Anaesthetics training today".

The publications did not only pertain to anaesthesia: *"Allocation of preregistration posts", "Promotion in the National Health Service and the effect of change", "Future prospects for British graduates and the health service" and "Do we need more doctors or not?*" [24, 28-30] are just a sample.

In 1977 there was the first publication on medical manpower [31], this was followed in 1978 by a series "Medical manpower in Britain" 1 – 5, [32-34] and these were followed a year later by "Medical manpower two years on" [35].

There are 47 further publications on a wide range of medical education/ training/career choices and, if you are truly interested in medical 'politics' regarding this era, then I suggest you go to the articles directly on line...they are listed below.

However the titles of some are very intriguing and so they are discussed below.

"The journey and the arrival" [36]. This was the title of the Frederick Hewitt lecture given in the Royal College of Surgeons in 1979[iii]. He describes anaesthetic training as "*....a journey, with an ill-defined beginning and towards an identifiable end.*" and "*Any rigidly planned programme of training that assumes a common starting point of knowledge, experience or attitude, is certain to fail.*" He, Parkhouse, addressed Hewitt's treatise that "*...it would be of great advantage, not only to the public but to the profession, to have a constant stream of experienced anaesthetists issuing from our great centres of education.*" It would appear an interest in anaesthetics as a career often started early... in the pre-registration year about 5% of respondents indicated anaesthesia as their preferred choice but this varied tremendously between centres and from year to year – there seeming to be no relationship between 'interest' and the type of 'teaching', once the choice had been made very few left the specialty.

In this 1979 lecture he said "*By any logical form of analysis it is clear that we have too many registrars and too few senior registrars and consultants.*

[iii] Frederick Hewitt (1857-1916) took up anaesthesia after developing visual problems. His reputation was such that he was appointed as anaesthetist to two kings. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2238538/?page=1

Taking a broader view, we have too many anaesthetists who are loosely called trainees and not enough in career grades of various kinds." But, it was a very changeable situation..."*The curious feature of this situation is that whereas three years ago there were vacant senior registrar posts in many regions and great difficulty in finding suitable applicants, there is now a superabundance of good candidates throughout the country.*" He commented on the difficulty of predicting workload requirements - they now had 'quality' anaesthetists but how many did they need; how many was enough? The number of surgical procedures in hospitals per 1000 population in the catchment area varied greatly (35-100/1000) and the ratio of anaesthetists to population was also very varied. Figures were not given.

He followed this with many figures and workforce diagrams. He finished on a cheerful note...with reference to a Canadian surgeon[iv]. "*Recruitment depends most on the morale and enthusiasm of anaesthetists.*" And... "*I am more and more impressed by the difference that enthusiasm and persistence can make, in spite of the difficulties that all of us share. We need to travel hopefully, for as Montaigne put it: 'The value of life lies not in the length of days, but in the use we make of them'.*"

Five years later..."What do young doctors think of their training and themselves?" [37]. This is interesting in the way in which the range of personalities and insight were displayed. "*Many respondents found it more difficult to answer questions about their own level of competence...than to deal with less personal questions about under-graduate or postgraduate training.*"

There were "*...very wide differences of view about the purpose of training, the need for lifelong learning, and perhaps the impropriety or unwisdom of admitting imperfection. Responses ranged from the view that anyone who did not feel fully competent at the end of postgraduate training should be shot, to the more common feeling that only an insufferably arrogant person would claim to have no professional weaknesses or deficiencies.*"

"Manpower: compendium of deliberate mistakes."[38], 1986. This is a good read...a voice of exasperation and frustration about government, the General Medical Council, the DHSS and their changes to the organisation of hospital training, career structures and the health system. "*...voices of those to*

[iv] McPhedran NT. Manpower Problems in Anaesthesia. Canadian Anaesthetists' Society Journal 1976; 25: 517-9.

whom the exigencies of the system deny free, open speech deserve to be heard. This may sound an extreme comment: "The hospital service is full of petty bureaucrats, inconsiderate, and often vicious people. I feel that the majority of these medical and nursing staff are [sic] more concerned with their own egos than patient care." I have read too many like it from my respondents to feel complacent or comfortable."

And ... "*...Also, we should recognise that a system as complex and elastic as the NHS needs a few cushions - well fashioned and not just hiding shoddiness under cheap embroidery*[v]*. Altogether, there is a lot more talking to do and it has to be done quickly. To restore the morale of the service and get away from the awful disenchantment with hospital careers that so many young doctors have we need something better than a panic response to a self-induced crisis.*"

"The views of doctors on management and administration" [39].

Another two years and we have a 14 page article on doctors and management.

The components of effectiveness in management, it was suggested, should be taught in medical school and onwards in a series of stages: (i) awareness; (ii) ability; (iii) accountability; (iv) advanced management. Relevance and importance were noted to be more evident in some specialties than others and it becomes more consciously important when doctors become consultants (or principals in general practice). There were differences in attitude, "*... administration [is] a waste of time and ...[they felt] that it would be better left to professional administrators and non-medical managers*" to those who could "*...see grave dangers if doctors [did] not participate actively in health service management*."

"*If high-level general management is to be taken seriously in the NHS there is a strong case to be made for professionally organized, intensive selection boards which could be arranged over a four or five-day period at venues such as the White Hart*[vi]*. As a prelude to this, for those who feel that they may be*

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[v] I bet his wife did needlework, as well as being a research associate.

[vi] http://www.whitehart.net/the-hotel/ **The White Hart Hotel is located conveniently at the foot of Cold Bath Road in Harrogate. It is somewhat unusual in not having undergone a transformation of name in 250 years of history. The name "White Hart" is ancient and comes from the time when large tracts of England were covered with forests, owned by the King and used for the Royal Hunt.**
The advantages of being in management!

interested or suitable, secondment should be possible from a clinical appointment either to attend an introductory course on general management or to become involved in a real-life NHS management situation where the sense of 'sink or swim' is useful as a test of motivation and as preparation for a rigorous selection procedure."

"Women, life and medicine - achieving the balance. An account of 1974 women medical graduates in 1987" [40], published in 1989.
Postal questionnaires with about an 80% return rate gave some insight into the position of women in the medical workforce.

It was reported that "*...the great majority of the women in the 1974 [graduation] cohort were content, at [that time], with their work*." It was suggested that this 1974 cohort was an 'in between' cohort: "...a reflection of women in society as a whole, of which they are a part: very nearly all working, but half part-time, satisfied at present with their work yet not achieving their full career potential."

The later 1983 cohort seemed far more confident, women were nearly 50 per cent of that cohort.

The replies reflected a great variety of attitudes. Common factors were: "*...the feeling of the need to 'achieve a balance', domestic and career*." "*Responsibility for the family: a wish to support her husband's career, the need to have work that can be coped with as part of life, not to waste medical training, feeling not part of the traditional male medical establishment, and a desire for patient contact.*"

It was acknowledged that there was some potential bias towards unfavourable comments because of the structure of the questions. However, Parkhouse and Parkhouse thought there were significant differences between their results and those of Isobel Allen's study. Their respondents were more optimistic, had a lower emphasis on 'patronage' and very few respondents felt thoroughly disillusioned with medicine.

They surmised that what was needed to give career 'fulfilment' to these highly intelligent and very well-trained doctors depended on personality at least as much as intellect.

Comparisons with women in other professions[vii] did not suggest that women doctors were relatively disadvantaged and that male doctors had many of the same grumbles as women.

These problems still exist today (2014) and not only are there problems for individual female practitioners but also for workforce strategists.

"Retirement intentions of doctors who qualified in the United Kingdom in 1974: postal questionnaire survey" [41], 2001.

Finally we come to the end-of-career scenario. The 1974 graduates were then about 50 years old and were asked about their future plans. Continuing to work until retirement age (65 years in the UK) was the plan for 15%; 20% said it was probable. Oddly, only 45% of those intending to retire early had made financial provision for this.

The reasons for early retirement included work-related pressure, increase leisure time, job dissatisfaction, disillusionment with the NHS, and wanting a healthy retirement. These problems were considered surmountable if there were more flexible working patterns, a reduced workload, improved staffing levels, preservation of pension rights for part-time working, fewer NHS administrative changes, and greater professional freedom.

It was thought that early retirement could really upset medical workforce planning and that policies needed to change, "*...from the extremes of either full-time employment or total retirement.*"

This work just about covers everything from the 'newborn' house-surgeon/house-physician to those about to exit the system. To the medical sociologist of the future I'm sure his work will be of great interest.

Books:

The Nuffield Department of Anaesthetics, Oxford 1937-1962. by R. & J. V. Mitchell & James Parkhouse (edits). Bryce-Smith (1963)

A new look at anaesthetics, with particular reference to specialised postgraduate education (New look at medicine... by James Parkhouse , 1965)

[vii] Fogarty M, Allen I, Walters P. Women in top jobs 1968-1979. Policy Studies Institute. London: Heinemann Educational Books, 198

Graduate medical education in the European region: Report on a capacity study (EURO ; 6301) by James Parkhouse (1974)

Specialist Medical Training in Britain: a Survey of the Hospital Specialities in 1975 by James Parkhouse and Robin A Darton (1979)

Medical Manpower in Britain by James Parkhouse (1979)

Doctors' Careers. Routledge. 1991. by James Parkhouse (1991)
Doctors' Careers: Aims and Experiences of Medical Graduates by James Parkhouse (4 Apr 1991)

Further snippets of information can be found from this source – accessed 31.10.13.
http://archives.li.man.ac.uk/ead/search?operation=full&rsid=dc.title%20any%2Frelevant%2Fproxinfo%20%22William%20Oates%20b%201933%20Goldthorp%22&firstrec=2221&numreq=20&highlight=1&hitposition=2223

- Notice of appointment to chair of anaesthetics at Manchester, Lancet 27 June 1970.
- Notice of appointment to chair of anaesthetics at Manchester, University of Manchester Gazette September 1970.
- Cutting Manchester University Medical Students Gazette 51. 1971, article about Parkhouse on occasion of his election to the chair.
- Manchester Medical Society biographical form 1973.
- Cutting, note on Senate and Council's message of thanks to Parkhouse, following his resignation from the chair of anaesthetics, University of Manchester Gazette May 1981.

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Stanley A Feldman

BSc MB FFARCS

"He gave up his biochemistry thesis on the metabolism of the woodlouse to study medicine in 1950"[i] . After qualifying in 1955 he trained in anaesthesia at Westminster Hospital, was a Research Fellow in Washington (1957-8) and became senior lecturer at the Postgraduate Medical School in 1962 and visiting professor at Stanford University, California. In 1990 he became the Magill professor at Westminster retiring in 1995[ii]; amongst many other appointments. His main interest was neuromuscular clinical pharmaco-physiology. However, he also published a few articles on equipment related topics.

Equipment:

Two of the first three papers in 1958 were about equipment. One was a generic paper on the design of vaporisers [1] and the other on the specific topic of "Vaporization of halothane and ether in the copper kettle" published in *Anesthesiology* [2]. Feldman was a Fellow in Anesthesiology at the University of Washington, School of Medicine, Seattle. The vaporizer consisted of "a copper container, a sintered bronze vaporizing surface (Porex), and a separate flow of metered gas which is bubbled through the liquid anesthetic agent". The sintered bronze vaporizing surface was found to be "highly efficient" and the use of copper in the container (and table-top) provided great thermal stability – the bottom line of this enquiry was that the precise control of potent volatile agents like halothane was possible.

Almost ten years later, in 1967, he published an article on monitoring in anaesthesia [3]. This was four years before the present author started his career in anaesthesia when monitoring was very basic. It is interesting in that Feldman does not specifically lay out rules for monitoring but discusses what

[i] Introduction to "Panic Nation"

[ii] J F Nunn. British Journal of Anaesthesia. London: Dec 1999. Vol. 83, Iss. 6; pg. 916-932

should be monitored to maintain physiological homeostasis. We should not become "servants" to our monitors, "ECG watchers" and become "obsessed by the necessity of maintaining the stability of the blood pressure at the expense of the general management of the patient". He advises against the absolute value of any one parameter when the patient is in a dynamic state most of the time. "To assess cardiac function from the ECG is like trying to measure respiratory function by monitoring the neural discharges from the respiratory centre". He emphasises the need to integrate multiple measurements to determine the causes of adverse change. Most of the measurements that he would have liked to have made were, at that time, exceedingly difficult. Many of the points made in this article are still pertinent today.

It was another 23 years before the next couple, 'the cuffed pharyngeal airway'[4, 5]. These papers described a nasal version of Archie Brain's laryngeal mask; containing some description of the development of the tube; the final version (a Portex, ivory polyvinyl chloride tube of 7.5 mm i.d. was used and passed through the nose into the pharynx where the cuff was filled with 15-30 mls of air. The pressure drop across the tube was acceptably low and the epistaxis rate 4%. A small percentage of patients required intubation - this technique does not seem to be widespread.

It would appear that equipment-related research was not a high priority.

Clinical anaesthesia

In 1961 a letter on the subject of 'Tracheal tug' was published by two people; Feldman and Scurr [8]; this is the only journal reference found with both authors, so well-known for their book "Scurr and Feldman", "Scientific Foundations of Anaesthesia". Tracheal tug – "a jerky type of inspiration seen when the intercostal muscles and the sternocostal parts of the diaphragm are paralyzed by deep general anesthesia or muscle relaxants; due to the unopposed action of the crura's pulling on the dome of the diaphragm and thence on the pericardium, lung roots, and tracheobronchial tree during each inspiration." [iii]

"The problem of haemorrhage during anaesthesia and surgery" was addressed by Feldman in 1961 [9], a description of bleeding diatheses and their management.

[iii] http://www.medilexicon.com/medicaldictionary.php?t=94812

There were intensive-care related publications; a report on "The experience with 50 patients treated by artificial ventilation" [10], "Disturbance of swallowing following tracheostomy" [11], of great interest considering the few intensive care units at the time. An article on profound hypothermia in 1971 was interesting [12]in the physiology it describes. It was an alternative to cardiopulmonary bypass at a time when there were difficulties with the equipment. The advantages and disadvantages were listed – no 'pump lung', a 'dry' heart, aortic surgery/limited operation time, time for cooling and warming, cold agglutinins and more equipment. 1n 1988 "Carbon dioxide brain damage and cardiac surgery" [13] was published.

Neuromuscular blockade

From 1959 to 1997 there were 43 publications on neuromuscular blocking agents [14-56]. The first was an interesting case of re-curarisation [14]. Re-curarisation or neostigmine resistant curarisation were phenomena of great interest at that time.

The neuromuscular studies fall into three main categories.

Recovery from curarisation [14, 16, 29, 36, 44, 57]

1959 An interesting case of recurarisation.
1963 Neostigmine resistant curarisation.
1974 Comparison of RX72601 with neostigmine. A study of anticholinesterase log/dose response curves in man.
1979 Residual paralysis in the recovery period.
1987 Etiology of failure of reversal of neuromuscular block
1989 Metabolic acidosis - a new approach to neostigmine resistant curarisation

The physiology of the neuromuscular junction [15, 17, 23, 25-27, 31-34, 37, 38, 44, 48, 49, 53, 54, 58]

1959 Effects of decamethonium upon conditioned reflexes in rats
1963 Effect of electrolytes, hydration and pH upon reaction to muscle relaxants.
1969 The excretion of gallamine in the dog. This was a confirmation of work by Mushin et al. [iv] who had found that 20-80% of the drug could be recovered in

[iv] Mushin WW, Wien R, Mason DF and Langston GT. Lancet 1949; 1:726

the urine of rabbits. Feldman et al. used a radioactive labelled preparation of gallamine.

1970 A new theory of the termination of action of the muscle relaxants.

It is not very often in medical journals that one finds the title of a paper including the phrase "a new theory of...". This paper in the Proceedings of the Royal Society of Medicine is an abridged article on the "Recent advances in muscle relaxants". Between 1905 and 1969 various hypotheses had suggested that the site of action for curare/acetylcholine was presynaptic/ synaptic/postsynaptic. Paton and Zaimis (1952 and 1961)[v] proposed a competitive type of block – in this paper they, Feldman and Tyrrell, tested the view that the degree of paralysis was dependent on the blood/ECF concentrations and that lowering the concentration would decrease the effect. This was found to be incorrect. They used the isolated forearm technique and with curare and gallamine showed that when the tourniquet was released (significantly lowering the drug concentration in the blood) the block still persisted. This implied strong binding at the receptor site. The effect of decamethonium (a depolarising agent) wore off very quickly suggested a weak binding with receptors. However if the decamethonium stayed in contact with receptors for a long time then they formed a strong enough bond to produce a curare like-effect (a Phase II block). These studies, and others with tetanic stimulation suggested that it really wasn't a competitive block but that acetylcholine displaces curare from the receptor site and the 'reversal' depended on the quanta of Ach around the receptor site.

Appiah-Ankam and Hunter[vi] in 2004 produced a review of neuromuscular pharmacology. Dealing with Phase II block first, the present understanding of the mechanism suggests that after repeated boluses or infusion of succinyl choline a presynaptic block occurs which reduces the synthesis and mobilization of Ach which, together with postjunctional desensitization and activation of the sodium-potassium ATPase pump, causes a block with features of a competitive block. The word "competitive" is still used for the non-depolarising type of block (Appiah-Ankam and Hunter p 5) at the postsynaptic receptors. The binding of antagonists with receptors is a dynamic process (association and dissociation) and if the ACh concentration is increased there is a greater chance of ACh occupying the receptor sites.

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[v]Paton WDM & Zaimis EJ (1952) Pharmacol Review 10;59. Paton WDM (1961) Proc.Roy.Soc. B154;21.

[vi] Appiah-Ankam J and Hunter JM. Critical Care and Pain, 2004;4:2-7

How can these contradictory views be resolved?

1971 Factors influencing action of muscle relaxants.

1972 The effect of non-depolarizing muscle relaxants on cholinergic mechanisms in the isolated rabbit heart.

1972 The dual action of suxamethonium on the isolated rabbit heart.

1976 Affinity concept and action of muscle relaxants.

1976 The effect of blood flow upon the activity of gallamine triethiodide.

1976 Effect of hypothermia on neuromuscular block induced with a gallamine.

1978 Muscle blood flow and rate of recovery from pancuronium neuromuscular block in dogs.

1979 Plasma concentrations of pancuronium and neuromuscular blockade after injection into isolated arm, bolus injection and continuous infusion.

1980 Clinical importance of affinity constant.

1987 Etiology of failure of reversal of neuromuscular block.

1993 The effect of residual receptor occupancy on sensitivity to repeated vecuronium.

1993 Tetanic fade during recovery from vecuronium block: comparison of s ystemic and isolated forearm administration.

1994 Curare modification of suxamethonium blockade.

1995 The effect of dose and the rate of stimulation on the action of rocuronium.

The clinical aspects of neuromuscular blockade were not ignored... [18-22, 24, 28-30, 35, 40-43, 45-47, 50-56]

1963 Prolonged paresis following gallamine.

1969 Diagnosis of non-depolarizing block.

1970 NB68, A new steroid muscle relaxant.

1970 Interaction of diazepam with the muscle-relaxant drugs.

A description of the effect of diazepam on gallamine and suxamethonium; the duration of the former was enhanced, the latter reduced – possibly due to action at a presynaptic site [21]. This was published in the British Medical Journal which is not renowned for its anaesthetic related content.

1970 Diazepam and muscle relaxants.

1970 A new steroid muscle relaxant. Dacuronium-NB.68 (Organon). [Dacuronium did not 'take-off'.]

1973 Paradoxical effect of halothane upon neuromuscular block with gallamine.

1974 Letter: Paradoxical interaction between halothane and pancuronium.

1978 Interaction of halothane and pancuronium bromide.

1981 Intubating conditions with ORG NC45. A preliminary study.
[ORG NC45 did 'take-off'; it was Norcuron, commonly known as vecuronium. This was a dosing study comparing two doses of ORG NC45 with pancuronium for tracheal intubating conditions at 60, 90 and 120 seconds. There was no statistical difference.

1984 Peritoneal closure and atracurium.

1984 Comparison of intubating conditions with atracurium, vecuronium and pancuronium.

1985 Competitive block - UK style.

1987 Vecuronium--a variable dose technique.
Vecuronium was given in doses ranging from 0.1mg/kg - 0.25mg/kg resulting in durations of action from 28-72 minutes – it was suggested that for long procedures a large initial dose had advantages.....[45]

1988 Reversal of muscle relaxants.

1989 Effect of rate of injection on the neuromuscular block produced by vecuronium.
Using a subparalytic dose of vecuronium, given by rapid injection or by infusion, it was shown that the rapid injection produced a higher peak concentration but the maximum block was similar [47].

1993 Resistance to decamethonium neuromuscular block after prior administration of vecuronium.
It was known prior treatment with small doses of non-depolarising reduces the effect of succinylcholine and so the effect was investigated using vecuronium and decamethonium. The effect was replicated – vecuronium doubled the dose of decamethonium required to produce the same effect. It was a nonparallel effect and so was not considered a simple agonist-antagonist effect [50] .

1993 Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration
A study, using vecuronium, compared tetanic fade with twitch depression using both a systemic injection and an isolated forearm

technique – there was less fade in the isolated forearm and it was suggested that twitch depression and fade "are independently mediated effects of vecuronium" [49].

1993 The effect of residual receptor occupancy on sensitivity to repeated vecuronium.

A combination of systemic doses of vecuronium and an isolated forearm suggested that the reduction in ED50 following repeated systemic doses was due to residual drug in the plasma, not at the receptor site [48] .

1994 Rocuronium — onset times and intubating conditions. [Ro — rapid onset]

A comment on the assessment of 'intubation times' for doses of rocuronium; careful interpretation of the studies with different methodologies is essential. Feldman suggested that the rapidity of onset of the rocuronium block appeared to be a pre-synaptic effect and that 90s was 'closer' to the time when conditions were excellent for intubation and that this difference (cf. suxamethonium) had to be considered a matter if clinical judgement when airway protection was a necessity [51].

1994 Sensitivity to second dose of mivacurium.

By using systemic doses of mivacurium with and without an isolated forearm it was possible to show that there was increased sensitivity to the second dose in both situations and that this was therefore not due to a receptor effect of residual drug in the plasma [52].

1994 Curare modification of suxamethonium blockade

Giving tubocurare before suxamethonium resulted in a slower onset low intensity block; train-of-four fade was similar to tubocurare blocks and it was concluded that there were effective amounts of tubocurare in the neuromuscular junction within 30s of injection and that this affected the suxamethonium block [53].

1995 The effect of dose and the rate of stimulation on the action of rocuronium.

The time to complete neuromuscular blockade was found to be dependent on the rate of ulnar nerve stimulation and thus in studies of neuromuscular block duration stimulation rates have to be consistent [54].

1995 Priming studies with rocuronium and vecuronium.

Rocuronium does not, but vecuronium does, prime rocuronium; the onset time can be reduced by 33%; both rocuronium and vecuronium prime vecuronium[55] .

1997 Tracheal intubation conditions after one minute: rocuronium and vecuronium, alone and in combination.
It was found that an ED95 dose of rocuronium combined with an ED95 dose of vecuronium produced better intubating conditions for intubation at 60s than twice ED95 doses or either drug – an obvious synergistic effect [56].

Miscellaneous

Oxygenation of cats by hydrogen peroxide during temporary ventilatory arrest [59]: in 1966 Stanley Feldman, together with JR Hoyle and JP Blackburn, were the authors of a 'Preliminary Communication' in the BMJ. They infused hydrogen peroxide intra-arterially to provide "an auxiliary means of oxygenation"; this maintained life in apnoeic cats for an hour. The experimental animal was the cat because it has the highest level of catalase in available experimental animals (! there has to be a link / pun here) and catalase is required to break down hydrogen peroxide. The hydrogen peroxide was infused into the thoracic aorta...it was determined that a 3-kg animal required 0.8 – 1.0 ml of hydrogen peroxide per minute. It was difficult to maintain a level of oxygenation below that which resulted in bubble formation. Acidaemia, methaemoglobinaemia, severe anaemia and oxygen embolism were all complicating factors in the study. This was an interesting study because of its application of lateral thinking in the search for an alternate method of oxygenation.

The place of the Faculty of Anaesthetists in postgraduate education [60]:

The Faculty of Anaesthetists holds a unique position in education in anaesthesia for it alone can consider the problem as a whole, relating training and education to the requirements which *it* establishes as necessary for a consultant anaesthetist. In formulating its policy for training in anaesthesia, it must consider three logical steps.

(1) Determination of what is likely to be required of an anaesthetist in the future.
(2) Decision on what standards are required for them to be able to fulfil this role and how these standards can be assessed.
(3) Provision of adequate training facilities and, after training, facilities to keep anaesthetists abreast of new developments.

The Faculty has a fundamental commitment to make sure that the basis of safe, sound, practical anaesthesia is taught. It must at the same time seek ways of widening its educational interests into those scientific disciplines which constitute the grammar of medicine and which allow communication with other specialties. By so doing, it will train doctors to be the safe clinical anaesthetists possessing the fundamental scientific knowledge that is likely to be required for the future even if it does not aspire to the production of what Parkhouse (1969) has termed an "undifferentiated thinker".

This seems as important today as it did then in 1970.

Anesthesia's debt to science and its contribution to medicine[61]....this was published in Acta Anaesthesiologica Belgica.

Anaesthesia and the research assessment exercise [62] – this is a letter to *Anaesthesia* about the "hidden pressure destroying academic departments". It said that clinically competent academic anaesthetists were being passed over for Chairs in favour of those pursuing pure basic research. Academic performance was being assessed by the Research Assessment Exercise and it appeared that the number of points awarded was proportional to the size of funds raised and so it appeared that money was being considered a measure of originality. Another point was that the Principals of the Universities were dictating the priorities for

research and instead of investigating safer anesthesia they were more interested in pure research – such as the mechanisms of anaesthesia. He suggested that there should be some form of peer review of an academic department's contribution to teaching and training.

Books

Stanley Feldman has been, and is, a prolific writer. The list below may not be complete.

Tracheostomy and Artificial Ventilation, second edition by Brian Crawley Stanley Feldman (1972)

Muscle relaxants by Stanley A. Feldman (1973)

Scientific Foundations of Anaesthesia by Cyril Scurr and Stanley A. Feldman (Jul 1974)

Principles of Resuscitation by Stanley A. Feldman and Harold Ellis (Aug 19, 1975)

Multiple Indicators: An Introduction (Quantitative Applications in the Social Sciences) by John L. Sullivan and Stanley Feldman (Nov 1, 1979)

Muscle Relaxants (Major Problems in Anaesthesia) by Stanley A. Feldman. (Aug 1979)

Developments in Drugs Used in Anesthesia (Boerhaave Series for Postgraduate Medical Education) by J. Spierdijk, S.A. Feldman, H. Mattie and T.H. Stanley (Jan 31, 1982)

Multiple Regression in Practice (Quantitative Applications in the Social Sciences) by William D. Berry and Stanley Feldman ?1985

Drugs in Anaesthesia: Mechanisms of Action by Stanley Feldman (Feb 1987)

Problems in Anaesthesia: Analysis and Management by Stanley Feldman and Willaim Harrop-Griffiths (Oct 1989)

Neuromuscular Blocking Agents: Past, Present, and Future : Proceedings of the David Savage Memorial Interface Symposium, London, 1-2 June, 1990 London, P. A. F. Denissen, W. C. Bowman and Stanley A. Feldman (Jun 1991)

Mechanisms of Drugs in Anaesthesia by Stanley Feldman (Jan 15, 1993)

Neuromuscular Block, 1e by Stanley A. Feldman (Jan 15, 1996)

Anatomy for Anaesthetists by Harold Ellis, Stanley J. Feldman and William Harrop-Griffiths (Mar 1, 2004)

Careers in Anesthesiology. Three Pioneer British Anaesthetists (Volume IX) by Stanley Feldman (2005)

Poison Arrows: The Amazing Story of How Prozac and Anaesthetics Were Developed by Stanley A Feldman (2005)

From Poison Arrows to Prozac: How Deadly Toxins Changed Our Lives Forever by Stanley A. Feldman (Apr 1, 2009)

Panic Nation: Exposing the myths we're told about food and health. Stanley Feldman and Vincent Marks. (John Blake, 2006)

As it says in the title, it exposes all those fads that the modern population seems to embrace. It is a multi-author publication and it is a joy to read — obesity, junk food, organic food are some of the 'food scares' section. The section on diets is equally robust – school dinners, food allergies, food labelling. Sun and skin comes under the heading of "Healthy Living" as does exercise and herbal remedies. These are only a few of the topics; the last section is devoted to Myth Interpretation – "the harm that pressure groups can cause, the misuse of numbers and epidemiology. A good read, not too heavy...should be given to few people I know.

Global Warming and Other Bollocks, Stanley Feldman and Vincent Marks. (John Blake, 2009)

This is another interesting read — whether you believe in global warming or not — it will make you think. Other sections include the epidemic of obesity, gridlocked Britain: A transport policy, and a section on questionable dogma – recycling / population ' ethics industry.

A Doctor's Tale by Stanley A. Feldman (Apr 26, 2010)

Confessions of a Doctor by Feldman Stanley (Jul 9, 2012)

This is "loosely biographical" and came into being after he was pronounced dead in 2008. Obviously in error, .he decided it was time to record some of the funny/funny-peculiar events of his life. Go and buy it – Kindle versions available as are a few of the other retirement publications.

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John E Utting

MA MB BCHIR FFARCS

 [i]

The University of Liverpool appointed J. E. Utting as professor and head of department of anaesthesia in April 1977 and he retired in December 1993. The University Department of Anaesthesia was in the Royal Liverpool Hospital.

Of the 48 publications presented here 19 were investigations into the actions of neuromuscular blocking agents...it could be reasonably considered that this was his main interest. These studies came at a time when two new drugs came on the market simultaneously; atracurium and vecuronium were both first trialled in 1979.

His interest in acid-base balance and awareness is also notable.

Acid Base research

Utting's first publication, with JS Robinson, was about acid-base matters. The problem of measuring acidity of plasma and blood and the buffering components had been under investigation for some time;
Rosenthal 1948, Astrup 1956, Nunn 1959, and resulted in the publication of the Siggaard-Andersen nomogram in 1960[ii]. They described the new silver/silver chloride electrode and the interpolation method for the estimation of pCO_2 in very small quantities of whole blood [1].

In 1969/70 he, together with Fadl, published four papers. The first [2] a study of maternal acid-base during the first and second stage of labour. They

[i] Courtesy of Liverpool Society of Anaesthetists. http://www.lsoa.org.uk/

[iiii] Siggaard-Andersen, Ole; Engel K (1960). A new acid-base nomogram. An improved method for the calculation of the relevant blood acid-base data. *Scan J Clin Lab Invest* **12**: 177

found that arterial pCO2 was lower than in non-pregnant women and the pH higher. This was enhanced by the end of the first stage; epidurals and drugs had little effect.

This was supplemented by investigation of the variability of pK1′ during labour [3] [iii]. The value determined was 6.106 at 38°C (SD 0.011), identical with non-pregnant controls.

Hyperventilation during pregnancy was the third publication in 1969 [4], a few paragraphs in Thorax. Their results showed that the 'normal' hypocapnia of pregnancy was associated with near normal lactic acid concentrations, concomitant metabolic acidosis and near normal pH. They said their results confirmed the belief that the respiratory muscles were not responsible for the lactic acid.

The last with Fadl [5], although published in January 1970, was actually a report of a presentation to the Royal Society of Medicine in April 11th 1969. It is an abridged version of an overview of their understanding of acid base changes during pregnancy.

Neuromuscular blockade

In 1970-71, with Hassan Ali as the first author, there were four papers on the subject of the method and quantitative assessment of neuromuscular block. Similar concurrent work was being done by many others.

The first - Stimulus frequency in the detection of neuromuscular block in humans [6]. To paraphrase... two methods of assessing neuromuscular block had been described; the height of the recorded twitch tensions in response to single stimuli applied at differing frequencies and reduction in amplitude of twitch tensions in response to a short train of four stimuli.

They found using the first method that as the frequency of stimulation was increased there was reduction in the amplitude of the recorded twitch response. The reduction appeared to depend on the degree of curarization. For the second method a short train of four stimuli at 2 Hz was used; again there was a progressive fade of successive twitch responses depending on the degree of curarization. It was therefore suggested that, using the first method, the amplitude of the twitch response at a higher frequency expressed as a percentage of that at the slower rate and, using the second method, the last

[iii] pK1′ being a component of the Henderson-Hasselbalch equation.

response of the train of four expressed as a percentage of the first might be useful in measuring degree of neuromuscular block. The latter is now the most commonly used technique.

On June 27 in 1970 the subject of quantitative assessment of residual curarization in humans was presented at the Anaesthetic research Society meeing in Aberdeen [7]. Full papers were published in 1971, parts I and II.

I [8]: This described a method for assessing the residual degree of neuromuscular blockade (after reversal) without the need for a control measure. In the study they did use control measurements but found that the control/T1 ratio[iv] was well correlated with the T1/T2 and T1/T4 ratios, so a control measure would not be necessary.

II [9]. This paper is similar; a train-of-four stimulation pattern was repeated at 10 second intervals. They used the ability to lift the head as an assessment of recovery from neuromuscular blockade and this was found to be related to the T4/T1 ratio and that a ratio of <0.6 was associated with obvious muscle weakness; modern work would suggest >0.9 for adequate reversal.

This work has stood the test of time.

The work on atracurium started in 1982 and was spread over six years. Four were on its use in patients with renal failure (or anephric) [10-13], one about its use in a patient with myasthenia [14], one with oesophageal varices (usually indicative of liver disease) [15] and three others [16-18].

The team worked with vecuronium at the same time; renal disease [13], liver disease [15, 19], myasthenia [20] and use of neostigmine [21].

Renal / Liver disease

[10]: In 21 anephric patients it was possible to give incremental doses of atracurium without evidence of cumulation. Even with high doses there was no evidence of residual curarization. It was stated that "This finding would seem to be compatible with what is known of the pharmacology of the drug."

[13] This was a comparative study in patients with or without renal function using vecuronium, atracurium, and tubocurare. Vecuronium was given to 21 normal and 21 anephric patients and there *"were no gross difference between the two groups in the effect or in the duration of action of either initial or incremental doses, except in two anephric patients who were resistant to the agent."* The duration of action of increments of atracurium and vecuronium

[iv] In the train of four stimulus pattern the resulting muscle twitches are labelled T1, T2, T3 and T4.

were not greatly different, the behaviour of vecuronium was similar to that of atracurium. However tubocurarine was shown to be longer acting and "*considerably less predictable. This was particularly so in the anephric group, in which its action sometimes persisted after neostigmine had been given."*

[15] The effects of atracurium and vecuronium were described in patients with portal hypertension and liver dysfunction. There was no evidence of gross resistance. However, ..." *the method of elimination would suggest that atracurium may be the better drug in patients with severe liver dysfunction, but the use of small doses of vecuronium is not contraindicated in this type of patient*."

Myasthenia is an uncommon condition. If anaesthesia is required the patients can be exquisitely sensitive to neuromuscular blocking agents. Two papers are presented here, one with atracurium and one with vecuronium [14, 20]. A third is about an association with carcinoid [22]. The two papers with atracurium and vecuronium are similar...in each case they used one fifth of the normal induction dose; for vecuronium this was found to be too small so they subsequently doubled the dose. They found that with these diminished doses they could maintain satisfactory muscle relaxation and good reversal with neostigmine at the end.

The third paper has to be at the extreme end of rarity. The carcinoid syndrome is rare (about 1:100,000) and myasthenia is rare at about 1:30,000; the combination 1:3,000,000,000. Vecuronium was used, in reduced dosage, as it does not release histamine.

'Awareness'

Using the Google Ngram viewer with the keywords '*awareness during anaesthesia*' the topic started to take off around 1967, and first peaked in 1976. A second peak occurred in 1999, probably associated with the use of BIS, a processed EEG monitor.

The first investigation [23], in 1970, assessed recall and dreaming under nitrous oxide and muscle relaxant anaesthesia. Tape-recorded music was used as a stimulus. No episodes of awareness were detected. However, 44 per cent of the patients dreamed and two-thirds of them could recall details. Hypocapnia, part of the 'Liverpool technique' (or Gray's technique), did not prevent dreaming.

This study coincides with his work with the train-of-four pattern of electrical stimulation to determine the magnitude of neuromuscular blockade so it is not surprising that at this time patients were not always adequately

paralysed with the neuromuscular blocking drugs and often moved. Patients who did move were more liable to dream than those who did not. Half of the patients described waiting for surgery as the most unpleasant part of their surgical experience, 20% considered postoperative pain was the worst, the third ranked complaint was being asked to lift their head when they were unable to do so. Unpleasant dreams came fourth.

Did premedication or the use of volatile agents influence dreaming [24]? This 1971 paper had four groups of patients, an unpremedicated nitrous oxide only (with muscle relaxant, as above), a group with morphine premedication, another using halothane and the last with methoxyflurane. In group 1- 57% of patients dreamed; group 2 - 23%; group 3 - 0% and group 4 – 23%. Awareness was not definitely diagnosed but a number of dreams were associated with the site of the operation.

In 1972 a letter to the British Journal of Anaesthesia [25] highlighted the problem of awareness further. In a study of 90 patients two presented strong evidence of being conscious during the surgery. This study was to show that giving halothane for fifteen minutes either at the beginning or the end of the anaesthetic did not abolish the risk of dreaming, or in this case, overt awareness. This was strong message that the 'Liverpool technique' was unsatisfactory.

This work was later presented in the Phillip Gett[v] memorial lecture [26].

Miscellaneous

A study of **perioperative complaints** [27]. One hundred patients were given a personality assessment (Eysenck and Eysenck, 1964) a day before their operation. The day after a standard anaesthetic the patients filled in a questionnaire about their experience. The patients "neurotic" score was higher than the general population; upper abdominal operations had greater scores than other procedures. The lie score was also higher than the general population! Pain, preoperative anxiety and the passage, or presence, of a nasogastric tube were also major complaints.

The lie score is of interest ... the lie scale was *"included to detect individuals "faking good"."* One of the questions on the lie scale, for example was

[v] Phillip Gett was Director of the Intensive Care Unit at Sydney Hospital. He was shot by a robber in New York in 1974.

"Are all your habits good and desirable?" Eysenck's view was that a lie score of 4 or 5 would suggest the answers were not acceptable. However if they excluded all patients with high lie scores the results from 28 patients would have been rejected. Other workers have questioned the validity of the lie score (Knowles and Kreitman, 1965).

An interesting foray into patient satisfaction. At least the use of nasogastric tubes has been minimised over the last four decades.

Postoperative pain: 1976 [28]. Smith and Utting were commenting on the poor quality of postoperative pain management. To quote *"The drug treatment of postoperative pain is fundamentally unsatisfactory with the drugs at present available; any improvement is likely only to be marginal. The hope would seem to be that the subject will be given more prominence in the education of both doctors and nurses. Patients, too, should be told that asking for an analgesic drug is not necessarily a sign of frank cowardice."*

The money motive: [29]... this was based on a paper that was read at a symposium on *Money and Medicine* in Manchester, November 1975. It is worthy of a 'full read'. It describes the social state at the time, about the union fights with the government of the day and the call for doctors to go on strike[vi]. He describes reasons why doctors have higher than average salaries, about the proximity of doctors to the public and the confidence that the public has in doctors. "...our strength becomes our weakness: our proximity to our patients may make them think highly of us, but it also makes us think highly of them. It is difficult deliberately to ignore someone in such close proximity merely to obtain one's own way." He expressed the view that striking would diminish goodwill. He also attacked the time spent in private practice at the expense of the 'main activity', work in the National Health Service.

He stated that it was the freedom in the practice of medicine that was more important than the money motive, and that it was of even greater importance to the patient.

[vi] A strike was called by junior doctors and some NHS consultants involved in private practice, who had rarely been seen before in the NHS hospital, turned up to 'man-the-pumps'. There was no compulsion to strike and no hard feelings to those who felt it against their principles.

Human misadventure in anaesthesia: [30] Since the early audit by Beecher and Todd of anaesthesia related mortality[vii] many morbidity and mortality studies have been published. This presentation by Utting was based on the data collected by the two other authors (T.C. Gray and F.C. Shelley) about anaesthetic accidents reported to the Medical Defence during the period 1970 to 1977. In general usage "*'misadventure is taken to be an unlucky chance or accident*". He made the point that human misadventure in anaesthesia is not as frequent as human failure. Six hundred and two anaesthetic accidents were reported during the eight-year period; 60% were either deaths or cerebral damage. He made the point that cerebral damage can be a greater catastrophe than death. Faulty technique was thought to be responsible for half the events and failures of postoperative care another major, and avoidable, cause. "*Over all error was deemed to be twice as common a cause of death and cerebral damage as was misadventure."*

It was good to see the understanding of misadventure being dissected with human failure (error) being part of the picture...this was to be further dissected by subsequent investigators; JT Reason being, probably, one of the most well known[viii].

Pitfalls in anaesthetic practice [31]; this was part of a symposium on complications and medico-legal aspects of anaesthesia which follows on from the previous section, but almost a decade later. It is a comprehensive article and has a section on 'Defensive anaesthesia'; that is to protect the anaesthetist from litigation. To quote - "*Features of practice which are more of medico-legal importance than direct patient benefit*"; note-taking, preoperative investigations on fit, healthy young patients, peer pressure for 'good medical practice'. He describes the problem of not re-using halothane within a 28 day period when the danger of halothane hepatitis is really rare and one may be forced by peer pressure to use something that may have greater risk, It is a good read.

Anaesthetists, lawyers and the public: [32] This was a letter in response to a previously published article about anaesthetists, lawyers and the public. Utting writes a strongly held opinion about medics vs. lawyers. He had obviously spent 15 years sitting in Courts of Jurisdiction and also, occasionally, acting as

[vii] Beecher. H.K and Todd. D.P. Ann. Surg. 140:2-35 (1954)
[viii] Reason JT. Human Error. Cambridge University Press. 1990

an expert witness. He was of the view that the competence, expertise and dedication of doctors exceeded that of lawyers. He described the apparent injustice of a anaesthetist culpable of a medical accident not being reprimanded but a porter being dismissed for the theft of £2. He believed that we, the medical profession, should be less inhibited about criticising our colleagues.

The era of relaxant anaesthesia [33] This is an editorial on the 50th anniversary of the introduction of curare. He describes the 'tetrad' of anaesthesia, "narcosis, reflex suppression, muscular relaxation and "controlled apnoea" ". By controlled apnoea he meant controlled pulmonary ventilation. It is an historical review.

As we get older we get more interested in history and the same is true here. In 2002 he writes on the subject of "*Matthew Turner: surgeon-apothecary of eighteenth-century Liverpool. His life and background*" [34].

Utting has a relatively small number of publications compared with some other academics but they are of high quality, have stood the test of time and show a great deal of thought, both scientific and social. A really interesting bibliography.

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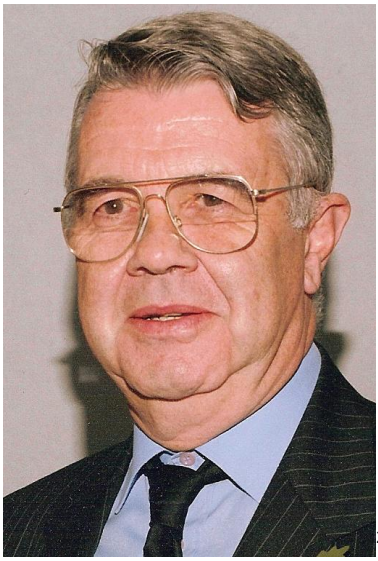

From 1963-65 John Norman was a research fellow in the Department of Physiology in Leeds. He was lecturer and then senior lecturer at the Postgraduate Medical School between 1967 and 1975 becoming the professor and head of department in 1975 in Southampton.. He retired in 1988[1].

[2]

John Norman wrote 16 editorials, five reviews, 10 letters and 45 papers.

His first two papers in 1965 were related: "*Simple Methods for the Determination of the Concentrations of Carbon Dioxide and Oxygen in Blood*" and "*A system for the measurement of respiratory and acid-base parameters in blood*". The first described electrode systems for the measurement of carbon dioxide and oxygen concentrations in blood with which they achieved accuracies similar to those of the classic techniques of Van Slyke and Neill (1924) [1]. The second – a similar paper using electrodes for the determination of pH, pCO_2, and pO_2, very quick at the time, a total time of 30 minutes [2].

The topics that Norman et al. covered were blood gases and respiration [8, 13-15, 17, 19, 28, 38, 51]; muscle relaxation [6, 7, 11, 12, 16, 18, 27, 29, 48, 64, 70, 71] and cardiovascular miscellany [9, 10, 20-22, 24, 25]

[1] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916

[2] Courtesy of Dr David Smith, Southampton

Blood gases and respiration

The next paper was about the oxyhaemoglobin dissociation curve, it is a physiological phenomenon that is essential knowledge for anaesthetic examinations and has great practical significance. *What is the effect of anaesthesia?* [8]. This was presented at the Anaesthesia Research Society at the March meeting in London in 1970.

In 1971, *"Does constant volume IPPV produce hypoxaemia*? It was concluded that it did not [13]; this was a study of ten patients post mitral valve surgery.

Also in 1971: "*The effect of light chloralose and pentobarbitone anaesthesia on the acid-base state and oxygenation of arterial blood in dogs".* Over the period of the eight hour anaesthetic changes were minimal [14]. Another paper, probably resulting from the same study, questioned the use of the Henderson-Hasselbalch equation. Blood samples from anaesthetized dogs with acid-base disturbances were compared with dogs without such changes. It was found that there was no relationship between pK' and temperature, that it increased with alkalaemia and decreased with acidaemia. The variation of pK' with pH was considerable. It was thought that the use of the Henderson-Hasselbalch equation in this situation was unacceptable and could lead to large errors [15].

1972: [17] "*The effect of postoperative artificial ventilation on arterial blood oxygenation*." Is this the same data and analysis that was used in the Anaesthesia, 1971 paper [13]?

1972: "*A comparison of the in-vivo CO_2 titration curves of arterial and mixed-venous blood in dogs"* [19].

1976: Patients spontaneously breathing under the effects of halothane (1-2 %) and nitrous oxide in oxygen were studied to see if respiratory indicators changed. There was no deterioration of blood gas values over two hours and the dead-space/tidal volume ratio and alveolar-arterial oxygen tension difference did not change [28].

1978: "*Resistance of Heidbrink-type expiratory valves".* At a flow rate of 30 l min^{-1} the average resistance of 70 valves was 318 Pa, 44% of them had resistances above the limit of 294 Pa; a nice simple laboratory project [38].

1983: "*Pre-oxygenation-how long?"* With a flow of 8 l min^{-1} delivered via a Magill or Bain breathing attachment the end-tidal nitrogen concentrations were 4% or less within 3 minutes. The fastest time was when the reservoir bag was prefilled with oxygen and tight fitting face masks [51].

Muscle relaxants:

The first two publications, one a presentation at an ARS meeting in Birmingham in 1969 and the second its full write-up later in the year [6, 7] are the result of a very fascinating investigation and had a follow up 32 years later [76]. Tubocurarine and suxamethonium were studied during a standard anaesthetic, with nitrous oxide and halothane, in New York and London. The recovery times were significantly ($p<0.005$) shorter in London. This was distinctly odd; even when drugs manufactured in the USA were used in the UK, the results were the same. When Americans who had lived in the UK were tested they responded in a similar manner to those in the USA. The letter in 2001 from Norman and Katz highlighted the fact that in 1947 the manufacturers (Squibs) had noted discrepancies in the dosage – "*...relatively more of the British preparation being used"*.

1970: "*The neuromuscular blocking actions of pancuronium"* [11, 12] The first, published in '*Anaesthesia*', was presented at the "Annual Meeting 1969", presumably the Annual Meeting of the Association of Anaesthetists. The full write-up was in the BJA. Pancuronium bromide was investigated - small doses caused a slow onset of action and a reduction in twitch height of 69%. A larger dose, as might be expected, was more rapid in onset and complete block was achieved. Recovery times increased with increasing dose and repeated doses produced greater durations of action. Rate of recovery was affected by respiratory acidaemia or alkalaemia.

In 1971 dacuronium bromide was investigated – this drug was not used in routine clinical practice. During the study one patient showed return of the neuromuscular block after apparent complete reversal with neostigmine – not good [16].

1972: "*Prolongation of suxamethonium-induced paralysis by propanidid*" [18]. The duration of total paralysis, of the adductor pollicis muscle, was greater by approximately two minutes in those patients given propanidid; an induction agent that had the viscosity of treacle and caused a short period of hyperpnoea; good for the uptake of volatile agents; propanidid did not last long in routine clinical use.

1975: "*Proceedings: The effect of tacrine on the neuromuscular block produced by suxamethonium in man"* [27]. This was presented at an ARS meeting in July in Newcastle upon Tyne. Tacrine increases the duration of muscle paralysis with suxamethonium significantly. Patients given

suxamethonium 1m kg^{-1} and tacrine 15mg had a three- fold time to recovery, consistent with the work of previous investigators.

1976: "*Proceedings: A trans-Atlantic comparison of the pharmacokinetics of suxamethonium"* [29]; another ARS presentation, this time at Northwick Park. Elimination rate, efficacy and the minimal effective dose was calculated from previously collected data. The London patients had the highest values for all three. The reason for the trans-Atlantic difference was still unclear.

1988: "*Effect of suxamethonium given during recovery from atracurium"* [64]. Suxamethonium was given when the twitch response was 50% of control. A dose of 3 mg kg^{-1} was needed to produce consistently 100% block.

1992: "*Comparison of atracurium-induced neuromuscular block in rectus abdominis and hand muscles of man"* [70]. Atracurium was administered anaesthesia with isoflurane and nitrous oxide in oxygen. Train-of-four stimulation was used over the 10th intercostal space and the ulnar nerve. Electromyograms were recorded over the rectus abdominis and hypothenar muscles. Onset of block was faster in the rectus abdominis than in the hand and recovery was faster in the rectus abdominis.

1993: "*Resistance to vecuronium"* (case report)[71]. This is a case report of the well known effect of anti-epileptic agents – patients taking them need much more muscle relaxant to maintain a satisfactory block.

Cardiovascular miscellany

This is a mixed bag:

1970: "*The effect of beta-blockade in the relationship between cardiac output and carbon dioxide"* [9] (ARS London meeting November 1969) and "*The effect of cardiac sympathetic blockade on the relationship between cardiac output and carbon dioxide tension in the anaesthetized dog"* [10]. The cardiac output increased as the $PaCO_2$ increased, practolol prevented it. It was concluded that the increase was due to sympathetic nervous activity.

1973: "*Fluid-loading and cardiopulmonary by-pass. A study of renal function"* [20]. Prior to going on by-pass blood was given to replace loss; in addition some patients were given Hartmann's solution (20 ml kg^{-1}). There were no differences in urine, sodium and potassium excretion.

1973: Halothane and the responses of the heart to autonomic nerve stimulation [21]. Halothane causes significant falls in heart rate, blood pressure

and the maximum rate of change of left ventricular pressure when measured at a fixed heart rate. Vagal slowing was not affected by the halothane nor was the increases in heart rate produced by stimulating the ansae subclaviae. It was concluded that the effects of halothane were not due to acetylcholine and noradrenaline release.

1973: "*Proceedings: The vagal contribution to changes in heart rate evoked by stimulation of cutaneous nerves in the dog" [23]*

1973: "*Proceedings: The use of practolol and bretylium to produce cardiac sympathetic nerve block"* [22] (ARS Edinburgh).

1973: "*Proceedings: Physiological stabilization of heart rate and blood pressure during peripheral nerve stimulation"* [24]. Presented at the ARS London meeting, at the Royal Postgraduate Medical School, Hammersmith Hospital in November.

1975: "*Proceedings: The effect of halothane on changes in heart rate evoked by stimulation to the radial nerve"* [25] (ARS Manchester).

It would appear that these last three projects did not proceed to a full write-up.

Editorials

1977 seemed to be the year for writing editorials:

1977: "*The perinatal period*" – the purpose of this editorial is a bit obscure – it recognises improvements in both maternal and neonatal well being and states that the "*anaesthetist has much to contribute*". I think it is suggesting that anaesthetic training should include neonatal work. This today is a super-specialty of paediatric anaesthetic practice [31].

1977: "*Opiates, receptors and endorphins*" – this was highlighting the the discovery of many more receptor sites (particularly opiate receptors) and how this would eventually enhance the development of new drugs [32][3].

1977: "*Learning and teaching in anaesthesia"* – Is anaesthesia learnt in the most effective way? This was his question. This was in response to decreasing pass rates in the examinations. He exhorted the use of new knowledge about how learning takes place and for some sort of continual assessment so that the trainee is aware of their progress [33].

1977: "*Trauma and immediate care*" – this was an era of training for major disaster management – every major hospital had to have a disaster plan

[3] Undergraduate training 1964-9 taught only three receptors, α, β and acetyl-choline.

and many had exercises. This was an editorial in a volume of the BJA devoted to the reporting of a symposium on the management of trauma [34][4].

1978: "*The preoperative assessment of patients"* – a description of the Goldman Cardiac Risk Index for assessing patient pre-operatively.

1979: "*Immunology in anaesthesia and intensive care"* – another editorial preceding a special issue on a symposium on immunology in anaesthesia and intensive care [42].

1979: "*Anaesthetic pharmacology*" – an editorial in a volume of the journal devoted to reviewing anaesthesia pharmacology. It was surprising to see that there was a comment suggesting that the practice of administering volatile agents in uncalibrated vaporisers was still happening [39].

1980: "*Muscle"* – a very short editorial – preceding reviews of the subject of anaesthesia and muscle [43].

1980: *"The intensity and duration of I.V drugs*" – a discussion of pharmacokinetics and in particular the way in which the results are presented. It was suggested that for the clinician it might "*be better to give some idea of the of the dispersion of results using standard deviations or tolerance limits*" [44].

1981: "*Metabolism and anaesthesia*" – another prelude to a symposium [46].

1983: "*Mechanisms of general anaesthesia*" – prelude to a symposium on neurophysiology [53]

1983: "*The i.v. administration of drugs*" – this is a lengthy editorial on more complex pharmacokinetics and shows the advances made by the use of computers. "*Pharmacokinetics is advancing from the descriptive to the predictive phase*" [52].1987: "*Complications and medico-legal aspects of anaesthesia"* - another prelude to a symposium [61].

1997: "*Anaesthetic pre-registration house officers*". Classically, in the UK, pre-registration house officers (first year of medical practice following graduation) are attached to medical and surgical firms. This editorial is about having pre-registration house officers in anaesthesia. The aim, evidently, was "*not to create anaesthetists but rather for them to learn from us how to be doctors starting out with knowledge of the management of the acutely ill patient*" [72].

[4] The only exercise the author was involved in was at night, in a railway yard, and one of the racing ambulances carrying a 'flying squad' did in fact fly off the end of a ramp causing major trauma to the ambulance and minor injuries to the hard-hat wearing rescuers.

1999: "*Monitoring spinal cord function during aortic surgery*" and "*Assessing paralysis"* – in the same journal.

The former editorial highlights the devastating effects of iatrogenic paraplegia or paraparesis and the techniques available to monitor spinal cord function – it reads more like a review than an editorial. The latter discusses the problem of different rates and depths of neuromuscular blockade when measured at different sites [74, 75].

Reviews

1976: "*Septicaemia"*
1978*: "An assessment of acid-base balance"*
1987*: "Education in anaesthetic safety"*
1988*: "Do we need more muscle relaxants?"*
1992*: "One-compartment kinetics"*

Letters:

1977: "*Performance of the Lack circuit"* (much concern about adverse comments from Barnes et al.[5] following their assessment of a pre-production model of the breathing system)
1979: "*Neuromuscular blocking drugs"*
1982: "*Co-axial breathing circuits"* (see below)
1983: "*Rebreathing and the Bain circuit"* (see below)
1983: "*The Lack system"* (this is a detailed response to criticism of the Lack breathing system which Nott, Walters and Norman had assessed –in 1977, 1982 and 1983 [35, 50, 54])
1984: "*More about the pharmacokinetics of vecuronium and pancuronium"*
1985: "*Nosworthy anaesthetic record"* (extolling the virtues of pre-computer anaesthetic record cards, perforated, enabling data analysis)
1990: "*Complications of the use of EMLA"*
1998: "*Drug designers in anaesthesia"* (a debate about who was the earliest drug designer – Charles Suckling with halothane or David Savage with pancuronium)
2001: "*Trans-Atlantic variation in response to neuromuscular blocking drugs"* (manufacturer noted difference, as above)

[5] Barnes, P.K., Seeley, H.F., Gothard, J.W.W., Conway, C.M. Anaesthesia 1976;31: 1248

Odds and Ends:

"Propofol: clinical strategies for preventing the pain of injection" – only i.v. injection in the antecubital fossa caused no pain, but pain on injection elsewhere was reduced by combining lignocaine in with the propofol [65].

"Use of anaesthesia. Preoperative assessment of patients" – the British Medical Journal is, by and large, aimed at physicians and general practitioners. This was an article under the section titled "*Today's Treatment*" outlining the importance of patient assessment at the time, 1980. Six years earlier, JB Burn had written about a preoperative assessment clinic[6]. So in 1980 there was the problem of anaesthetists still seeing patients the night before or just before surgery; if there was a problem it was too late and there was pressure not to disturb the surgical list [45].

"*The British Journal of Anaesthesia. An informal history of the first 25 years"* [77]. Fifty one of John Norman's publications were in the BJA and so it is fitting he should write such a history!

Anaesthesia: v. 1: Topical Reviews Hardcover –1980 – edited by
J. Norman and J. G. Whitwam

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In 1966, at the University of Leeds, Richard Ellis was a MRC research fellow. He became Senior lecturer in 1971 and reader in 1976. In 1992 he was appointed to a developmental chair and became head of department at Leeds General Infirmary. More than 50% of Ellis's work is associated with malignant hyperpyrexia and the content of this bibliography will reflect this, but brief comments on his other publications are included.[i]

Studies unrelated to MH

Like many before and after him Ellis started publishing with a case report: "Postoperative Respiratory Inadequacy; an Instructive Case" [1] The postoperative respiratory problem was due to a dual neuro-muscular block following suxamethonium which was treated with anti-cholinesterases. Another respiratory paper appeared in 1971 which was a survey of respiratory problems in the post-operative period [2].

Assessment of premedicant drugs was also a favourite 'intro' to research; droperidol 1972 [3], lorazepam 1973 [4], and various forms of morphine later in 1988 and 1989 [5, 6].

There are always some titles that catch the eye: "The management of the cut-throat" (1966), "Cardiorespiratory response to dangling on a rope in simulated rock-climbing accident" (1973)[7], "A study of body temperatures of anaesthetized man in the tropics" (1977), and "Time of death of an organ donor" (1980).

[i] Picture courtesy of JG Jones

Cut-throat*:* A review of a series of 22 patients, tracheostomy was advised for patients where the airway has been entered (intubation under local analgesia) [8].

Dangling on a rope: [7] This is an interesting investigation of how different means of securing a climber to a rope can change the physiological status. A waist loop that was commonly used was very painful and was said to cause death within 20 minutes even without trauma due to the fall. This commonly used technique was compared with shoulder and pelvic harnesses. Blood pressure changes with the waist loop were great (both up and down) and the shoulder harness was too painful for measurements to be made. The pelvic harness was comfortable and the cardiovascular changes minimal. Analysing their results they concluded that the waist loop caused an oxygen debt, lactic acidosis and hyperkalaemia and could result in a cardiac arrest.

Twenty African patients undergoing surgery in hot and humid conditions still had a decrease in body temperature in a local temperature of 28.7°C and a relative humidity of 72%. A thermal equilibrium occurred at 30 minutes [9].

Brain death: Gained legal acceptance on 22 February 1978 when the Bradford and Calderdale Coroner, Mr Turnbull, accepted it as a diagnosis in an inquest. Seeing a 'pink and warm' relative diagnosed as dead is a problem for some and needed "considerate explanation" by the medical staff; the medical staff, too, has to accept "brain death" as death. This was just two years after Mr Turnbull's decision [10].

Propanidid: "The neuromuscular effects of propanidid" [11], "The neuromuscular interaction of propanidid with suxamethonium and tubocurarine" [12], "The site and mode of action of propanidid on the peripheral motor unit" [13] and "Effect of propanidid on peripheral motor function in myasthenics" [14] .

Studies relating to blood gases and pH and their effect on nerve tissue: "The interaction of PCO2, pH and halothane on nerve action potentials" (1968) [15], "Some effects of PCO_2 and pH on nerve tissue" (1969) [16] and the "Effect of hyperbaric oxygen on nerve tissue" (1970) [17].

In the late 80s and 1991 there was a set of papers on local anaesthetic blocks, femoral and "3 in 1" lumbar plexus block (used to facilitate muscle biopsy) [18-20]. And, of course there were odds and ends [21-31].

Malignant hyperpyrexia[ii]

Although Ellis's name is attached to a large body of work on the clarification of aetiology, diagnosis and management of patients susceptible to malignant hyperpyrexia there were many other workers associated with the Leeds Group. P. Jane Halsall (47 co-authored papers with Ellis), Philip M. Hopkins (25), D.G. Harriman (14), I.M. Clarke (8), A.D. Stewart (6), P.A. Cain (5), I.T. Campbell (5), A.S. Christian (5), D.E. Iles (5), Rachel L. Robinson (5) and not forgetting the European Malignant Hyperthermia Group.

To see a brief time-line of the research go to the end of the chapter.

1971

Ellis is renowned for his work on the investigation of the rare condition malignant hyperpyrexia (MH). The first time his name was associated with MH was in 1971 with NP Keaney, DGF Harriman, K Kyei-Mensah and JH Tyrrell [32], 'Halothane-induced muscle contracture as a cause of hyperpyrexia'. This was a presentation to the Anaesthetic Research Society (ARS) in March, in Belfast.

This was followed by a letter to the British Medical Journal in the following October [33]. It is an interesting detailed letter in that it points out a variety of problems with a 'leader' in a previous issue and sets out a definition of the condition.

MH is described as a "confused subject"; they highlight the relevance of the muscle contracture, (is it causative or secondary?), note that the writer of the leader was unaware of halothane and methoxyflurane causes irreversible contractures, etc, etc. They describe the use of procaine to reverse the effect. They, Keaney and Ellis, said that although the aetiology was unknown a working definition was required and they created one "… *malignant hyperpyrexia is a specific potentially fatal condition occurring during anaesthesia in which heat production exceeds physiological heat loss to an extent that causes a progressive rise of body temperature at a rate of at least 2oC per hour."*

[ii] A disclaimer; the author is not an expert on the subject of MH, its biochemistry or genetics. Every care has been taken but it is possible that some details in this bibliography may not be without error.

However they do say that muscle contractures are probably secondary, together with acidosis, hypoxia etc.

1972

Screening for MH is the subject of one paper in 1972 [34]. They present what they consider to be a more specific method than previously available using a motor-point muscle biopsy which undergoes histopathological examination and exposure to halothane and suxamethonium under near physiological conditions.

The second [35] is about the structural and neuro-pharmacological aspects of malignant hyperpyrexia. This was about the examination of motor-point muscle biopsy which all showed variable structural features of myopathy, differing from family to family. The in-vitro test, presumably the one described above, was described.

1973

This article in *Anaesthesia* contains a description of Ellis's first involvement with MH in 1971. He was asked to suggest a safe anaesthetic for a patient whose sister had an MH event and they did a muscle biopsy at the same time, found a myopathy and the muscle formed a contracture with halothane and methoxyflurane [36]. They studied another 18 patients and suggested the in vitro testing of muscle as the basis for diagnosis of MH

A new screening test for susceptibility to malignant hyper-pyrexia was presented at the ARS meeting at Imperial Chemical Industries Pharmaceutical Division in Macclesfield (April 1973) [37]. They described how muscle from patients susceptible to MH had histological abnormalities consistent with myopathy and, because of problems with the established screening methods; a new test had been devised. It can detect susceptibility to non-rigid MH and so by using both tests it is possible to differentiate between the two types of hyperpyrexia. The test stretches the muscle strip by about 30% and measures the resting tension; it is then allowed to relax. The resting tension in the hyperpyrexia group was significantly higher than normal muscle. They also said "... increased stress relaxation in hyperpyrexia muscle suggests that there could be a structural abnormality in the muscle proteins to account for MH."

"Histopathological and neuropharmacological aspects of malignant hyperpyrexia". [38]. This publication in the *Proceedings of the Royal Society of Medicine* describes the histology and analysis of a biopsy of the symptomless brother of a girl who died of MH. "These pharmacological results were so different from control responses that we thought our findings could represent a more specific test of the susceptibility to malignant hyperpyrexia than serum enzyme estimations." They found "... a perfect correlation was obtained between the neuropathological and the neuropharmacological results." And this ***"... encourages us to believe that positive identification of the patient susceptible to malignant hyperpyrexia is possible."*** Is this the key publication to the future of MH identification?

[39] This is a letter in the correspondence section of the BMJ referring to a report by Denborough et al.[iii] on the description of core-like areas in type 1 fibres in MH myopathy. They (Ellis et al) preferred the term "moth-eaten fibres". Their view was that 'central core disease' should be reserved for those appearances that "resemble the original descriptions". Ellis et al were making the point that, in their view, central-core disease patients do not have susceptibility to MH. It was a strongly worded critique and went on to describe their experience in obtaining muscle biopsies that included the "motor point".

Malignant hyperpyrexia myopathy [40]. The basic points of this was of five patients, three died (their families were investigated) and two survivors were examined along with their relatives. Those whose muscles reacted to stimulation with contracture were considered liable to develop malignant hyperpyrexia. All had structurally abnormal muscle, their histopathological and histochemical characteristics were described but the myopathy in reactors was asymptomatic. Serum creatine phosphokinase estimation was stated to be unreliable as an indicator of MH.

1974

At the ARS meeting in Kings College Hospital (March '74) Ellis and Clarke described the therapeutic value of procaine and lignocaine in malignant hyperpyrexia [41]. They showed how procaine could potentiate the muscle abnormality in the hyperpyrexic patient. They cautioned against its use.

[iii] Denborough MA. Dennett X. Anderson RM. British Medical Journal. 1(5848):272-3, 1973 Feb 3.

A publication that probably stimulated many departments of anaesthesia to act was this with the title "A pack for the emergency treatment of malignant hyperpyrexia" [42]. The pack included a battery powered multi-site thermometer, instant ice bags (to be placed over axillae, groins and praecordium), dextrose 5%, sodium bicarbonate 8.4%, procaine 2%, dextrose 50%, dexamethasone, chlorpromazine (to prevent shivering), diazepam, practolol, isoprenaline, insulin, adrenaline. Sterile infusion sets with assorted intravenous needles, syringes, intravenous cannulae etc, record forms and lithium-heparin blood-sample bottles.

"Neuromuscular disease and anaesthesia" was a review article with 85 references [43].

Malignant hyperpyrexia induced by nitrous oxide and treated with dexamethasone [44], a very interesting case report. A young girl, whose father had died of MH, needed dental extractions under anaesthesia, muscle biopsies were to be done at the same time. Diazepam, thiopentone and nitrous oxide resulted in a pyrexic reaction; temperature had risen at a rate of 6^{o}C per hour. Dexamethasone had dramatic results. A second anaesthetic was with nitrous oxide and oxygen, her body temperature increased again. A third anaesthetic was induced and maintained with thiopentone and was uneventful. She and her sister had normal serum creatine phosphokinase levels. The three main facts from this case report are that nitrous oxide can cause MH, dexamethasone is effective (and preferable to procaine) and creatine kinase is not always raised in MH susceptible patients.

They concluded that the first treatment should be a high dose dexamethasone 1-2 mg/kg.

1975

Procaine had been used to treat contractures (see 1971) and this study evaluated the effect of its effect (and that of lignocaine) in in-vitro experiments [45]. It was shown that procaine could cause or accentuate a contracture and that in some cases the dose required to abolish a halothane induced effect grossly in excess of clinically acceptable doses. There was no significant difference between procaine and lignocaine. They challenged the view that procaine was an appropriate treatment for MH.

[46] This was another ARS presentation, this time at the Research Department of Anaesthetics in the Royal College of Surgeons (obviously prior to the formation of the 'independent' college of anaesthetists. It was about nitrous

oxide causing MH and being successfully treated with steroids. Was this not published in 1974 [44]?

Having disposed of procaine they now disposed of serum creatinine phosphokinase (CPK) as a screening blood test [47]. It did not correlate with halothane-induced muscle contracture or the presence of myopathy, and CPK values were inconsistent in both normal and MH patients.

[48] "New causes of malignant hyperpyrexia": This is an anonymous short article (normal in the BMJ at that time) about recent developments in the understanding of MH and describing the possible multiple agents that may cause MH and the use of high dose steroids in its management. One can speculate on the identity of the author.

1976

[49] This is another letter. It is critical of Denborough's criticism of their findings that CPK was of no value in assessing MH susceptibility. They were of the opinion that if their contracture tests were positive all the other tests would also be positive.

1977

Calcium was known, from the very earliest physiological studies on muscle, to be involved in muscle contraction. It was therefore sensible to investigate the role of calcium in conditions involving abnormal muscle, and so they did [50]. Muscle from MH susceptible patients (diagnosed using the halothane contracture test) were analysed and there was no difference between normal patients and MH susceptible patients in either calcium or magnesium concentrations.

Another avenue for their research was to see what drugs depressed the halothane induced contractures, in this case pancuronium and methylprednisolone [51]. They were both effective and so were deemed safe to use in MH susceptible patients

1978

Acidosis occurs during MH and so the rate of acid production was investigated [52]. Halothane was shown to double the rate of acid production in MH susceptible muscle but had no effect on normal muscle. It was not lactic acid.

[53] "Plasma cholinesterase and malignant hyperpyrexia": This is a comment about a report by Whittaker et al. [iv]. It would appear that MH patients had an increased incidence of fluoride-resistant genes controlling plasma cholinesterase. Ellis et al. admitted finding a correlation and said that the inheritance of MH was likely to be of a polygenic nature.

1979

One of the confusing aspects of MH is that some patients, subsequently found to be MH susceptible, had anaesthesia involving triggering agents and did not develop the condition. They reviewed the patients' medical histories but could not find any common factor [54].

1980

[55] This was an article in a British Journal of Anaesthesia symposium devoted to muscle, its physiology and diseases.

The article on MH in the British Journal of Hospital Medicine [56] has not been sighted.

[57] Muscle: An editorial in the British Journal of Anaesthesia

1981

The metabolic processes in muscle are complex and in an attempt to determine the abnormality in MH susceptible patients (MHS) a laboratory controlled study of exercise in MHS patients and normal control subjects was performed [58]. There were nine patients in each group and they were exercised on a bicycle ergometer. Some experiments were carried out in fasting patients and some after a 600-kcal meal.

The results, in brief, showed that MHS patients had no increased heat production compared with controls and had no dietary-induced thermogenesis at all. They had higher insulin levels, and triglycerides rose over the course of the experiment. Pyruvate levels rose in the control subjects but not in the MHS patients.

One suggestion was that blood was shunted away from thermogenic tissue and another was that there was an underlying abnormality of sympathetic control mechanisms in the MHS subjects.

[iv] Whittaker, M., Spencer, R., and Searle, J. (1977). Br. J.Anaesth., 49, 393.

A "Collaborative study of the frequency of the fluoride-resistant cholinesterase variant in patients with malignant hyperpyrexia" [59] was the first genetic investigation into MH by the Leeds group. Previously reported work had shown an increase in the frequency of the E1u E1f genotype for cholinesterase. The Leeds work could not reproduce these results.

1982

It was now 20 years since MH was first described by the Australian anaesthetists Denborough, Forster, Lovell, Maplestone and Villiers[v], and the condition was still relatively unknown territory.

Some muscle diseases are associated with enlarged muscles and MHS patients were studied to examine the possibility that MHS patients also had enlarged muscles. They assessed body fat at the same time [60]. The amount of body fat was calculated from skinfold measurement and using antero-posterior photographs the diameters of the left thigh were assessed.

Male MHS subjects had significantly less body fat than the controls and upper thigh diameters in the MHS females were significantly greater than controls. However, they suggested that these differences were subtle and appeared to vary with sex.

1983

Another physiological study was carried out using exercise as the stimulant for abnormal responses [61]. Body temperature and blood chemistry were measured in five MHS subjects and five normal subjects during progressively severe exercise. As the exercise increased central temperature increased more in the MHS subjects. The temperature in the MHS subjects was significantly delayed and this was thought to be due to a delay in the onset of vasodilatation. It was concluded that this was evidence of abnormal heat dissipation mechanisms. Free fatty acids, cortisol levels and blood lactate concentrations were also higher in the MHS subjects than in the controls.

The thermal results from this study do not seem to be totally aligned with the 1981 paper [58] but they were measuring thermo-genesis then rather than measuring temperature.

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[v] Denborough MA, Forster JF, Lovell RR, Maplestone PA, Villiers JD. British Journal of Anaesthesia 1962; 34 (6): 395–6.

Dantrolene was initially used for treating muscle spasticity but in 1975 a paper by GG Harrison[vi] showed its usefulness in MH. This paper [62] investigated the action of dantrolene on the sarcolemma. It was shown to have no effect on contractures induced by 2:4 dinitrophenol, a small effect on caffeine contractions, but a marked effect on the contractures produced by K^+. They suggested that the site of the MH abnormality could be on the sarcolemma which was now where dantrolene was thought to work.

1984

A busy year with six publications.

The topic of MH was addressed to the paediatric speciality in the journal *Archives of Disease in Childhood* [63]. It is a general overview of the topic as it was known at that time.

[64] This is an editorial about the formation of the European Malignant Hyperpyrexia Group; a collaboration of eight countries. "...from now on work from members will conform to the agreed format." The goal was to define MH more accurately and to differentiate it from other conditions.

Suxamethonium is the major armament in the anaesthetists' arsenal when control of the airway with rapid intubation is required but it sometimes causes muscle spasm (as distinct from fasciculation, which is normal). The muscle spasm was considered an early indicator of the condition and was used as the trigger for further investigation of the patient's MH susceptibility. This paper [65] involved the analysis of 277 case histories and reinforced the view that muscle spasm induced by suxamethonium means that MH should be considered a likely diagnosis.

[66] This was a report by the Neurochemical Group to the 606th meeting of Biochemical Transactions held at University of Cork, 27-30 September 1983. The colloquium was on Molecular Aspects of Malignant Hyperpyrexia and Muscular Dystrophy. Ellis's team presented '*A biochemical abnormality found in muscle from unstressed malignant-hyperpyrexia-susceptible humans*'. After much biochemical description the bottom line was "*The human results lend further support to the suggestion that MHS subjects have an increased sympathetic activity, even in the unstressed state."*

[vi] Harrison GG. Br J Anaesth 1975;47 (1): 62–5

[67] “Malignant hyperpyrexia: A role for the community physician in Community Medicine”. This article was not viewed.

“Dantrolene sodium and dystrophia myotonica” [68]: This paper described the use of dantrolene as a possible muscle relaxant during surgery in this condition associated with myotonica; it was not sufficiently effective for intubation or surgery.

1985

This paper [69] approached the abnormal thermoregulation and thermogenesis process of MHS patients from a different angle. They cooled the MHS and control subjects. Skin cooling was similar in both groups but there was slightly increased heat production in the MHS group with a more significant increase in core temperature. The MHS subjects developed higher glucose levels and plasma noradrenaline was greater than some of the control subjects.

1986

[70] “Susceptibility to malignant hyperpyrexia”: A letter – in response to an article by Dr Moxon[vii]. It was critical of her “... narrow view of the importance of the diagnosis of malignant hyperpyrexia susceptibility...”. Her response was that “The purpose of the article was not to take a narrow view of the diagnosis of malignant hyperpyrexia, but rather to discuss some of the problems [*social, logistic, financial*] which continue to arise in a District General Hospital ... The advantages of a precise diagnosis are not disputed.”

“The work of the Leeds Malignant Hyperpyrexia Unit” [71]: This was the first report from the unit and covered the years 1971-1984. It included a review of the results obtained from 1127 patients. To say this was a substantial body of work is an understatement.

This next study was an investigation into the effects of glycopyrrolate and atropine on heat production and loss during exercise in normal volunteers [72]. There were no significant differences in resting and peak heat production

[vii] Anaesthesia 1985; 40:693-5

and, as might be expected, sweat evaporation was greater after saline placebo compared with atropine, but not after glycopyrrolate. Their conclusion after considering all of the results was that non-evaporative heat loss compensated for the reduction in sweating due to anticholinergic drugs.

1987

This was another exercise study, this time on a treadmill, walking at 40% of maximum oxygen consumption. This showed that "non-competitive, low-intensity, steady-state exercise" was not contraindicated in MHS patients [73].

1988

[74] "Ambulatory laboratory investigations for malignant hyperthermia susceptible patients". *Acta Anaesthesiologica Belgica* . This article has not been sighted.

[75] "The diagnosis of MH: its social implications": This is an opening editorial for a symposium on MH. It was not sighted – the BJA website strangely comes up with an Erratum notification – it is the next item in the table of contents.

Sudden infant death syndrome (SIDS) has been looking for a cause ever since it was described. This paper [76] considered its relationship to malignant hyperpyrexia (MH). There were two studies: 151 MH-susceptible families and 106 SIDS families; they completed questionnaires designed to identify the incidence of either MH or SIDS events. In a third study 14 SIDS parents had muscle biopsies and in-contracture screening for susceptibility to MH. The results suggested no association.

1989

Following the 1984 study about muscle spasm the occurrence of masseteric muscle spasm (MMS) in children was studied [77]. Fifty percent of the children had no muscle abnormality. Although both adults and children can get muscle spasm in response to suxamethonium, an exaggerated response should still be considered as a possible sign of MH.

[78] "Implications of the inheritance of MHS". *Annales Francaises d Anesthesie et de Reanimation*. This is an interesting short article in that it expresses points that have not been made so clearly elsewhere. One comment

is the "... disturbing tendency for doctors to fabricate association between rare diseases [and MH] which prove to be unfounded." It is also pointed out that in their database of almost 2,000 patients there is not a higher incidence of kyphoscoliosis, hernia, strabismus, orthopaedic abnormalities, greater muscle mass, or greater athletic performance. A positive genetic test for MH may also lead to discrimination for certain types of occupation, or even marriage (particularly in Japan).

[79] This was a letter to *Anaesthesia* about Malignant hyperthermia in the Wolf-Hirschhorn syndrome [viii]. To quote "We read with interest and disquiet of the suggested relationship between malignant hyperthermia (MH) and the Wolf-Hirschhorn syndrome (Anaesthesia 1988; 43:386-8)." ... "We believe the authors are responsible for reporting a far-from-proved relationship between two rare diseases. Unfortunately all the bibliographic computers will regurgitate this unproved relationship quite uncritically and generations of anaesthetists will be misled." This is a very strongly worded critical response. The original authors, R Ginsburg and G Purcell-Jones replied equally strongly defending their position.

[80] Stress as a factor in the triggering of MH and was assessed by measuring adrenal cortical reserve in patients undergoing muscle biopsy and a control group. They used the Short Synacthen Test and there was no significant difference between the groups.

1990

A review of the last 30 years of MH was published in 1990 [81] and highlighted the changes in its apparent incidence and future genetic screening.

[82] This was an editorial commenting on a paper in the journal on prediction of MHS by a statistical evaluation of clinical signs[ix].

[viii] A syndrome caused by deletion of part of the short arm of chromosome 4. The patients have delayed growth and development, intellectual disability, seizures and a characteristic facial appearance.

[ix] W. Hackl, W. Mauritz, M. Schemper, M. Winkler, P. Sporn and K. Steinbereithner Br. J. Anaesth. (1990) 64 (4): 425-429 [the prediction of MH had a maximum sensitivity and specificity of 78% and were therefore unacceptable for clinical use]

The clinical picture of the presentation of MH, high levels of creatine kinase and myoglobinuria were used to classify allowed the probability of MH to be determined [83]. As expected some predictors were found to be more important than others – a high creative kinase, myoglobinuria and a clear contemporaneous description of the clinical events.

Using a myotonometer [84], the myotonic response of masseter muscles to suxamethonium was measured in 50 "*apparently healthy patients*". The majority showed a short-lived myotonic response, the maximum increase (>1kg) was found in five patients and >500g in 12 patients. This might be classed as masseteric muscle spasm so the value of this myotonia as an early sign of malignant hyperthermia was questioned.

A study of muscle relaxation rates following a tetanic stimulus of adductor pollicis muscle was measured in 26 patients, 11 were MHS, 15 MHS negative [85]. The results suggested that relaxation rates could not be used for MH screening.

1991

[86] An editorial: This was commenting on a paper in the journal[x] and reflected on the previous lack of consistent differences between the effect of exercise in MHS and MHN subjects. The study referred to used an in-vivo probe and did demonstrate a difference after short-duration violent exercise. They thought it was important because if there was a difference non-invasive NMR screening for MH might be possible and a 'physiological' abnormality in the muscle might be consistent with the associated defect in the ryanodine calcium receptor in the sarcoplasmic reticulum.

Heat stress due to exertion was studied in two military personnel [87]. Muscle testing revealed an abnormal response to halothane. One of the fathers had an abnormal response to halothane, and the father of the other patient had an abnormal response to ryanodine. The results suggested that heat stroke may be associated with an "abnormality of skeletal muscle that is similar, but not identical, to that of malignant hyperthermia."

Two patients who were suffering from arthrogryposis multiplex congenita developed hypermetabolic reactions during anaesthesia [88]. It was suggested

[x] Allsop P, Jorfeldt L, Rutberg H, Lennmarken C, Hall GM. British Journal of Anaesthesia 1991; 66:541-545.

that the reaction was not malignant hyperthermia and was independent of the anaesthetic drugs used.

This paper is the paper that hypothesises that the ryanodine contracture test is a specific in vitro test for MH [89]. The sarcoplasmic reticulum has a calcium release channel and ryanodine binds avidly to it. It was shown to differentiate between MH susceptible and normal patients when tested with a contracture response.

1992

[90] A letter to Anaesthesia**:** This was in response to a case report of a patient who may have had an MH episode. The diagnosis was questioned and a member of the Department of Anaesthesiology, A A Broekema, of the University Hospital Groningen who responded, was not one of the original authors. The diagnosis was defended.

[91] This was a short communication in the British Medical Journal about the detection of susceptibility to malignant hyperthermia and communication in susceptible families – "New genetic tests and better communication among affected families could help." Detection of clinical MH remains the responsibility of the anaesthetist in the operating theatre, but detecting susceptibility to MH in members of known MH families is dependent on communication between family members. A member of two families died due to MH because of this and so better communication was "essential to avoid further anaesthetic tragedies".

[92] "Malignant hyperthermia", in Minerva Anestesiologica, the Journal of the Italian Society of Anesthesiology, Analgesia, Resuscitation and Intensive Care

[93]. Testing for MH with caffeine and halothane gave conflicting results if they were tested separately or together. When used concurrently a contracture occurred, but when used separately there was a normal response; these patients were termed" K-type". In this study the K-type was not correlated with the MH susceptibility as accepted by the European MH group

[94] This is a letter to '*Anesthesia and Analgesia'* about masseter muscle spasm in response to letters in response to a paper[xi]. They were

[xi] Littleford JA, Patel LR, Bose D, Cameron CB and McKillop C. Anesth. Analg. 1991;72:151-60

unhappy about the suggestions by other workers about the response to masseter muscle spasm and stated that "...any patient with *abnormally severe* MMS must be considered MH susceptible until proven otherwise".

Postoperative pyrexia; in this study of 30 such patients postoperative pyrexia was shown to have no relationship to MH [95]. Another negative outcome was an attempt to show the existence of a generalised membrane abnormality by using a spin labelled electron spin resonance technique; there was no difference between MHS and normal patients [96].

[97] "Inconsistency of data linking the ryanodine receptor and malignant hyperthermia genes". "This is a comparison of the caffeine halothane muscle contracture test with the molecular genetic diagnosis of malignant hyperthermia."

1993

"Genetic linkage analysis of chromosome 19 markers in malignant hyperthermia" [98]:

MHS <u>in some</u> families may be caused by a variation in a gene located on chromosome 19 in close proximity or identical to the ryanodine receptor gene (RYR1), expressed as a calcium release channel of the sarcoplasmic reticulum. The analysis of DNA samples from three large MHS British families strongly suggested that the MHS gene was located in the same region of chromosome 19q. Because genetic heterogeneity could not be excluded they could not recommend DNA markers as a replacement for in vitro contracture tests.

[99] This is a letter about a report by authors who worked in the New Zealand MH referral centre at Palmerston North. They suggested that the MH event was triggered by stress rather than drugs used for the anaesthetic. Ellis et al disputed the diagnosis but the response from the NZ authors was strong and insisted that the clinical and biochemical information suggested an increased metabolic rate.

[100] This is a letter to the editor of the journal *Human Mutation*. In the letter the authors describe how a suggested mutation (described by other workers) could be used as a pre-symptomatic test for MH. They refuted this idea with their analysis of 100 British families. They did not find this mutation and therefore the idea of its usefulness was rejected.

A comparison of ryanodine, halothane and caffeine for contracture testing was reported in MH and other neuromuscular disorders [101]. The

ryanodine contracture test was not specific for MH but, in conjunction with halothane and caffeine, might help accurate phenotyping of individuals for further genetic analysis.

This paper describes the genetic mapping of the beta 1 and gamma-subunits of the human skeletal muscle L-type voltage-dependent calcium channel on chromosome 17q. However, it also excludes the genes as causative of MH [102]; an achievement but another negative outcome for a screening test.

1994

[103]; this paper describes the effects of benzamil on the sodium-calcium exchange in muscle. It caused contracture of skeletal muscle samples from MHS patients but not from normal muscle. It also increased the contracture response of both types of muscle to halothane. At low concentrations it reduced the contracture response to halothane in MHS patients.

An editorial in *Anaesthesia* in 1994 [104] restated the belief that genetic testing alone was insufficient for the diagnosis of MH, IVCT was still necessary.

Localization of the gene encoding the alpha 2/delta-subunits of the L-type voltage-dependent calcium channel to chromosome 7q and analysis of the segregation of flanking markers in malignant hyperthermia susceptible families [105]:

The genetic heterogeneity of MH suggests other sites of calcium regulation than the ryanodine receptor (RYR1). RYR1 is linked to less than 50% of MHS European families. They describe the cloning and partial DNA sequence analysis of the gene CACNL2A on chromosome 7q. D7S849 and flanking genetic markers were found to co-segregate with the MHS locus. These results suggested that mutations in or near CACNL2A might be involved in some forms of MH.

It is always good to have some scoring system to provide an indication of the likelihood of an uncommon disease entity. This paper, "A clinical grading scale to predict malignant hyperthermia susceptibility" [106] tried to do this for MH. They used the Delphi [xii] method with 11 experts. The scale ranks the likelihood that an anaesthetic event is indicative of MH and that further

[xii] The Delphi method is an iterative technique, using experts, to get a consensus of opinion. http://en.wikipedia.org/wiki/Delphi_method

investigation of family history will confirm MH susceptibility. They felt that the clinical grading system provided a comprehensive clinical case definition for the malignant hyperthermia syndrome and would aid research into the condition. This was an improvement on the 1971 definition.

1995 was a quiet year.

1996

"Should patients with central core disease be screened for malignant hyperthermia" [107]? This was in the section devoted to 'Letters to the Editor'; a very long letter. This described a study of six families in an attempt to address the assumption that all patients with central core disease (CCD) are susceptible to malignant hyperthermia and therefore do not require screening. They showed this assumption was wrong. The data indicated CCD and MH are not the same even though a similar genetic locus was implicated in both.

This raised the issue of defining (diagnosing) CCD and MH myopathy. Although histology may be similar the authors thought that clinical information should be included in the final decision. "If the patient is symptomatic [of CCD] and susceptible to malignant hyperthermia a diagnosis of central core disease is appropriate. However, if symptomatic and susceptible to malignant hyperthermia, malignant hyperthermia myopathy is probably better."

Not all MHS families are represented by ryanodine receptor mutations or linkage to the region of 19q on chromosome 19. Some families have a linkage to chromosome 17, but some families are not linked to either. The view was that the muscle contracture test still remained the only reliable test of MHS. This paper [108] describes a linkage analysis in a large family group with malignant hyperthermia. They had none of the ryanodine receptor gene mutations but had linkage to intragenic ryanodine receptor markers. This resulted in accurate prediction of MHS in 11 untested subjects who were at 50% risk[xiii].

[xiii]The author himself was involved in this study. I was working in New Zealand and received a letter from Pat Ford asking if I could find a relation of one of the MHS families in New Zealand. Being an expat UK national, I knew there was a general impression in the UK that NZ was so small everybody knew someone who knew the person they were looking for! Auckland, the biggest city in NZ (25% of the population), was a good start. The family name was relatively unusual and so, in fact, it only took two phone calls to find

1997

"The G1021A substitution in the RYR1 gene..." [109]: A single base change in the RYR1 gene has been proposed to underlie MHS in up to 10% of cases. They investigated this substitution in 151 subjects and detected G1021A heterozygotes in seven families. This mutation was not found in MH-negative subjects, nor was it found in families with central core disease. This, together with other findings, reinforced the view that DNA testing for MH status was still unreliable.

The aim of this study [110] was to evaluate statistical models that might predict MHS from the results of their in vitro contracture tests (IVCTs), again with a view to improving the assessment of genetic linkages. Logistic regression was used and of the individual contracture tests the ryanodine test was most closely correlated with MH status. Models were also made with combinations of tests and data from individual contracture tests and receiver operating characteristic curves were used to enhance the discrimination of the assessment model. The reproducibility and generalizability of the model was also assessed. The study required the testing of a total of 250 subjects

The purpose of this next study was to determine the sensitivity and specificity of IVCT test results [111]. The patients studied were those who had had fulminant MH and a set of low risk control subjects. After strict exclusion of potential confounding subjects they found a diagnostic sensitivity of 99.0%, a specificity of 93.6% (95% confidence interval 89.2-96.5%).

1998

"Genetic heterogeneity and HOMOG analysis in British malignant hyperthermia families" [112]: This a review of the status quo re MH genetics. It confirmed genetic heterogeneity in the " ...UK MH population together with the possibility of the presence of two MH genes in some pedigrees ... "; the danger of just using DNA to diagnose MHS was restated.

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the correct family. The direct descendant had died but he had an extended family throughout the country and they were able to be tracked down. Two problems ensued – one was that one branch of the family was doctor-phobic and the second was that arranging for blood to be sent via the USA back to the UK was bureaucratically insurmountable. In the end the DNA was extracted in Auckland and sent via normal postage to the UK.

1999

Patients with central core disease (CCD), a myopathy, were thought to be susceptible to MH. Eight CCD families were screened for 13 mutations of the ryanodine receptor gene; none were detected. They produced "unequivocal evidence" that CCD was genetically heterogeneous and not all individuals with CCD were susceptible to MH [113].

2000

"Multiple interacting gene products may influence susceptibility to malignant hyperthermia" [114]: It had been assumed that abnormal single genes were responsible for MHS. This was not seen in some families so a new genetic model was proposed, that susceptibility is due to the effects of more than one gene. They used the 'transmission disequilibrium test' on the data from 130 MH families and the results supported the new model.

2002

"RYR1 mutations causing central core disease are associated with more severe malignant hyperthermia in vitro contracture test phenotypes". [115]: CCD patients are at risk of MH and mutations in RYR1 (19q13.1) account for the majority of MH and CCD cases. Five of the fifteen RYR1 considered causative of MH are associated with CCD. Mutation type was shown to affect IVCT response to caffeine, halothane, and ryanodine. The RYR1 mutations associated with both CCD and MH had greater caffeine and halothane responses than those associated with MH alone. They made the point that this "was the most extensive study of MH patient clinical and genetic data to date."

2004

Hypokalaemic periodic paralysis (HypoPP, another rare muscle condition) had been associated with MH and therefore there was a potential link between these disorders. This investigation [116] of two independent HypoPP patients, one diagnosed as MHS, suggested that the two conditions occurred independently.

2010

"Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group" [117]. These guidelines, in two sections, relate to the recognition of MH and the management of the crisis. The

early and late signs were listed together with possible differential diagnoses - insufficient anaesthesia, infection, insufficient ventilation, anaesthetic machine malfunction, anaphylactic reaction, phaeochromocytoma, thyroid crisis, cerebral ischaemia, neuromuscular disorders, laparoscopic surgery, Ecstasy or other recreational drugs and malignant neuroleptic syndrome.

It is now time to produce a brief time-line of the MH story.

The 1972 publication [34] highlighted a possible more specific method for screening for MH; this work was taken further in [35, 37] and in [38] it becomes clear this is a 'breakthrough'. From this 'specific test' for MH evolves the investigation of the genetic basis of the condition. In 1974 it was refuted that procaine and lignocaine were good for the management of MH [41, 45] and in 1975 CPK [47] was demoted as a useful screening test. Dexamethasone became the favoured treatment [44, 48]. In 1977 the influence of Ca^{++} was investigated but there was no difference between MHS and MHN [50]. In 1978 it was found that halothane doubled the rate of heat production and there may have been some relationship with plasma cholinesterase – it was then suggested that MH was polygenic [53]. The first genetic study in 1981 [59] could not reproduce the CHE results. Between 1981 and 1983 the hypothesis was that it was a sympathetic/heat distribution disorder. In 1983 there was also the first mention of dantrolene by the Leeds group and this was thought to act on the sarcolemma [62]. In 1984 the European Malignant Hyperpyrexia Group came into being; muscle spasm was investigated [65], and it was still thought to be a sympathetic disorder [66]; this continued in 1985 [69]. In 1989 they refuted the idea of MH being related to many other disorders [78].

1991 was a significant year with the advent of the ryanodine contracture test [89]. In 1993 it was stated that genetic testing was not totally indicative and that the genetic testing should be combined with contracture tests [101, 105, 108, 109, and 114]. In 1997 they created a model to predict MHS and the model had high sensitivity/specificity [110, 111].

A job well done by the whole team.

[xiv] Swiss cheese and MH: The author has the infamy of perhaps being the only anaesthetist to give suxamethonium and halothane to a known MHS patient. To those unfamiliar with the Swiss cheese metaphor, the patient and anaesthetist progressed through all the holes in the checks and balances associated with a patient going for

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surgery. A terrifying MH episode ensued which was managed by colleagues who came to the rescue with an MH pack; the patient survived as did the anaesthetist.

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Jones JG
MD FRCP FRCA
Hon FANZCA

 [i]

Between 1968 and 1970 J Gareth Jones was lecturer in anaesthesia in Birmingham and, for the following four years, the North Senior Fellow at the Cardiovascular Research Institute, University of California, San Francisco.

He then became a senior scientific staff member in John Nunn's Division of Anaesthesia at the MRC Clinical Research Centre, Northwick Park Hospital, Harrow. However, his first research exposure (as a medical SHO) was in the MRC Pneumoconiosis Research Unit in South Wales.

"My bosses were Archie Cochrane (famous for Evidence Based Medicine), John Cotes (developed the open circuit oxygen breathing systems used by Hillary and Tenzing on the first Everest Summit), and John Gilson (who developed the RAF oxygen masks). After this I was a medical registrar specialising in cardiology and did [the]*MRCP* [exam]*".*

Between 1986 and 1991 he was professor in Leeds. He was then appointed foundation professor in Cambridge, linked to the Department of Medicine, and adjacent to the Department of Anaesthesia in Addenbrooke's Hospital[ii]. His work revolved around respiratory and cerebral physiology, the former on how anaesthesia is related to perioperative hypoxaemia and the latter on awareness and memory.

Jones JG was a Member of the Royal College of Physicians and was, therefore, more physician-inclined[iii] in his early career, and was heavily involved in respiratory physiology. "*From 1964 to end 1967 I was research fellow in Sir Melville Arnott's Dept Medicine in Birmingham. Here I did my MD*

[i] Photograph courtesy of JGJ. All text in italics is his.

[ii] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916

[iii] A good anaesthetist needs to be a good physician but not all physicians would make good anaesthetists.

*(19**6**7) on Ventilatory Function, Distribution and Mixing of Inspired Gas. This involved use of a new rapidly responding respiratory mass spectrometer developed by the Australian physicist Kemp Fowler working with John West at Hammersmith. My supervisors were John Bishop and Gordon Cumming with grants from the US Air Force. Cumming was involved in studying the mathematics of branching systems, gaseous diffusion in the lung and employed both single and multi breath tests using analog and digital computing in data analysis."*

Whilst a lecturer in Anaesthesia in Birmingham he continued to work in the Dept of Medicine laboratories, being joined by S W Clarke. *"We studied the effect of gravity on the lung and studied gas flow in branching tubes and fluid mechanics of two phase gas liquid flow. Some of this was done with the RAF at Farnborough using the human centrifuge, pressure chambers and vertically rotating chairs."*

He wrote four papers with Gordon Cumming [1-4]. The 1966/7 studies were about nitrogen clearance curves [1]. Curves were generated from a physical model and volunteers breathing oxygen. They were able to measure one litre of lung volume with a standard deviation of 10 ml. Following this work with normal subjects they studied patients with chronic bronchitis [3]. They used two techniques, the multi breath technique where nitrogen was washed out with oxygen and the single breath method using either nitrogen washout or 50ml argon boluses inhaled to different depths down the airways to study diffusion. This work was carried out under contract to the European Office of Aerospace Research (OAR), U.S. Air Force.

1969 was the transition year, a very busy year; six papers were published in high quality physiology journals and two in the British Journal of Anaesthesia. There was a presentation at an Anaesthetic Research Society (ARS) meeting in London in the previous November (but published in the BJA in February '69, "*Two-phase gas-liquid flow in airways*" [5]) and then a later one at an ARS in Birmingham which was on the "*Influence of age on basal airway closure*" [6].

The first 15 years of Jones' time in anaesthesia were spent mainly on the changes in lung function that occur during anaesthesia.

In November 1970 there was an Anaesthetic Research Society meeting in London and there was a presentation on "*The effects of nitrous oxide uptake on alveolar oxygen concentrations*" [7]; it was published in the BJA in the following

February. As was common a full paper was published later in the year [8]. These were tricky experiments. Volunteers, inaccessible and completely enclosed in a body plethysmograph with an arterial line coming out through the wall, were given a variety of concentrations of nitrous oxide and many variables were measured as they lost consciousness. They showed an increase in alveolar oxygen tension which was proportional to the inspired N_2O concentration. The difference between the alveolar and arterial oxygen doubled. The reasons are complex but involve *"lung shrinkage"* (reduced functional residual capacity) which also caused an increase in the alveolar/arterial difference; this supported the work of Stoelting and Eger (1969)[iv]. Alveolar oxygen concentration increases and so adds a small degree of safety.

In 1970 he went to the USA. "Although I had reverted to physician/physiologist I was immediately involved with John Severinghaus in a project to induce high altitude pulmonary oedema (See "The Hypoxia Hilton", on Google) *[9]*. Back at sea level my main research was to elucidate the mechanism of expiratory flow limitation in the large airways (with R Fraser and J Nadel) *[10-12] [see RCA Bulletin article[v]]*. This was my main project resulting in an understanding of the mechanism of expiratory flow limitation. Our paper was seen at the review stage by others who, although quoting our work in their subsequent paper, claimed to have discovered the Wave Speed theory of flow limitation which was none other than our own equation. This work was more than 30 years ahead of its time being relevant to modern tracheal transplantation.

Some of the subjects studied were -

The effect of pre-inspiratory lung volume on the result of the single breath O_2 test [13]

Respiratory gas exchange in patients with spontaneous pneumothorax [14]

Postural changes in pulmonary ventilation [15]

Inhaled argon boluses in man [4]

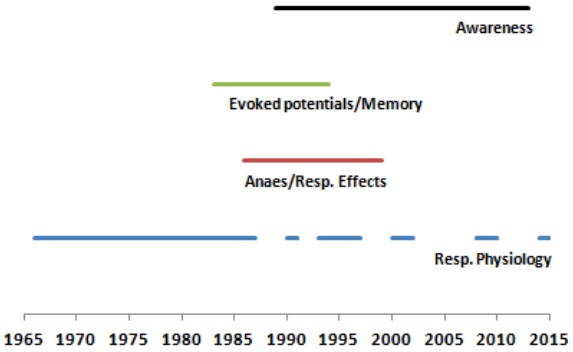
[iv] Stoelting and Eger. Anesthesiology 1969;30:273-7, the concentration of alveolar gas – the second gas effect.

[v] RCA Bulletin 2003, 17, p850

Oscillations in expiratory gas flow during a forced vital capacity manoeuvre [13]
The effect of expiratory flow rate on regional lung emptying [16]
Effect of acceleration on regional lung emptying [17].

This last one is of particular interest - it was collaboration between the Department of Medicine, Queen Elizabeth Hospital, Birmingham and the Royal Air Force Institute of Aviation Medicine, Farnborough. It was determined that there was virtually no gas-trapping when extrapolated to zero Gz but progressively larger volumes of trapped gas as acceleration increased to 4Gz causing increased V/Q abnormalities.

The work pattern over the years:



Choice of journals:

British Journal of Anaesthesia	(47)
Journal of Applied Physiology	(14)
Anaesthesia	(13)
Anesthesiology	(5)
Clinical Science	(4)
Respiration Physiology	(3)
Lancet	(3)
Journal of Physiology	(2)

In 1976 they (Jones and Minty) studied the contribution of the chest wall and the abdomen to breathing; this was presented at another ARS meeting, this time at Northwick Park [18]; as previously, the work was published in full later, three years later [19, 20]. They created a mathematical model of the chest wall, an analogue computer, and used mercury-in-rubber strain gauges around the body to measure the changes in circumference. The subjects were assessed before and after anaesthesia. They determined the error between the computed tidal volume and that actually measured at the mouth and it was 8%. The contribution of the rib cage to tidal breathing was from 5 to 42%.

The second paper was about the mechanics during halothane anaesthesia. Whilst awake, movement of the abdomen/diaphragm complex was responsible for 70+% of the tidal volume (rib cage 5-30%). Halothane anaesthesia caused a reduction in the contribution of the rib cage. They showed an increase in abdominal volume and a reduction in rib cage volume at the end of expiration. It is a complex dynamic situation but it was concluded that halothane predominantly affected the rib cage musculature predisposing to paradoxical ventilation. It was also suggested that the reduced lung volume might be due to "loss of postural control of the chest wall and a central shift of blood volume".

In publications in 1976 (ARS) and 1978 Jones and Minty also reported on the comparison of active and passive closing volume manoeuvres in conscious subjects [21, 22].

In 1978 there were two studies about the lower airways [23, 24]; they were adjacent in the same journal. The first was on narrowing of dependent airways and the second on the effects of pulmonary venous congestion on the airways.

The first was a study of anaesthetized dogs; they assessed closing volume[vi] and used tantalum bronchography to measure the calibre of airways. It demonstrated that the elasticity of lung parenchyma and vagal induced changes in airway calibre, affect closing volume. They showed that there was a

[vi] Closing volume is the volume of lung inflated when small airways in the dependent parts of the lung begin to collapse during expiration. In normal health, closing volume is less than FRC and accounts for the residual volume (RV) of the lung at the end of expiration.
www.frca.co.uk/article.aspx?articleid=100423

vertical gradient of airway diameters in the supine lung and a "*preponderance of the effect of vagal stimulation in the lower zone*"; this is where the lung recoil is least. It was suggested that because halothane virtually abolishes the effect of vagal stimulation on closing volume and on airway resistance makes it useful when intubation is required for severe bronchospasm.

The second study measured changes in airway calibre when there was pulmonary congestion; a balloon was placed in the left atrium. Closing volume increased by about 50%. Seven out of 10 dogs had impaired gas exchange; this was not due to increased lung water. In a second group disabling of the vagus returned the closing volume to baseline values. It was also shown that isoprenaline abolished the effect. It was concluded that "*the vagus mediates the changes in lung mechanics associated with pulmonary vascular congestion*".

"*Returning to the UK in 1974 I was involved in Intensive Care which meant a major change in research direction. I started studying alveolar wall injury in relation to ARDS. I developed a new method using Technetium labelled chelates (DTPA) and other molecules to study alveolar injury and recovery after acid aspiration and fat embolism in animals . Modifying the technique for use in man we were the first to show in the Lancet that symptomless smokers had very leaky lungs (this paper has been very extensively quoted)* [25]*. This finding influences the administration of aerosolised insulin in diabetic smokers. Widdicombe* [vii] *... described the salient features of our physiological findings, but there are many overlapping aspects of my work in this period including fat embolism, acid aspiration, cigarette smoke inhalation, complement activation, fire smoke inhalation. In the latter we collaborated with the Royal Navy and the MoD Porton Down (Beeley, Minty* [26-28] *) studying the effects of high dose steroids after smoke inhalation. The results were used in the Falklands in soldiers with smoke injured lungs. During this period I returned to San Francisco in 1977 to work with JF Murray on lung injury with further papers on pulmonary edema, lung permeability etc."* [29-31]

"Returning to the UK in 1978 I developed a new method for measuring airway resistance in patients anaesthetised with different general anaesthetic agents (Lehane, Jordan, Royston, Altman) [32-34]*. This used forced airflow oscillation and on-line computing to derive resistance. The work shed light on change in FRC and hypoxaemia during anaesthesia. During this time we were also studying ventilatory control (with various novel methods) and the effects of*

[vii] Widdicombe J J Appl. Physiol. 82(1): 3–12, 1997

morphine, morphine antagonists, diazepam and sleep (Catley, Jordan, Royston, Thornton, Heneghan). This was both in volunteers and in post op patients. This marked a step forward in realising that post-op hypoxaemia was the result of apnoeic periods, sleep and ventilatory depression with opioids. Submitted to Anesthesiology the paper was at first rejected by three reviewers (who thought it too novel) but, without protest on our part, later accepted by the Editor." [35]

In 1984 [36] changes in lung volume and their affect on PAO_2-PaO_2 during anaesthesia were investigated. The established wisdom was that the decrease in lung volume during general anaesthesia caused an increased oxygen tension gradient between alveoli and blood. The lung volume in anaesthetised patients was increased by tilting the patients head-up. There was no improvement in PAO_2-PaO_2 and changes in cardiac output made no difference either.

The theory that the impairment of gas exchange in anaesthetized man is caused by abnormalities of dependent lung ventilation due to abnormal diaphragmatic mechanics was further investigated in 1985 [37]. In this study of abnormal gas exchange in rabbits (induced by reducing lung volume to residual volume) two methods of increasing the lung volume were employed, the use of positive end-expiratory pressure (PEEP) and phrenic nerve stimulation (PNS). PNS produced greater movement of the diaphragm and improved gas exchange significantly more than PEEP. It was concluded that it supported the theory abnormal diaphragmatic mechanics contributed impaired gas exchange during anaesthesia.

In 1996 two reviews were written about the airways and anaesthesia [38, 39].

The next category is more clinical – pulmonary dysfunction associated with anaesthesia.

Going back again to 1985 the respiratory effects of postoperative analgesic regimens were assessed [35]. One group received intravenous morphine and the other received bupivacaine regional anaesthesia. There was comparable analgesia throughout but the respiratory effects were different. About 2/3 of the patients receiving morphine had 456 episodes oxygen desaturation less than 80%. The patients had obstructive apnoea, paradoxical breathing and periods of slow ventilatory rate. The difference was marked; those patients who had regional anaesthesia never had oxygen saturation less than 87%. It is

obvious that regional anaesthesia has a greater margin of safety compared to the continuous administration of morphine.

This was supplemented by a paper titled "*Episodic postoperative oxygen desaturation: the value of added oxygen* [40]. Postoperative analgesia with intravenous morphine was monitored continuously for changes in breathing pattern and arterial oxygen saturation. Patients breathed either air or 28% oxygen for alternating two-hour periods. Although oxygen did not change the incidence of abnormal respiratory patterns oxygen desaturation below 80% did not occur.

An editorial in the August BJA 1987 was on "*Anaesthesia, and atelectasis: the role of V_{TAB} and the chest wall*" [41]. V_{TAB} is thoraco-abdominal blood volume. This editorial lays out the various thoughts on the aetiology of intra-operative respiratory dysfunction.

A review in *Anaesthesia* in 1990 [42] on the mechanisms of perioperative hypoxaemia was thought to be mainly due to reduced muscular tone of the chest wall and changes in bronchomotor and vascular tone. These changes persisted into the postoperative period and their effects were enhanced by episodic obstructive apnoea which, in turn, was enhanced by opiate analgesics. Oxygen reduced the degree of resulting hypoxaemia. In the same year was a paper on postoperative hypoxaemia, it was a comparison of extradural, I.M. and patient-controlled opioid analgesia [43].

In 1991 he moved to Cambridge. *"In Cambridge, with David Sapsford, we also developed a new method for measuring, non-invasively, shunt and ventilation perfusion ratio. We applied this in ARDS patients, in patients during thoracotomy and used it to predict instability in oxygen saturation in the post operative period (Roe, de Gray)* [44, 45]. *Later I showed that it could be used in neonates (H. Smith)* [46] *and after fat embolism (Newell)* [47]. *After I retired I studied the effect of downstream pressure on oxygen delivery by venturi devices* [48] *and continued to use the Gas Exchange method in Edinburgh infants with bronchopulmonary dysplasia (Stenson, Quine, Rowe)* [49, 50]. *This method is now being used to improve targeted oxygen delivery in infants with damaged lungs. I have shown that it can predict the likelihood of in-flight hypoxaemia in pressurised aircraft (Jones, Bakewell, Heneghan, Jones, Snape)* [51]."

1991: The effect of nitrous oxide sedation on breathing and oxygenation (using pulse oximetry) after hyperventilation to a $PE'CO_2$ 3kPa was studied [52]. This was below the apnoeic threshold. Those who breathed nitrous oxide all became apnoeic and their oxygen saturation fell to an average

of 75%. Those breathing air did not become apnoeic but desaturated to an average of 92.5%. Postoperative hypoxaemia after general anaesthesia or sedation may be explained by this apnoeic effect and its importance in obstetric patients was stressed.

In 1993 the relationship between inspired oxygen partial pressure and oxygen saturation (P_IO_2 and SaO_2) was explored [53]. A complex, ideal lung, physiological model was created including the effect of shunt and V/Q effects, these involved nine compartments representing the variability of V/Q, and blood supply. Depending on the model's settings the plots of P_IO_2 vs. SaO_2 caused changes in the shape of the ideal curve in specific ways so that a series of simple measurements of P$_I$O2 and SaO_2 provided information regarding shunt and V/Q abnormality.

Four years later this technique was used to study gas exchange during thoracotomy [45]. A plot of P_IO_2 and SaO_2 was used to determine the shunt and ventilation/perfusion ratio. There was an increase "*... in shunt from 13.8% to 20.8% and a worsening ventilation/perfusion ratio from 0.5 to 0.2*". The technique enabled an assessment of shunt and V/Q and the prediction of SaO_2 at different values of SpO_2.

At the same time gas exchange during and after anaesthesia for upper abdominal surgery was investigated [54]. P_IO_2 was varied to produce a plot of P_IO_2 vs. SpO_2. Thirty hours after surgery the changes were such that it was concluded that the shunt and V/Q abnormalities during anaesthesia correlated with the SpO_2 30 h post-operatively. It was suggested that the technique could be used to identify patients at risk.

Finally, in this group, is a study of gas exchange following fat embolism after trauma [47]. As above they quantified shunt and V/Q mismatch over time. They both improved over a week but deteriorated after general anaesthesia for surgery.

This was obviously a very sophisticated analytical method. To the best of my knowledge it has never been introduced into clinical practice.

And now for something completely different:

"The next phase was Depth of Anaesthesia. This work is reviewed in Ghoneim's book "Awareness during Anaesthesia". I was probably the first to produce a booklet on Awareness under Anaesthesia (ICI Pharmaceuticals, Anaesthesia Rounds No 21, 1988). I was joined by Christine Thornton and we focussed on developing EEG methods for measuring the graded effect of various

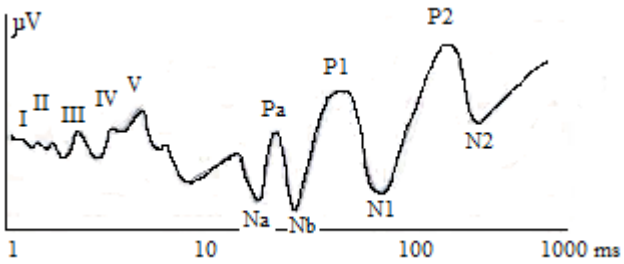
general anaesthetics on the brain. The Brain Stem response in the Auditory evoked potentials was the first part of the study and later this moved up to the middle latency (early cortical) responses. This was later taken up by Schwender et al. in Germany and by Kenny et al.

Thornton continued this work in London when I moved to Leeds and later she showed that working memory was very sensitive to 0.2 MAC equivalent doses of anaesthetic. We (Baddeley, Andrade, Sapsford, Munglani) [55-58] *independently showed similar results in Cambridge and developed the Coherent Frequency in the EEG as a measure of depth* [of anaesthesia]. *It is an extraordinary sight to witness the videos of experiments where volunteers are given sub MAC doses of general anaesthetic. They, appear to be fully conscious, respond to questions and painful stimuli yet a few minutes after the anaesthetic is discontinued have no recall of the conversations or the painful experience."*

Evoked Potentials

C Thornton was involved in seven of these publications about evoked potentials, six as first author.

Evoked potentials are detected in the brain in direct response to specific stimuli; aural, visual or motor. Below is a schematic diagram of such an evoked potential waveform.



Brainstem waves between 1 – 10 ms
Early cortical (or middle latency) waves 10 – 100 ms
Late cortical > 100 ms
Event related potential occurred at 300 ms (P2 or P300)

In 1983 the effect of enflurane concentration on the auditory evoked response (AER) was studied [59]. Anaesthesia was with 70% nitrous oxide in

oxygen, and the enflurane concentration was increased from 0 to 1% over half-an-hour. The latencies of all waves, and the interpeak latencies, showed significant increases. The amplitudes of Pa and Nb showed significant decreases. The study demonstrated a dose-related direct effect of enflurane.

This work was carried on in 1984 [60] with the addition of halothane to the study. Anaesthesia was induced with thiopentone and anaesthesia was again maintained with 70% nitrous oxide in oxygen. Halothane was given up to 2.5% and enflurane up to 5%. Linear dose-related increases were seen, with both agents "*in the latencies of waves III, V, Pa and Nb and the interpeak intervals I-V and III-V, with decreases in the amplitudes of Pa and Nb.*" When the agents were discontinued a reversal of the changes occurred in some or all of these waves. It was clear that halothane and enflurane delayed neural transmission and the effects "*approximately related to their known anaesthetic potencies*".

A depth of anaesthesia monitor has been the goal of many researchers; for volatile agents it is not a major problem as modern monitors can measure the agent in exhaled breath but it would be welcome for use with intravenous agents where the drug concentration can only be approximated. In 1986 [61] the AER was measured during anaesthesia with nitrous oxide and an infusion of Althesin. Blood concentrations of alphaxalone were measured and there were dose-related changes in latency and amplitude of waves Pa and Nb. There were no changes in the brainstem waves. This supported previous work that suggested that Althesin did not work below the superior colliculus.

In 1987 isoflurane was compared with halothane and enflurane [62]. When compared on a MAC-based basis (a measure of potency) no differences were found on the effect on the amplitude of the early cortical waves although latencies were different. The consistent dose-related effect on the amplitudes of the cortical waves implies, and they actually suggest, "*...that the AER could be a promising index of the depth of anaesthesia".*

A good depth of anaesthesia monitor has to respond not only to the anaesthetic agent (inhaled or intravenous) but also in a consistent way to surgical stimulation. In 1988 patients were studied during anaesthesia with thiopentone, nitrous oxide, halothane and pancuronium [63]. The anaesthetic concentration was held constant and baseline AER recordings were made. With surgical stimulation the amplitude of waves Nb and Pb/Pc increased. They again suggested that AER "*may, therefore, provide a useful index of depth of anaesthesia, which is the balance between the effects of surgical stimulation and anaesthetic depression on central nervous system activity*". However, they also

described "*unambiguous autonomic responses" that were not correlated with changes in the AER.*

Tunstall's isolated forearm test[viii] is a documented test for wakefulness during anaesthesia. This was used in 1989 to assess the AER as an indicator of wakefulness [64]. The concentration of nitrous oxide was reduced during anaesthesia and when Nb latency decreased below a pre-fixed threshold four of the patients (out of seven) indicated awareness. Volatile anaesthesia abolished the response, increasing the Nb latency. They considered the three wave AER pattern to be "associated with a depth of anaesthesia at which awareness occurs".

The AER was also used to assess the ability to perform a task and to remember it; this was in 1991 [55]. Subjects with headphones had to respond to a random burst of sound. They breathed either air or increasing concentrations of nitrous oxide. Amplitude, latency of the P300, and minimum reaction time all changed in a dose-dependent manner. Even at concentrations of nitrous oxide where memory of the events were absent a majority of the subjects still pressed the button (akin to a positive Tunstall test without any memory of the event). It was thought that the P300 wave could be useful as a tool for studying awareness during anaesthesia.

In 1993 they 'converted' the complicated arrays of latencies and amplitudes into one measure – the coherent frequency [65]. The coherent frequency was calculated from a Fast Fourier Transform of AERs – the fundamental frequency being very large compared with the 1st and 2nd harmonics. In brief the coherent frequency and psychological tests changes in a consistent way to 'depth of anaesthesia' and stimulation.

There is obviously an overlap between this and the following section but the keyword used for the references below was 'memory'. Interestingly they are either editorials or reviews.

An editorial is defined as an article expressing an opinion on a topical issue and a review is an attempt to summarize the current state of understanding on a topic.

Awareness/Memory

[viii] Tunstall ME. British Medical Journal 1977; 1: 1321.

The first of eight editorials/reviews was in 1986, in the BMJ [66]; "*Hearing and memory in anaesthetised patients*". It outlined the understanding of short term and long term memory, conscious awareness, unconscious awareness and unconsciousness. These were linked to the ability to recall events. It was pointed out that autonomic responses did not correlate with episodes of awareness. The questions to be asked were; '*What was the frequency of awareness?*' and '*Can depth of anaesthesia be measured?*' It was said that anaesthetic agents universally depress the cortex but only some depress brain stem activity and so the third question was '*Can the AER be used to detect blockage of the auditory pathway?*'

Five years later (1991) there was an editorial on '*Awareness and memory in anaesthetized patients*' in the BJA [67]. In a previous article by Prys-Roberts unconsciousness was described as a threshold event. Jones disagreed and considered that the onset of unconsciousness was a continuous spectrum. It included a review of learning mechanisms and the concept of "*pre-conscious processing of sensory information*"[ix]. It also described the effect of unconscious pre-conditioning (positive suggestions during anaesthesia) that helped with postoperative recovery. Evidence suggested that the affects of anaesthesia are mainly on short term memory and that cortical waves are good indicators of depth of anaesthesia.

Another BJA editorial in 1991 [68] was on '*Conscious awareness during general anaesthesia - what are we attempting to monitor?*' Tunstall's isolated forearm technique was described as the closest available to a gold standard method for comparing methods of determining depth of anaesthesia. Of the techniques being studied AER seemed the most promising – **but,** some previous work (in 1964 by Libet et al [x]) demonstrated that before conscious awareness can occur, 'neuronal adequacy' has to happen; this takes up to 500ms. However, conscious awareness occurs at about 50ms (early cortical evoked response). It is complicated – reaction times may only take 200ms, so conscious awareness not necessary for 'automatic' reactions. The time during which 'neuronal adequacy' develops needed to be investigated and so the recent work the Jones' team did with N_2O on P300 was cited [55]. The effect was to maintain reaction time but no registration of the event in memory. It was pointed out that neurophysiology was the way to get to a depth of

[ix] Dixon NF. Preconscious Processing. Chichester; John Wiley and Sons,1981

[x] Libet B et al. J of Neurophysiology 1964;27:546-578

anaesthesia monitor, not peripheral affects like oesophageal sphincter pressure.

A review article was published in 1992 [69]. Very briefly - general anaesthesia causes cerebral depression; anaesthesia can be "light" or "deep"; surgical stimulation may arouse a patient; it is difficult to detect conscious awareness; the median frequency (10Hz when conscious) should be below 5Hz to avoid a response to verbal command; the AER may be used to assess "depth of anaesthesia" but it was not yet certain which features were the most reliable.

There were another two such articles in 1994, one in the BJA [70] on '*Perception and memory during general anaesthesia*' and one in the BMJ [71], '*Memory of intraoperative events*'. The BMJ has a general readership, rather than the specialised readership of the BJA, but there was a public interest and anxiety in the matter of awareness during anaesthesia, the incidence being estimated at 1:10000. In the 1960s it was suggested that the anaesthetic technique using unsupplemented N_2O had an incidence of 0.6%[xi]. This was a general overview for the BMJ's readership.

The BJA article was in a Postgraduate Educational Issue and was therefore much more detailed. Jones estimated the incidence of awareness without pain as 4/1000 in obstetric patients and 2/1000 in non-obstetric patients. He described the use of clinical signs for assessing the risk of awareness – particularly respiratory sinus arrhythmia (RSA) as this did have a neuronal (vagal) basis from the brainstem. He stressed the importance of work by Schwender[xii] . The importance of the timing of the Nb wave determined the state of consciousness and memory. It was in this article that the coherent frequency was highlighted and it was said that if the coherent frequency was less than 10Hz and the middle latency waves were isoelectric then both consciousness and implicit memory were abolished.

If you want a real overview of the topic read this review of 1997 [72]. It discusses the structure of memory (using slightly modified nomenclature than previously – declarative (explicit) and non-declarative (implicit) memory and working memory). Jones was concerned that awareness remained a serious complication of general anaesthesia. If during an apparent adequate anaesthetic an adverse implicit memory was retained, postoperative behaviour

[xi] Hutchinson R. BJA 1960;33:463-9

[xii] Schwender D. Wachheit Während Narkose. Wiesbaden: Wissenschaftliche Verlags Abteilung Abbott GmbH, 1989, 1-136

might be altered and postoperative recovery influenced. The article includes details about use of the lower oesophageal sphincter as a measure of depth of anaesthesia, the frontalis electromyogram, RSA, the processed EEG (including BIS) and the AER (transient and steady state). The coherent frequency was the flavour of the month and it was said that consciousness was lost at 20Hz.

1998: This review covered much of the research covered before but addressed the problem stated in the title "*Is amnesia for intraoperative events good enough?*" [73]. Many drugs produce profound amnesia and so, does it matter if the patient is in pain during the procedure if they can't remember it afterwards? If abnormal emotions were to be found only after 'light' anaesthesia then increasing the depth of anaesthesia should be considered beneficial. If they occur regardless of the depth of anaesthesia then more analgesia and postoperative support should be considered. The last sentence was "*Amnesia may not be good enough but it may be the best we can achieve without further research"*.

A couple of years later, on a slightly different tack, the investigation of saccadic eye movements was reviewed. Saccadic eye movements are rapid movements by both eyes that we use routinely for scanning words and faces, and our surroundings, to build up a picture of our surrounding world [74]. The review was an evaluation of the efficacy of peak saccadic velocity as a measure of sedation. The physiology and pharmacology of eye movements was discussed and it was thought that saccadic eye movements could be used as a monitor of anaesthetic sedation. Two years following this review, in 2002, Carpenter et al. published a study on the effects of sevoflurane on saccadic eye movements [75]. The double-blind experiments involved breathing either 0.15% end-tidal sevoflurane, in oxygen, or pure oxygen. As might be expected the pure oxygen had no effect but the sevoflurane caused increased median latency of the saccadic movements. Thus it was considered that it might be possible to use these measurements to determine impairment following sedation.

In May 2005 there was a letter in the Bulletin (No. 31) of the Royal College of Anaesthetists from "*JG Jones, Formerly Professor of Anaesthesia of Cambridge University*". This was in response to a previous article on awareness by Absalom, Siegmeth and Bergmann. He was putting forward the view that if "*profound analgesia and amnesia will do*" then measuring depth of

"*unconsciousness may owe more to commercial zeal than clinical need*" [Paraphrased]. He was highlighting the reported incidence of awareness as being between 1:80,000 and 1:90,000 and that the costs of BIS monitoring was not trivial. He said that "*almost £1,000,000 would be spent to detect/prevent one case of debilitating awareness.*" The authors responded – in brief – "*there is no evidence that awareness without recall does not affect clinical outcome*" and that patients expect an anaesthetic in which there is lack of awareness.

Eight years later, in 2013, there was a similar communication [76] following a major study on awareness during anaesthesia from Oxford (Pandit et al Anaesthesia 2013; 68:343-53). This showed that awareness during anaesthesia was much less common than had been suggested. It also confirmed a similar claim made by Agarwal and Jones JG in Ghoneim's book (see above). Once again, a statement against the universal use of depth of anaesthesia monitors, the National Institute for Health and Clinical Excellence [should not] consider mandating such monitoring.

Other 'consciousness' related papers: [77-79]

Miscellany:

The need for basic sciences to the understanding and practice of everyday anaesthesia: [80]

This was an audit of the attitudes of post-fellowship (examinations) anaesthetists about Basic Sciences in the part I examination for the FRCA. Sixty five percent of the basic science syllabus was considered essential. The topics considered irrelevant were biochemistry, endocrinology, membrane theory and immunology. "*Paradoxically, there were many topics which anaesthetists regarded as essential but on which they were unable to give a tutorial*". It was suggested that the syllabus was overloaded with detail irrelevant to clinical practice.

Jones personal 'trek' through research can be seen in the Bulletin of The Royal College of Anaesthetists (No.8, July 2001); this one covers his time in Cardiff, Birmingham, work at Farnborough and the decision to go to San Diego. A second one in 2003 (Bulletin 17) deals with discoveries in America. Both are a good read. Bulletin 14 (July 2002) "Behind the scenes at the Final exam". Bulletin 52 (November 2008) "No Jekylls at Hyde Terrace" about his time in Leeds and Bulletin 84 (March 2014) "The CRC Division of Anaesthesia". All a must read, containing much hilarity.

Gareth Jones was a member of Council of the RCA and Editor of the RCA Bulletin, he was a co-editor (with Ian Hindmarch and E. Moss) of one book; Aspects of Recovery from Anaesthesia (A Wiley Medical Publication) 1987. He also wrote a chapter on pulmonary physiology in Tom Healy's (and Paul Knight's) edition of the Wylie Churchill-Davidson's text book[xiii].

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The work by Jones and his co-workers obviously falls into two main categories. Respiratory physiology was his forte and the research work reported was complex in theory and difficult to do in practice. Notable outcomes – regional anaesthesia less detrimental to postoperative oxygenation than opiate infusions, supplemental oxygen is good and not smoking 48 hours prior to surgery is also good. The work investigating 'depth of anaesthesia' was also complex and absolutely fascinating – particularly some unravelling of the problem of awareness and memory.

This is a vast body of work and the author admits to not reading a large majority of the material. However this will have given a glimpse of the research carried out in its many forms and places. I would like to thank Gareth Jones for his help with the final amendments.

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In 1977 Tony Adams was a clinical lecturer in the Nuffield department of Anaesthetics in Oxford having been an anaesthetic consultant since 1969. He became the foundation professor at Guy's Hospital in 1979 and in 1982 the Chairman of the Division of Anaesthetics of the United Medical and Dental Schools of Guy's and St Thomas's Hospitals[ii].

Equipment and measurement

His first five publications appeared in 1967 and were about equipment/ventilation and measurement; a very busy year.

It is an interesting set of publications - a paediatric ventilation system was designed with the aid of DER Fox from Cape Engineering (Warwick) [1]. This self-filling ventilator attachment delivered tidal volumes from 10 ml to 700 ml, which is a very impressive range. It worked with most ventilators, was a non-rebreathing system, and could be used for manual inflation of the lungs.

Two papers with Morgan-Hughes on electrodes for measuring pH and blood gases [2, 3], a paper describing three dry gas meters [4] and a presentation at an ARS meeting in Sheffield on rebreathing using a Magill circuit [5]. This was later published as a full paper in *Anaesthesia* [6]. The bottom line was that as long as the fresh gas flow was greater than the alveolar ventilation then rebreathing did not occur – this was just confirming what Mapleson had predicted in 1954[iii].

[i] Photograph courtesy of http://londonsurgicalskills.co.uk/The 20Tutors.htm
[ii] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916
[iii] Mapleson WW. Br.J.Anaesth.,1954;26:323

The three dry gas meters were assessed with the help of the Meter Testing Department, North Thames Gas Board, Willesden[4]. (It's interesting who you work with when starting out in research!) They concluded that "*The dry gas meter is cheap, robust, and accurate enough for measuring gas volumes in most applications*." Are they still the 'gold standard' for measuring gas volumes?

The papers with Morgan-Hughes (and Sykes) on electrodes were aimed at reducing inaccuracies in the measurements of pH and blood gases. Errors had been noted by MKS of up to 0.3 units in pH, 15mm Hg in PCO_2 and 20mm Hg in PO_2 during the use of electrode systems. It was thought that these errors could lead to incorrect clinical management.

The paper addressing problems of the oxygen electrode was about the determination of the 'blood-gas factor'; an adjustment for the fact that the output from the electrode was lower for a sample of blood than for the gas with which the blood had been equilibrated. A lot of investigators had noticed this but there wasn't a system of equilibrating the blood quickly and then transferring it directly to the electrode. Their tonometer solved this problem. It was a completely thermostatted bubble tonometer incorporating a humidifying unit. There are many factors that can influence the blood-gas factor and they admit that it "may not be of great importance in many clinical situations". However, if the result of the analysis is to be further processed to calculate shunts, for example, then the errors could be significant and their tonometer would enable quick calibration.

The second paper [3], *pH and blood-gas analysis - Methods of measurement and sources of error using electrode systems* is a 'how-to do it' type of paper, addressing all the potential problems – and there are many – read the original. At the end they 'advertise' the second installment – "*The second part of this article, dealing with the measurement of carbon dioxide tension, together with references and acknowledgements will appear in the January 1968 issue of Anaesthesia".* This paper could not be found on Medline (Jan 2014). It was found using Google: "Methods of measurement and sources of error using electrode systems. Part 2 Measurement of carbon dioxide tension and acid-base [7].

The other equipment-related subjects were...

1970 Effects of ventilation [8-11]:

i. The effects of variations of inspiratory flow waveform on cardiorespiratory function during controlled ventilation in normo-, hypo- and hypervolaemic dogs
   Four waveforms, sine, square, early peak and late peak, were used and the results were uniformly negative in that there was no significant change in cardiorespiratory function.

ii. The effects of variations in inspiratory:expiratory ratio on cardiorespiratory function during controlled ventilation in normo-, and hypo-and hypervolaemic dogs.
   Three different inspiratory: expiratory ratios (1:2, 0.5:2.5, and 2:1) were used. Changes in deadspace/tidal volume were not statistically significant and there were no significant changes in cardiac output due to changes in the I:E ratio. Different combinations of I:E ratio and volume status did cause significant changes in the arterial-alveolar PCO_2 difference, in the PCO_2 difference , arterial PO_2 and in venous admixture.

iii. The effects of variations in end-expiratory inflation pressure on cardiorespiratory function in normo-, hypo-and hypervolaemic dogs
   Cardiac output decreased less in the hypervolaemic group. But the deadspace/tidal volume ratio increased in all groups. When using a negative pressure the venous admixture increased, but did not affect the deadspace/tidal volume ratio.

iv. The effect of mechanical ventilation after open-heart surgery: Mechanical ventilation after open-heart surgery (most patients were having aortic valve surgery) “rarely causes much fall in cardiac output”. This was assessed by the small changes in arteriovenous oxygen content difference when they changed to spontaneous breathing. Some patients’ shunts increased with the onset of spontaneous breathing which led to hypoxaemia. The authors were very cautious about advocating prolonged IPPV post surgery as “technical problems associated with mechanical ventilation may result in an increased morbidity and mortality.”

1971 Models of the lung [12]... this is part of a three way discussion about the intricacies of the functioning and mathematical treatment of lung models and refers back to [8].

1975 A transportable anaesthetic apparatus [13]... this is the description of a miniature version of a Boyle's anaesthetic machine that could be attached to a patient's trolley whilst being wheeled between operative areas in the hospital. There was also an assessment of the Bain circuit for controlled ventilation [14].

1976 A scavenging system, a co-axial breathing circuit and scavenging valve, and the Bain anaesthetic system 1976 [15-17]. In the 1970s the scavenging of exhaled anaesthetic gases/vapours was a hot topic and many systems were designed, both by equipment manufacturers and individuals. A co-axial breathing circuit (The Bain system): An improved version of the Bain circuit, made by Respiratory Care Inc., incorporated a valve which allowed attachment to British anaesthetic machines. This was described and the system was further investigated during controlled ventilation. The results of the study showed that a highly predictable $PaCO_2$ could be obtained if the fresh gas flow was determined by body weight. The *"...mean $PaCO_2$ at a fresh gas inflow of 70 ml/kg/minute = 40.8 mmHg; mean $PaCO_2$ at a fresh gas inflow of 100 ml/kg/minute = 34.3 mmHg)...It is suggested that it may qualify as a universal breathing system."* They also determined that by interposing a 1 m length of corrugated 22 mm diameter anaesthetic breathing tubing between a lung ventilator delivering air and the Penlon Bain-type co-axial anaesthetic circuit air-dilution of the respired gas mixture was unlikely. A reasonably common practice.

1977 The Bain circuit [18]and a new generation of anaesthetic ventilators [19]. He described the 'new generation' as being constructed on the moving-part fluid logic principle; they were considered to be simple, inexpensive and robust with facilities for PEEP, a scavenging system and for relief of over-pressure.

1978 A laboratory study of the Nuffield lung ventilator with the injector technique [20]... using a Nuffield lung ventilator he showed that the control module was an efficient means of automatically controlling the ventilation of the lungs using an injector technique through a bronchoscope. The effects of

compliance, airway resistance and the driving flow rate through various injectors on the oxygen concentrations and tidal volume were determined. A 14 gauge injector provided seemed optimal.
There was also a paper on the hazards of excessive airway pressure and their prevention [21].

1990 An end-tidal carbon dioxide detector [22]. This was the description of a colorometric method for detecting carbon dioxide - a disposable device with a pH-sensitive chemical indicator. It was found to be a reliable, rapid and easy method for the detection of oesophageal intubation. A letter concerning false-positives with the end-tidal carbon dioxide detector was published in 1992 [23]. After ingestion of a carbonated beverage a colour change indicating correct tracheal tube placement could occur even though the endotracheal tube has actually been placed in the oesophagus. They explained that these false-positives were also found with other CO_2 detectors.

1991 Oxygen delivery systems [24]: The inhaled concentration of oxygen was measured in the oropharynx whilst the volunteers breathed through either a low flow oxygen mask or through nasal catheters. The bottom line was that both were equally effective but the nasal catheters were cheaper.

1993 Checking anaesthetic machines [25]... an editorial. "*The aims of checklists are to prevent the development of problems. Compliance with the existing guidelines leaves much to be desired. Why anaesthetists do not follow these, or some other guidelines, is difficult to understand, particularly when ample evidence exists in the literature of the folly of not doing so. It is hoped that the pictorial checklist will persuade more anaesthetists to check their equipment responsibly before each operating session."* Well said.

1994 Breathing system disconnections [26]; disconnections of various bits of breathing systems had been 'tolerated' for quite some time[iv]. Adam's publication goes into great detail; covering causes and possible remedies. Disconnections occurred so often as to be considered as routine and grudgingly accepted for easy access to the airway; they were however a cause of preventable serious injury and death. Disconnections occurred most frequently

[iv] Harrison MJ, Tomlinson PA, Mann MS. (letter) Anaesthesia 1984;39:721

at the connection of the tracheal tube to the breathing system. Separations occurred primarily at conical fittings and many specifications were obsolete because of changes in materials. The clinicians were also concerned about accidental extubation, a risk associated with tight fitting joints. Alarm misuse or devices with inadequate alarm systems were also a problem. The 'hanging bellows' anaesthesia ventilators also presented a serious hazard as the bellows still appeared to fill even in the presence of a disconnection.
Pacemaker failure [27]. This is a case report of cardiac arrest in a patient with a fixed-rate ventricular pacemaker; interference caused by activation of a nerve stimulator resulted in pacemaker failure.

1996 A new tracheal tube [28]. A new Portex tracheal tube was compared with the Oxford tube in performing simulated grade 3 difficult intubations. One of the side issues highlighted in this study was a learning effect; intubation time decreased progressively over the period of the study. Their "estimate of the learning "half-life" was 15 intubations; we conclude that 30 simulated grade 3 intubations would be a reasonable objective for trainees before handling high-risk cases."

2004 Dead space and paediatric anaesthetic equipment [29]. Dead space and paediatric anaesthetic equipment...this, another laboratory study using a model lung, showed that functional dead space with a breathing filter created too much dead space. However, a poorly fitting, leaking, facemask reduced the dead space – "*to near optimal conditions*".
About 20% of Adam's publications relate to equipment or measurement.

Ventilation
This topic, related to equipment, was investigated in relation to how it affects the cardiorespiratory system and eyes.

Firstly, effects on the cardiovascular system; the effect of the waveform [8], the inspiratory/expiratory ratio [9] and the end-expiratory inflation pressure [10]. These were followed by the effect of mechanical ventilation after open-heart surgery [11].

Secondly... effects on the eye... Normocapnic anaesthesia with trichloroethylene [30, 31], and with enflurane [32]. Measurements of intraocular pressure showed that a normocapnic anaesthetic technique using 0.4% trichloroethylene with large tidal volumes (14 ml/kg) reduced IOP by 13-

20%. So it was considered that trichloroethylene was suitable for lens extraction surgery when it was desirable to avoid halothane. Similar studies were done with halithane and enflurane.

Distantly related to ventilation is the Valsalva manoeuvre. Adams used it as a test of circulatory responses in neurosurgical patients. It was an unreliable predictor of a patient's ability to tolerate the upright or sitting position [33].

Pharmacology

In the 60s and 70s deliberate hypotension gained popularity as a method of reducing blood loss, the goal was "the dry surgical field". The combination of halothane and curare was efficacious but greater control was sought and so short acting agents were investigated...the agent de jour was sodium nitroprusside. Adams investigated this agent for its effect on myocardial contractility and haemodynamics, it was presented at the ARS meeting in Cardiff in November 1972 [34][v] and was published in full in 1974 [35].

The following year he was the author of an article on "Techniques of vascular control for deliberate hypotension during anaesthesia" in the BJA [36], this was part of a special issue in which GEH. Enderby wrote on "Some observations on the practice of deliberate hypotension", JM Leigh on The history of controlled hypotension", B. Nilsson, K. Norberg and BK Siesjo – "Biochemical events in cerebral ischaemia" (a slightly worrying juxtaposition), L Strunin - "Organ perfusion during controlled hypotension" and MJ Lindop, "Complications and morbidity of controlled hypotension".

There were a variety of other drug related papers; two of interest are those relating to intravenous 'aspirin' [37, 38]. Both compared the efficacy of morphine with lysine acetyl salicylate, both as infusions; one in a series of patients after herniorraphy and the other after thoracotomy. In the hernia patients it was determined that lysine acetyl salicylate (LAS) provided equivalent analgesia with less drowsiness, nausea and vomiting. In the

[v]Deliberate hypotension was popular; in that same journal were items about sodium nitroprusside by JAW Wildsmith et al. Br. J. Anaesth. (1973) 45 (1): 71-74 and by H Eppen, Br. J. Anaesth. (1973) 45 (1): 124 and another about trimetaphan by B Collier, Br. J. Anaesth. (1973) 45 (1): 123-124 s

thoracotomy study mean pain scores were not significantly different and LAS was not associated with any significantly greater blood loss.

In the author's experience intravenous aspirin is not commonly used, intravenous paracetamol is.

Clinical

Throughout the almost 40 years of publications, there was a wide variety of clinical observations. Amongst them are papers on preoxygenation [39], air embolism [40, 41], three-dimensional echocardiography [42], aspiration of gastric contents [43] and others.

Here are three of interest:

Acute amphetamine abuse [44]: Acute amphetamine abuse by a 22-year-old girl [sic] led to serious intracranial hypertension during a neurosurgical procedure. It was difficult to maintain adequate anaesthesia with a ventilation technique using pancuronium, N_2O/O_2 and supplements of fentanyl.

Hysteria. A cause of failure to recover after anaesthesia [45]:
A case report of a 22-year-old female *(another 22 year old — in 1979 described as a girl, now in 1991 as a female!)* who was suffering severe dental phobia and was undergoing dental conservation. She had, three years previously, had a dental appointment and had become unresponsive and hyptonic for 11 days. Following the described general anaesthetic for dental work she again, after apparent recovery from the anaesthetic drugs, remained unresponsive. Four hours later a tetanic stimulus (50 Hz for 5 seconds) was applied to the ulnar nerve, she then awoke, fully orientated in time and space.

The third paper also involved young persons [46] – an **assessment** of the ability and confidence of clinical medical students **to insert endotracheal tubes** correctly and quickly and to recognize oesophageal misplacement was evaluated. It was determined that ninety-three percent of students intubated correctly on their third attempt. It was said however that it was the ability to recognize oesophageal intubation promptly that is a life-saving skill and that this skill "*should be taught during the introductory anaesthesia programme through the use of clinical patients*." Without being pedantic, the "use" of patients sounds politically incorrect nowadays.

The remaining references are a mixed bag but they do include a selection of cardiac-surgery/anaesthesia related topics [47-50] and a selection on airway management/difficult intubation studies [51-54]. Two papers on the subject of delayed respiratory depression due to opiates (Fentanyl) reflect an interest at this time of this phenomenon. The first was based on case reports and the concept of recirculation of opiates by secretion of the opiate into the stomach and then subsequent reabsorption in the jejunum was discussed [55]. This was followed a year later by a 30 patient study where plasma concentrations of fentanyl were measured and clinical observations made [56]. Their final comment was that it was "*no longer wise to regard fentanyl as a short acting drug*" and to be careful with additional postoperative analgesics.

So what was Adams' main interest? Maybe it can be summarised by the keywords — breathing systems and equipment, cardiorespiratory physiology and cardiac anaesthesia.

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Graham Smith

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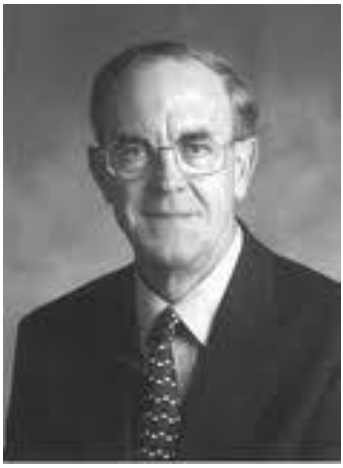

Graham Smith studied medicine as an undergraduate at Guy's Hospital Medical School, in the University of London, where an intercalated Hons BSc course in physiology lead to the early development of an interest in academic medicine[i]. After qualifying in 1966, he commenced training in anaesthesia in 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 Alistair 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 Alistair 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 PaO_2 and P_AO_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.

[i] 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 lead 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 lead 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.

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 13th 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.

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 Chmielewsk [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 ng ml^{-1} at 08.00 h and 19.5 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 anesthesia 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[ii]. 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.

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

[ii] Evans,.J M, et al, Anaesthesia, 1976, 31, 847 and Evans, J M, et al, Lancet, 1976, 1, 17.

were carried measuring catecholamines. The high-pressure gas chromatograph had obviously arrived!

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.

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[iii] position (steep head-down tilt).

[iii] Friedrich Trendelenburg was a German surgeon (1844–1924).

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 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 1991by 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_2 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_2O 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_2.

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] ($PaCO_2$ 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 Alistair 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 Alistair 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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Felicity Reynolds

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 [i]

Felicity Reynolds was a senior lecturer and head of Department at St Thomas' Hospital from 1978 until 1984 when she became Reader in pharmacology applied to anaesthesia. From 1989 – 1994 she was the Chairperson of Guy's and Thomas' Division of Anaesthetics and became professor of Obstetric anaesthesia in 1992; she retired in 1996[ii]. Information from the Obstetric Anaesthetists' Association's website has provided further details of her career. She qualified in medicine in 1960 and trained in anaesthesia in Southampton gaining her Fellowship in 1963. After a year in Uganda she spent eleven years in pharmacology. Her MD in 1971 was titled '*The systemic toxicity of local anaesthetic drugs, with special reference to bupivacaine.*' The OAA website details her many awards.

She wrote many reviews [1-12], editorials [9, 13-23] and letters [24-41], [42-50], [51-56] and [57-68]. Some of these will be addressed later.

The vast majority of her publications are about anaesthesia/ analgesia for maternal and foetal health. In 1968 her first publication, with AH Beckett, was on the topic of the measurement of bupivacaine, lignocaine and mepivacaine in blood using gas-liquid chromatography [69]. This was obviously a key paper as it provided a tool for many investigations. Concentrations as low as 0·04 μg/ml of local anaesthetic could be measured. This publication was followed a year later by '*Blood levels of bupivacaine in obstetric analgesia*' [70]. For almost thirty years this was a topic of investigation [71-76], these citations being just the tip of the iceberg.

In the second paper, with Taylor, Rouss and Beazley, a study of bupivacaine for paracervical blocks with or without epinenephrine, bupivacaine was shown to provide effective analgesia without high maternal or

[i] Photograph courtesy of FR

[ii] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916

foetal blood levels, or foetal bradycardia. However the delivery did not take place within an hour of injection. A follow up paper in 1972 [77] was not so positive. The same technique was used in patients due to undergo Caesarean section. The babies were delivered between 5 and 30 minutes after the injection. Under these conditions plasma concentrations of bupivacaine alone were double those where epinephrine was also used. However, concentrations of bupivacaine were not high in the neonates. The authors' bottom line was that because local anaesthetic toxicity was considered a possible cause of foetal bradycardia and intrauterine death, there was reasonable evidence to restrict the concentration of bupivacaine to no more than 0.25% for paracervical block in obstetrics.

Paracervical blocks went 'out of fashion' about this time and continuous epidural (extradural) blocks became a routine method of providing analgesia for delivery. Subsequent work on blood levels of bupivacaine was therefore related to epidural analgesia. Not only was the efficacy of the epidural examined but the effects on the neonate.

It is impossible to have a strict demarcation between studies but the structure of this chapter is along the lines of a) obstetric related pharmacokinetics, b) bupivacaine and fentanyl for epidurals, c) effects of agents on the foetus/neonate d) Caesarean Section and then e) maternal health. This will be followed by some miscellany.

a) Obstetric related pharmacokinetics

After the first two papers in 1968/69 we move on to 1970 [71] "*Maternal and neonatal blood concentrations of bupivacaine: a comparison with lignocaine during continuous extradural analgesia*". Lumbar extradural analgesia was carried out in 29 patients during labour. A set of patients had either bupivacaine or lignocaine for extradural analgesia. The concen-trations of the agents in maternal blood and umbilical blood were measured. The results suggested that bupivacaine was a more practical drug and had less potential toxicity.

1971 [72] "*Plasma concentrations of bupivacaine during continuous epidural analgesia in labour: the effect of adrenaline*". This was important to do because of the almost routine use of adrenaline in local anaesthetic solutions to prolong the duration of the nerve block. It was a double-blind study; the duration of action with adrenaline was not significantly increased but maternal plasma concentrations were low in both groups but lower with adrenaline at

the end of labour when higher doses of bupivacaine were used. Neonatal concentrations were always low but a marked difference between the two groups of the maternal/umbilical vein concentration ratio was inexplicable.

Also in 1971 were two studies using mepivacaine. Mepivacaine is a homologue of bupivacaine. Its metabolism and excretion were tested in male volunteers [78]. Sixteen per cent of the mepivacaine and 6% of bupivacaine was excreted unchanged. However, the blood concentrations of bupivacaine fell more rapidly initially than those of mepivacaine. The other study [79] was a comparison of the potential toxicity of bupivacaine, lignocaine and mepivacaine. The methodology was complex but the conclusion was that bupivacaine produced lower blood concentrations and mepivacaine the highest, bupivacaine was therefore considered to have the higher safety margin. [In the author's experience mepivacaine has not been seen to be used in clinical practice.]

1972: The placental transfer of bupivacaine after paracervical block has been described above in the introductory paragraphs [77]. A letter to the *Lancet* in this year pointed out some errors in an editorial on the use of vasoconstrictor agents in local-anaesthetic preparations [80].

1973: [73] Another paper on "*Maternal and foetal plasma concentrations of bupivacaine after epidural block*". In brief, the concentration of bupivacaine in those mothers who had bupivacaine and adrenaline was 0.36±0.03 μg/ml (SE), without adrenaline 0.54±0.05 μg/ml, significant at $p<0.001$. The umbilical vein concentration was also lower with adrenaline. It was suggested that without adrenaline the data showed that 5% of mothers could exhibit systemic toxicity if the bupivacaine dose exceeded 320mg.

Over the next 13 years vasoactivity was studied in detail. The method of choice was the intradermal injection of the test drugs.

1976: [74] "*The effect of concentration on vasoactivity of bupivacaine and lignocaine*". Doses of the drugs were given intradermally to volunteers and it was observed that vasoconstriction occurred at low concentrations and vasodilatation at high concentrations. Only bupivacaine 0.5%, had a longer lasting effect. The next paper was another intradermal study, this time of aptocaine [81]. Aptocaine was more active and long-lasting than lignocaine and prilocaine and appeared longer-lasting than bupivacaine. It had marked vasoconstrictor activity and it was suggested that aptocaine merited clinical trials for use in dentistry.

1978 [82] "*An intradermal study of the local anaesthetic and vascular effects of the isomers of bupivacaine*". A vasoconstrictor effect was only seen with the L(-)-bupivacaine and it had a longer duration of analgesic action than the (D+)-isomer

1981 [83] "*An intradermal study of the local anaesthetic and vascular effects of the isomers of mepivacaine*". Both were vasoconstrictor but the L isomer produced more vasodilation (and haemorrhagic change). The L isomer lasted significantly longer.

1985 [84] "*Comparison of the vasoactivity of amide and ester local anaesthetics. An intradermal study*". The two types of local anaesthetic were tested for their vasoactivity, the ester-linked local anaesthetics, procaine and amethocaine and the amide-linked - cinchocaine, lignocaine, mepiva-caine and prilocaine. The ester-linked agents produced vasodilatation, mepivacaine (amide) caused vasoconstriction but the other three amides had more variable effects.

1988 [75] "*Effect of adrenaline on extradural anaesthesia and plasma bupivacaine concentrations during caesarean section*". In a randomised study, patients having elective CS received either 0.5% bupivacaine with or without adrenaline. The plain group needed more additional analgesia and plasma bupivacaine concentrations were higher. Did bupivacaine concentrations remain higher in the extradural space with adrenaline [Author]? In the emergency CS group there were no significant differences. It was concluded that "*... extradural adrenaline does not usefully reduce systemic absorption of 0.5% bupivacaine, but may improve its efficacy in extradural anaesthesia for elective Caesarean section*."

1988: [85] "*H2 antagonists and bupivacaine clearance*". H2 receptor antagonists, cimetidine and ranitidine, were given to women undergoing elective Caesarean section under epidural anaesthesia. No significant difference was found between the control, cimetidine and ranitidine groups. Neither did the H2 receptor antagonists alter other pharmacokinetic parameters.

1989: [86] "*Effect of time and adrenaline on the feto-maternal distribution of bupivacaine*". This was a study of 80 women, half for elective and half for emergency CS. They were allocated to receive either plain bupivacaine or bupivacaine with adrenaline. The concentrations of bupivacaine in maternal veins, umbilical vein and artery were not affected by adrenaline, but were correlated with the first dose to delivery interval. Foetal accumulation of

bupivacaine did not occur beyond a first dose to delivery interval of 30-40 minutes.

1992 [76] "*Plasma total and free concentrations of bupivacaine and lignocaine in mother and fetus following epidural administration, singly or together*". Forty six women for elective CS were given various combinations of bupivacaine, adrenaline and lignocaine. Protein binding occurred more in the mother than the baby. Plasma concentrations were considered to be below toxic levels; adrenaline did not reduce the maximum levels of free bupivacaine in the mother but did appear to increase foetal uptake of bupivacaine.

2000 [87] "*Chemical stability of bupivacaine, lidocaine and epinephrine in pH-adjusted solutions*". In some centres epinephrine and sodium bicarbonate may be premixed with local anaesthetic solutions in order to facilitate the quality of epidural anaesthesia for emergency Caesarean sections. The study was to assess the stability of such a pre-mixed solution. The alkalinised solutions reduced the epinephrine concentrations significantly over 24 hours but bupivacaine and lidocaine concentrations were unaffected. The authors did not recommend the practice.

The unique aspect of obstetric pharmacokinetics is the placenta and the transfer of drugs across its membranes; not easy to study in patients. From 1984 to 1992 a series of studies were carried out on the placental transfer of drugs in the rabbit, bupivacaine, lignocaine, pethidine and anticonvulsants.

In 1984 doe rabbits were given an intravenous infusion of pethidine, lignocaine, bupivacaine and antipyrine concurrently and the umbilical 'blood' flow rate was varied [88]. Concentrations of the drugs in maternal plasma and umbilical effluent were measured. The results showed the same pattern as is observed in humans. It was determined that placental clearance of drugs increased with flow rate, the transfer rate was reduced by maternal protein binding and was flow-dependent at low flows and permeability-dependent at high flows for the less lipid-soluble compounds.

In a very similar study reported in 1985 [89] the flow rate and protein content of the placental perfusate were varied. The clearance of unbound antipyrine was unchanged with perfusate protein, the 20-30% protein bound lignocaine and pethidine clearance increased slightly and bupivacaine (80% bound) increased 'markedly', but was one-tenth to one-fifth that of the other drugs. From this work it was concluded that the foetal dose would "*be greatest in healthy babies with good placental blood flows and high plasma proteins*". However, bupivacaine did have the lowest transfer rate.

In 1989 Laishley, Carson, and Reynolds wrote two papers on the effect of adrenaline on the distribution and transfer of bupivacaine to the rabbit foetus [90, 91]. Adrenaline may influence transplacental distribution of drugs by decreasing uterine blood flow. In this study it was associated with higher concentrations of bupivacaine in the placenta but there was no other significant effect on foetal bupivacaine concentrations. In the other complex study it was concluded that neither adrenaline nor minor alterations in maternal placental flow affect placental transfer of bupivacaine.

In 1992 [92] in another rabbit pharmacokinetic study pethidine was eliminated more rapidly than bupivacaine and the elimination rates were ranked as maternal plasma > placenta > amniotic fluid > foetal brain > foetal plasma. Analysis showed that the "... *maternal plasma half-lives for pethidine and bupivacaine were 1.0 and 2.0 h, and placental half-lives 1.9 and 2.5 h, respectively. The apparent fetal plasma half-life of pethidine was 9.9 h while there was apparently no net elimination of bupivacaine from fetal plasma*". These latter half-lives are significantly long.

Anticonvulsants are used in obstetric practice for the management of eclampsia. In 1976 Reynolds demonstrated that salivary drug concentra-tions correlated with the amount of free phenytoin in plasma and that it was a convenient way to monitor patients [93]. There are eight further communications about anticonvulsant monitoring [63, 94-100]. Of im-portance is the kinetics of phenytoin during pregnancy and the puerperium. They measured phenytoin levels in 11 pregnant epileptics and in non-pregnant women. The saliva:plasma ratio increased to maximal values at delivery and returned to non-pregnant values within 2-8 weeks. Dose increments had to be changed to maintain therapeutic levels and after delivery doses were reduced to avoid toxicity.

The other drug added to the mix was fentanyl – a combination of fentanyl and bupivacaine in epidurals became commonplace. The word combination 'epidural fentanyl' first appeared in 1981 (Google Ngram viewer). The pharmacokinetics was examined [101, 102] but there were many more clinically orientated studies (see below) – of pain in labour [103-107], of the effect on the neonate and of the effect on gastric emptying.

In the 1983 study [101] patients in labour were given either epidural or intramuscular fentanyl, together with an epidural test dose of bupivacaine. Pain relief was quicker and more effective for those given epidural fentanyl; they couldn't rule out a systemic effect by the fentanyl. A study in rabbits three

years later [102] showed that the transfer of fentanyl from the maternal circulation across the placenta was intermediate between that of pethidine and bupivacaine. The clearance of unbound fentanyl was higher than the others and was not affected by them.

These pharmacokinetic studies entailed an enormous amount of both clinical and laboratory work.

b) Clinical use of bupivacaine and fentanyl for epidurals

1n 1982 (one year after the Ngram's detection of the phrase 'epidural fentanyl) a study of the effect of extradural fentanyl was published [103]. This was a double-blind trial in the first stage of labour where either fentanyl or saline was mixed with the test dose of extradural bupivacaine. Within one hour additional bupivacaine was required in about ¼ of patients in the fentanyl group and in about ¾ of patients in the saline group; a significant finding. There were no serious side-effects although some patients in the fentanyl group had mild itching.

Further work in 1985 [104] reinforced the efficacy of extradural fentanyl and that the presence of fentanyl in the systemic circulation makes a negligible contribution to analgesia; similarly with perineal pain in labour (1989) [105]. A comparison of epidural fentanyl and sufentanil was carried out in 1993; it showed very little difference [106].

Motor blockade limiting the movement and expulsive efforts of the mother can be a clinical problem and was investigated in 1995 [107]. Women in labour were given either epidural plain bupivacaine (0.125%) or 0.0625% bupivacaine containing 2.5 mcg/ml fentanyl. Those patients having the lower dose bupivacaine took longer to full cervical dilation. In this study fentanyl did not reduce the incidence of perineal pain. More women had motor blockade after 0.125% bupivacaine; however, satisfaction with epidural analgesia was similar in both groups. The following year the relationship between motor blockade and spontaneous delivery rates were addressed [108]. A motor block was less common in the fentanyl/low-dose-bupivacaine combination group but this did not produce an increase in spontaneous deliveries. This scenario was re-addressed seven years later producing a similar bottom-line – there was no increase in normal delivery rate with the low dose, reduced motor blockade, drug combination [109].

c) Effects on the foetus/neonate

1984: [40] A letter to *Anesthesia and Analgesia* about neonatal neurobehavioral responses after epidural anaesthesia destroys the conclusions reached by Kileff ME et al. that 2% lidocaine was a suitable substitute for bupivacaine. Reynolds "*... emphasize[s] that 0.5% bupivacaine correctly placed in the epidural space in a dose of 2 mg/kg or that less is outstandingly safe and unlikely to produce central nervous, or still less, cardiovascular, side effects*."

Ten years later in another letter she addressed "*The effects of maternal epidural anaesthesia on neonatal behaviour during the first month*" again [59]. She destroys the methodology of another set of researchers – Sepkoski et al. Their approach certainly seems crude.

Moving on - in 1995 the effect of maternal hypoxaemia (the influence of analgesia) on neonatal outcome was studied [110]. In retrospect, 51 parturients were recorded as having either "*... no analgesia, pethidine with intermittent Entonox, extradural bupivacaine* ... "*or a bupivacaine/fentanyl mixture.* The lowest incidence of hypoxaemia, SpO2 < 94%, was in the extradural bupivacaine group. No correlation was found between maternal hypoxaemia and measures of neonatal outcome.

Again, in 1997 [111] it was found that the dose of fentanyl used in combined spinal/epidural analgesia appeared to have a negligible effect on neonatal condition.

Another study in 1998 reinforced this [112], an erratum appears in Anesthesiology 1998 Dec;89(6):1615, it is a correction to a table.

In 2002 Reynolds et al. assessed the effect of epidural versus systemic labour analgesia on foetal/neonatal acid-base status at birth by a systematic review of trials, from five countries, comparing epidural with systemic opioid analgesia [113]. They included both published and unpublished results. Epidural analgesia was associated with improved acid-base status even though epidural analgesia can cause maternal hypo-tension, fever, longer labour and more instrumental deliveries. They suggested that these potentially adverse factors outweighed the benefits of neonatal acid-base status.

In 2005 another meta-analysis indicated that the foetal welfare following Caesarean Section was uninfluenced by the type of neuraxial block or general anaesthesia [114].

In 2010 a review of "*The effects of maternal labour analgesia on the foetus*" was published [11]. In brief, it said that foetal metabolic acidosis is caused by labour pain and stress, and systemic opioids cause foetal/ neonatal

depression and affect breast feeding, doing little to help the stress and pain. Meta-analysis of studies showed that the Apgar score[iii] is better after epidural analgesia and neonatal acid-base balance is improved. A similar review came out in 2011 [12], " *Labour analgesia and the baby: good news is no news*." Reynolds again said that "*Widespread ignorance of the benefit to the newborn of neuraxial labour analgesia in the UK among non-anaesthetists needs to be combated*" and that the only promising alternative was remifentanil.

d) Caesarean Section (CS)

The CS rate has increased over the last few decades in western obstetric practice. The anaesthetic technique used changing from routine general anaesthesia to neuraxial block – spinal or epidural analgesia, or a combination of both.

Posture during labour, and Caesarean Section, has been a point of discussion for many. The supine pregnant woman at term runs the risk of reduced blood pressure because of inferior vena cava compression. Reynolds investigated the effect of posture post-epidural insertion on the effect of the neuraxial block 1983 [115]. The patients were either turned to the right lateral position or the supine position. The only significant difference was that motor block occurred more in the lateral position ($p<0.02$). The circulatory disadvantage of the supine position was still considered a significant drawback.

Another aspect of the technique used was studied in 1984 [116]; there were many confounding factors but it was suggested that there was a small subset of patients where epidurals may have increased the likelihood of instrumental delivery.

Changing from epidural analgesia to anaesthesia for CS can be required at any time and in 1991 [117] the effect of 20 ml of 2% lignocaine + 1/200,000 adrenaline was assessed; it produced quick onset blocks that provided adequate anaesthesia for surgery in all patients.

Postoperative CS pain was also addressed – either epidural diamorphine or intramuscular papavaretum (Omnopon) [118]. Epidural diamorphine was best and patients liked the pain free mobility. In '93 a similar study [119], comparing on-demand epidural diamorphine with intravenous

[iii] A scoring system for the assessment of babies immediately after birth devised by Virginia Apgar

patient-controlled diamorphine the magnitude of side effects were similar in the two groups and overall satisfaction was high, but the patient-controlled analgesia group scored higher.

It has always been easy to get a higher epidural block but to get a lower one can be a problem. In a '94 study epidurals were either inserted with the patient either in a 25° head up position or in the horizontal position. The head up position resulted in more sacral sensory blocks [120]. Later, in 2001, the effect of the supine wedged position, compared with the lateral position, on spread of spinal anaesthesia was investigated [121]. There was no significant difference between the groups in fall of blood pressure or requirement for a vasopressor but the spinal block in supine patients rose more rapidly and was more predictable.

No procedure is without its hazards; general anaesthesia - airway problems, local anaesthetic techniques - nerve damage. Dural puncture is another potential complication which, with an epidural needle, can lead to loss of CSF and result in a debilitating headache. It is commonly associated with the novice 'epiduralist' but it can happen even when done by the experienced practitioner. An audit of 257 (191 responded) obstetric units in the UK determined the rate of accidental dural punctures in the years 1991-1995. The highest rates were in smaller units (3.6%) and lowest (0.19%) in a larger high throughput unit. The rate using saline to detect the epidural space was 0.69%, air 1.11% ($P<0.001$) [122].

Finding the dural space is obviously of prime importance and the intricacy of how this is achieved comes down to both intellectual and practical skills. A letter in 2005 discusses the various ways of holding the needle and syringe (Son of Doughty technique) [33]! An accompanying letter by JA Wildsmith reports a conversation with Andrew Doughty where he replies that 'his' so-called technique is based on "*You are ashamed of yourself if you puncture the dura"*.

Both spinal anaesthesia and epidural anaesthesia have advantages; combined spinal-epidural anaesthesia entered the scene in the 1990s; a more complex procedure and the possibility of increased risk of damage. In 2000 an audit of 222 departments reported a total of 56 patients with prolonged neurological problems [123]. Eighteen problems were attributed to the regional technique but there was no obvious difference in incidence between the techniques. The numbers were too small.

Seven cases of neurological damage were reported a year later and were of significant clinical effect [124]; the needles were thought to be inserted at the L2-3 interspace. The tip of the lower end of the spinal cord is usually at the L1-2 level but the surface anatomy makes it difficult to be absolutely sure of the level used. Because of this, it was recommended that anaesthetists should not insert the needle above L3.

In the last three decades informed consent, about risks associated with procedures, has become mandatory. A survey in 1995 [125] of 523 members of the Obstetric Anaesthetists' Association showed that the majority (63%) would recommend regional anaesthesia, 5% general anaesthesia and the remainder would allow the patient, after full discussion, to decide. This was followed by a letter [42], stating that doctors in Britain and Ireland tailor information on risks to what the mother needs and wants to know; "... *it should not be regarded as paternalistic ….*" A General Medical Council directive about full disclosure, with the danger of scaring patients, needed to be revisited.

In 2005 Wee, Brown and Reynolds wrote an article on the anaesthetics aspects of the National Institute for Clinical Excellence (NICE) report guidelines for CS [126]. It is a comprehensive practical guide.

We will now have a brief diversion and go to Malawi. An audit of 8070 caesarean sections; 94% were emergencies and eighty five women died, almost two thirds died postoperatively on the wards. Amongst many major causes of morbidity/mortality were the lack of adequate anaesthetic training and the use of general as opposed to spinal anaesthesia. The perinatal mortality was 11.2% in the first 72 hours. It was recommended that improved training in anaesthetics, wider use of spinal anaesthesia and improved postoperative care might reduce mortality [127].

e) Maternal health

Reynolds interests were not only for the drugs, the techniques and the baby. Maternal health was always important.

1993 [128]: The factors associated with long term backache after childbirth were studied. Thirty percent reported long term backache; 15% said they had had no previous back pain. Younger women, unmarried women, those reporting other antenatal symptoms and those who had epidural analgesia reported more. …"*There were no differences in the nature of the backache between those who had or had not received epidural analgesia in labour*."

1995: "*Maternal sequelae of childbirth*", an editorial in the British Journal of Anaesthesia, amongst many other things, addressed the problem of blaming all sequelae on the epidural [9]. This was a common theme.

The next, in 1996, [10] was a case- report-based review discussing the problem of sciatic nerve palsy after delivery by Caesarean section. To determine the cause was very important as the cause might be unrelated to the epidural and it was suggested that opioids in epidurals reduced the amount of local anaesthetic used and therefore the nerve block/motor block was reduced. Weakness or flaccidity could then be seen as caused by something other than the epidural and nurses should be educated to recognise the importance of this sign of neuropathic problems.

Backache was a perennial topic of dispute and in 1996 [129], in a prospective randomised study, the relationship between motor block and long term backache was reported. The conclusion was that … "*There were no significant differences between the treatment groups in the incidence of postnatal backache overall or of new backache or any symptoms after childbirth.*" Backache prior to, or during, pregnancy were associated with backache after childbirth.

Other reports in 1997, 1998, 1998 [18, 41, 48] were supplements to this work. Backache usually resolves soon after delivery and epidurals were often blamed. Similar backaches were reported by 40% of mothers who did not have regional anaesthesia and the backache may be related to hormonal changes, ligamentous laxity and the expulsive forces associated with labour. There was some criticism of the work of others[iv] in this article which stimulated another letter, Reynolds reinforced her view. A correction was published later but it is a typographical error rather than scientific.

[45] "*Epidurals and backache: again?*" 2002: It is worthwhile reading this in full. She takes the BMJ to task because "*... it took more persuading* [the BMJ] *to publish prospective studies with negative results, and it flatly refused to publish one showing epidurals were good for babies—good news is no news."*

[iv] MacArthur C, Lewis M, Knox. BMJ 1997;315:679

Letters

Felicity Reynolds was a multi-letter writer. To the journal *Anaesthesia* she wrote 16 [24-39] , to the BMJ nine [42-50], to the BJA, *The Lancet* and the *International Journal of Obstetric Anesthesia* four each [51-54] [63-66] [57, 60-62]. There were other letters to other journals.

Not all the publications regarding aspects of obstetric anaesthesia have been noted but there is a sufficient amount to show the depth of her investigations.

And now for something completely different, but not completely non-obstetric:

Upper oesophageal sphincter pressure

One of the major risks of anaesthesia, at any time but particularly during pregnancy, is the risk of regurgitated stomach contents entering the airway and flooding the lungs. With RG Vanner as the lead author there are three papers in 1992 on the subject of upper oesophageal sphincter pressure – the effect of cricoid pressure, inhalational induction and intravenous induction of anaesthesia [130-132]. Cricoid pressure is the application of force to the cricoid cartilage in such a way as to occlude the lumen of the oesophagus and therefore impede the passive flow of gastric contents into the pharynx.

Firstly the effect of cricoid pressure: The upper oesophageal sphincter pressure was measured in 24 patients and the median pressure prior to anaesthesia was 38 mmHg; after anaesthesia and paralysis it was 6 mmHg. Using a special yoke providing cricoid pressure with a force of 40 N the sphincter pressure increased to above 38 mmHg. However, the application of cricoid pressure by operating department assistants (anaesthetic technicians/assistant) achieved this level in only half of the patients. Laryngoscopy made little difference.

Inhalational induction: (not common in adults but can be necessary). It was shown that halothane did not have a dose-related effect on sphincter pressure and, unlike thiopentone or suxamethonium, main-tained a degree of upper oesophageal sphincter tone. Three patients in the study of 30 did have sphincter pressures of less than 10 mmHg and therefore gastric reflux into the pharynx was a possibility.

Intravenous Induction: It was shown that midazolam and thiopentone both reduced the sphincter pressure to low levels and that the rapid fall with thiopentone was such that it occurred before loss of consciousness. From this it

was suggested that cricoid pressure should be applied very early during the induction process. Ketamine had no effect on the oesophageal sphincter pressure.

The bottom line was, apply cricoid pressure early and the anaesthetic technicians have to apply more pressure to achieve oesophageal occlusion.

Odds and ends

A title that caught my attention was "*A book that informed my practice*". It turned out to be a book review [133] – "*What a Blessing She Had Chloroform*" *by Donald Caton, Yale University Press, 1999*. A small quotation from the review "*Historically, women have demanded analgesia in labor when the medical profession approached it with caution, yet now that it has become vastly safer, many women reject it as dangerous.*"

 [v]

So true, with the passage of time safety has increased a thousand fold but expectations that nothing should go wrong have increased in a similar manner.

Another eye-catcher "*Logic in the safe practice of spinal anaesthesia*" [20]. The word logic is not often seen alongside a clinical technique. She is once again addressing the danger of using the L2-3 interspace – it's too high – the risk of conus damage too great and identifying the space by surface land-marks prone to inaccuracy.

Finally, again in 2008, "*Obstetric problems? Blame the epidural!*" [134].
I don't need to comment; she has said it all!

[v]Photograph courtesy of Obstetric Anaesthetists Association. http://www.oaa-anaes.ac.uk/content.asp?ContentID=39

Books

Anesthesia and the Fetus by Yehuda Ginosar, Felicity Reynolds, Stephen H. Halpern and Carl Weiner (Nov 20, 2012) Wiley Blackwell

Pain Relief in Labour by Felicity Reynolds, Robin Russell, Jackie Porter and Mark Scrutton (Oct 22, 1997) BMJ

Regional Analgesia in Obstetrics: A Millennium Update by Felicity Reynolds (Jun 23, 2000) Springer

Epidural and Spinal Blockade in Obstetrics by Felicity Reynolds (Nov 1990) Obstetric Anaesthetists' Association

Effects on the Baby of Maternal Analgesia & Anaesthesia by Reynolds and Felicity Reynolds (Jan 1993)

Lectures

She has delivered numerous eponymous lectures, has had many honorary awards and became the founding editor (now editor emeritus) of the International Journal of Obstetric Anesthesia. See the http://www.oaa-anaes.ac.uk/ website for details.

A truly productive academic life!

An anecdote

At a research meeting I attended the opening remark by the chairman was "Good morning gentlemen". Felicity Reynolds was the first speaker. "Good morning ladies" she said. The audience laughed. The chairman was bemused.

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JAW (Tony) Wildsmith

MD FRCA FRCPEd FRCSEd FDSRCSEng

JAWW was a consultant and senior lecturer in Edinburgh from 1977 until 1995 when he became professor in an independent department of anaesthesia in Dundee[i]. JAW Wildsmith is internationally known for his work on the use of local anaesthetics.


[ii]

His published work has been categorised as follows, some will inevitably overlap:

Comparisons of local anaesthetic agents, opiates and sedatives
Treatises on particular agents
Spinal, epidural and neuraxial anaesthesia
including baricity and spread of local anaesthetics
Axillary, brachial and other nerve blocks
Toxicity and allergy
Dental anaesthesia
Sedation

And then there were other subjects.

Carotid surgery
Intensive care
History

His publication history covers 39 years and started in 1972[iii]. The first four years, 1972-1975 inclusive, covered the subjects of serum

[i] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916
[ii] Supplied by JAWW
[iii] Italicised text in quotes are either directly from JAWW or from publications

cholinesterase, pregnancy and suxamethonium [1], results of resuscitation from cardiac arrest [2], the effect of posture on the measurement of oesophageal pressure [3], haemodynamic effects of sodium nitroprusside [4] and sustained handgrip in patients with diabetes mellitus [5]. Another 1974 paper was on the subject of maintaining pulmonary nitrogenation during anaesthesia [6] and followed by blood-gas changes during nitroprusside induced hypotension [7, 8]. This was a staggering amount of research for a 'trainee', and of a very varied nature.

"My career in anaesthesia, including the academic component, was off to a prompt start for two reasons: first, I decided the specialty I wanted to pursue while still an undergraduate so I went straight to the RIE [Royal Infirmary of Edinburgh] *department from my house jobs; second, having passed the primary fellowship examination at the earliest opportunity, it was pointed out to me that I could not sit the final for another two years so that I had a year (assuming that it took a year to prepare – which it did!) to broaden my experience in some way. My earliest mentor, AHB Masson, suggested research training as an option, and that appealed so what followed is as much his fault as anyone's! The University of Edinburgh was kind enough to award me a research fellowship for this training, but I quickly realised that the best way to learn about any method is to use it, this perhaps influencing the wide range of the research topics..." "A key study was one on the haemodynamic effects of induced hypotension with sodium nitroprusside, this involving collaboration with both DB Scott (who had the necessary equipment) and WR MacRae (who used the agent clinically). Both became long-term supporters, and SNP was the subject of my MD thesis."*

"A year on I became a registrar, widening my clinical experience and passing the final fellowship examination ASAP. While gaining this wider experience I came to the view that regional anaesthesia was a much underused solution to many anaesthetic problems, a decision not without longer term significance! A full time clinical training post did not allow much research opportunity, but a lectureship in anaesthesia, specifically dental anaesthesia, became available. Contact with dentists sparked my interest in the early history of anaesthesia, and obviously the post offered time for research. During this period BG Covino, an American friend and regional anaesthesia collaborator of DB Scott, spent some time in Edinburgh, and between the three of us we devised a study of systemic concentrations of local anaesthetics after brachial plexus block, my first venture into regional anaesthetic research."

He became a consultant in 1977 and his first local anaesthetic related publication was in 1977.

"Appointed a consultant, I felt that it was high time someone was examining the routine use of spinal anaesthesia; then a little used technique in the UK. It was used in Edinburgh, but only for very major abdominal surgery and primarily for its hypotensive effect. Scott and Covino encouraged me not only to use the technique clinically, but also to study it, and study it as if it were an entirely new method. So began a series of studies which really only ended when I retired. I continued with studies of induced hypotension to complete my MD, but my interest in regional anaesthesia matters widened and came to dominate. A visit to the USA for the 1979 ASRA annual meeting made me feel that the Old World needed a similar society, and I helped to organise ESRA's first meeting in Edinburgh in 1982. Contact there with two people had particularly significant consequences. First, I met EN Armitage and, finding a like mind; I had a ready and complementary collaborator for Principles and Practice of Regional Anaesthesia, now in its fourth edition. The second person was Covino, by then chairman of department at the Brigham & Women's Hospital in Boston where he had started to build an unequalled regional anaesthetic research group. An invitation to join it was a huge opportunity, allowing me to extend my expertise into laboratory work, pursue my interest in the history of anaesthesia, meet many more like minded individuals than were then to be found in the UK, and show that I could work successfully in another setting."

"Back in Edinburgh AA Spence had followed JD Robertson as professor and, taking a much more pro-active approach to research, was very supportive of my adding laboratory studies to the existing programme of clinical research. My return coincided with a reorganisation of surgical services and I elected to join the newly formed (the first such in the UK) specialist vascular surgical unit which included the very research orientated surgeon, CV Ruckley. The other consultant anaesthetist in the unit was JH McClure with whom I had already collaborated on regional anaesthetic studies, and we settled down to a very productive period of clinical development and research activity. Scott had, for many years, obtained funding for a clinical research fellowship from the Swedish company Astra, and I was able to continue this after he retired, a major focus being studies of their new drug, ropivacaine, on which I wrote the Expert Clinical Report for the European Regulatory process. During this period I served as an elected member (1986-90)

of Council of the Association of Anaesthetists. Chairing the Education & Research committee gave me experience of organising postgraduate meetings and assessing research funding applications from others. Being asked to lead a working party on high dependency care stemmed very much from my involvement with vascular surgery."

One of the 'easier', if one should ever consider clinical research easy, forms of research is the comparative study. Over 25 years there were 13 studies; JAWW was, as the leader, the raiser of the money (grants), advisor to the primary author and editor/sub-editor of the paper.

Comparisons of local anaesthetic agents, opiates and sedatives

1983 midazolam vs. diazepam [29]. Sedation during spinal anesthesia with midazolam and diazepam was studied. The average doses required were 12 mg and 27 mg respectively for surgery of about one hour duration. Drowsiness post-operation was greater with diazepam and amnesia was greater after midazolam.

1991 ropivacaine vs. Bupivacaine (extradural) [67]. Various concentrations of ropivacaine (new at the time) were compared with 0.5 or 0.75% bupivacaine. There was little difference but ropivacaine had a slower onset, shorter duration and less intense motor block when compared with the same concentration of bupivacaine.

1991 extradural bupivacaine + diamorphine (either i.v. or extradural) [68]. Diamorphine 0.5 mg/hour was given either extradurally with bupivacaine 0.125% or as a supplement intravenously. The intravenous diamorphine group had inadequate analgesia but the patients in the extradural group had better analgesia but were drowsier.

1994 ropivacaine vs. bupivacaine [86], efficacy and kinetics. Three sets of patients received 1% ropivacaine, 0.5% ropivacaine or 0.5% bupivacaine extradurally. The groups' blocks were similar; however, the motor block using 0.5% ropivacaine was less dense and wore off more quickly than with bupivacaine. Cardiovascular changes were similar in all three groups. Ropivacaine's half life was shorter and the peak plasma concentration higher than bupivacaine.

1996 comparison of spinal needles [95]. A model involving fresh human lumbar dura was used to determine fluid leakage after puncture with

Sprotte, Atraucan, Quincke and Whitacre spinal needles. Unsurprisingly finer-gauge needles and pencil-point designs produce less leakage than traditional bevelled designs. The new Atraucan was considered worthy of further study.

1998 continuous vs. intermittent bupivacaine extradural anaesthesia [106]. Patients received either intermittent 0.375% bupivacaine hourly or as a constant infusion. The intermittent technique provided a more reliable sensory block.

2000 economic comparison of regional vs. general anaesthesia [120]. This was a complex audit. A computer database provided information about all aspects of the procedures. Regional anaesthetics took five minutes longer but recovery time was 10 minutes shorter. Anaesthetic times were five minutes longer for regional. A local field block with sedation *"was considerably cheaper than a general anaesthetic technique*", £67 vs. £102.

2001 ropivacaine vs. bupivacaine sciatic nerve block [128]. There was no difference.

2003 ropivacaine in glucose 5% vs. bupivacaine in glucose 8% [142]. Ropivacaine provided reliable spinal anaesthesia. The effect was shorter and was accompanied by less hypotension.

2005 plain vs. hyperbaric solutions of ropivacaine [149]. The onset time for hyperbaric ropivacaine was shorter than the plain solution; it spread higher and lasted much longer. The block was more reliable in the hyperbaric group and subsequent mobilisation was quicker.

2008 hyperbaric racemic bupivacaine vs. levobupivacaine vs. ropivacaine [168]. There were no differences in onset time, spread or time to maximum spread. However recovery from ropivacaine was quicker.

The study that is most intriguing to the author is the 1996 spinal needle study.

Treatises on particular agents:

Lignocaine [27, 66]

A letter confirming an acute allergy to amide local anaesthetics: [27].

The effects of two plasma concentrations of lignocaine on performance were assessed using a battery of performance tests [66]. Subjects were aware of the effects and it was suggested that patient's reports of effects might be useful.

Prilocaine [47, 61, 65, 100, 102]

Two of these papers involved the use of prilocaine for intravenous anaesthesia. Intravenous regional anaesthesia was performed using either prilocaine with saline or sodium bicarbonate. The bicarbonate increased the speed of onset and full recovery was slower [61]. In the second paper fentanyl was added - there was no change in the speed of onset but the incidence of nausea increased after tourniquet release; so no benefit [65].

Bupivacaine [18, 20, 23, 39, 45, 52, 54, 62, 67, 68, 77, 78, 86, 98, 106, 127-129, 142, 168, 176] Two have been selected -

A letter: Intravenous regional anaesthesia using bupivacaine has a higher risk of systemic toxicity than prilocaine and so prilocaine must remain the drug of choice [18].

The second letter reiterates the dangers of leakage past a tourniquet and subsequent toxicity – there is also a short piece of doggerel in response to a spelling error. I leave you to discover it! [23]

Ropivacaine [67, 86, 126-128, 131, 142, 149, 153, 155, 168, 176]

Hypersensitivity due to ropivacaine [153]: Another letter about hypersensitivity, this time in response to a report by two Japanese clinicians who were treating pain associated with herpes zoster with epidural ropivacaine over a two week period. The discussion was around whether it was hyper-sensitivity or toxicity or due to plasticisers in the containers.

Intermittent vs. continuous administration of epidural ropivacaine with fentanyl for analgesia during labour [155]. In this randomized, double-blind study of primigravid patients it was determined that the intermittent group, which required fewer additional injections, had better analgesia and therefore the technique represented a superior mode of analgesia.

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Neuraxial anaesthesia

KEYWORDS	
Spinal anaesthesia	[19, 26, 28, 29, 32, 39, 49, 56, 58, 60, 69, 77, 87, 97, 101, 109, 123, 124, 129, 131, 142, 149, 152, 158, 165, 168, 173, 175, 176]
Extradural/Epidural anaesthesia:	[42, 45, 54-56, 67, 68, 78, 79, 83, 84, 86, 90, 98, 106, 109, 112, 123, 126, 135, 153, 155-157, 162, 171, 178]
'Neuraxial'	[167, 172, 177]

Spinal anaesthesia:
The first 'spinal' was given by either Corning, in 1885, or Bier in 1898.

It is fascinating to see certain subjects of study remaining popular over decades. The subject of baricity of solutions for spinal anaesthesia in JAWW's work covers three [19, 26, 28, 32, 149, 168].

Baricity - Glucose, and Posture, and spread of local anaesthetics:

Baricity - Glucose [26, 62, 88, 129, 131, 142]

1982. 1, 2 and 4 ml of isobaric amethocaine was injected at two rates of injection (1 ml per 5 s and per 10 s). Larger volumes had little effect on the height of the blockade and the extent of block was less predictable [26].

1990. The spread of intrathecal injections of bupivacaine containing glucose was measured. The greatest spread was with 8% glucose compared with 0.83% and 0.33%. The lowest concentration produced greater variability in spread, 8% the fastest onset of sensory block [62].

In 1994 another similar study produced similar results [88]. In 2001, however, it was shown that "... the *spread of spinal solutions in the pregnant patient at term is not dependent on density*". CSF density decreases during pregnancy and this study used glucose 8 mg ml^{-1} and glucose 80 mg ml^{-1}. Speed of onset and patient satisfaction were similar [129]. Also in 2001, it was the turn of ropivacaine plus glucose [131]. The onset of sensory block was

significantly faster with the higher concentration of glucose but the maximum cephalad spread was similar. There was no significant difference between the motor block and the time to complete regression. The final publication in this group [142] was a comparison of ropivacaine with bupivacaine, both with glucose). Ropivacaine took, on average, three minutes longer to get a sensory block to T10; the average duration of sensory was twice as long with bupivacaine and they required more treatment for hypotension. As might be expected the ropivacaine patients mobilized sooner. An erratum was published late as the points on a graph were incorrectly labelled.

Posture [3, 24, 35]

1981. Effects of posture on the spread of isobaric and hyperbaric amethocaine [24]. The spread of isobaric solutions was not affected by gravity; the spread of hyperbaric solutions was affected but posture was ineffectual in controlling the spread. Dose affected duration rather than spread.

1983. Barbotage and spinal anaesthesia [32]. This was a letter in response to an article by PJ Nightingale. Wildsmith was stressing that volume does not affect spread and that 'plain' 0.5% is mildly hypobaric at body temperature.

[35] This publication in 1985 was a letter in disagreement about what was stated in a paper by I F Russell[iv]. Russell was of the view that "... *the spread of analgesia against the effects of gravity implies that postural changes independent of gravity are responsible for the extension of analgesia.*"

2002. Head-up tilt and subarachnoid block [140]. "*I have concerns.*" Another letter in response to another article, this time by Loke et al.[v]. JAWW questioned the idea that although the difference of the height of the block by one dermatome may have been statistically significant, was it clinically significant? It was similar with the changes in blood pressure. The response of Loke et al. maintained their viewpoint and they said that "*the possible impact of the collective data should not be dismissed so lightly*".

Predicting the spread of local anaesthetics in the spinal canal was another theme. [26, 58, 77].

Predicting the spread of spinal anaesthesia [58] 1989.

[iv] Anaesthesia 1984; 39: 865-7

[v] Loke et al. Anaesthesia 2002; 57: 169–72

An editorial: This was an overview of the problem of predicting block height with special reference to a research paper in the journal. He discussed the hypothesis that low lumbar injection of local anaesthetic goes into a "*lumbar CSF collection*" and that this "buffers" the spread. This hypothesis was supported by other previous work[vi].

Prediction of the spread of repeated spinal anaesthesia with bupivacaine [77]1992. Another letter: This time it was about a paper by Tuominen et al.[vii]. They reported a study of patients having repeat spinal anaesthetics and said that "*Individual anatomical properties*" affect spread more than expected which suggested to JAWW that baricity was said to be "*relatively unimportant*" and he argued against this. There was a slight barb in the tail of the authors' response – "*We do appreciate the vast literature on regional anaesthesia ... However, we are also prepared to accept new opinions...*".

Spinal anaesthesia was conventionally a single shot technique. However this was to change [69, 87].

A study of 20 patients using a 24g catheter – two patients required a general anaesthetic; one because of inadequate spread of local anaesthetic and the other because of kinking of the catheter preventing a second dose being given [69].

And…

The management of blood pressure: A review article on the topic of prevention and management of hypotension (due to central neural blockade) was published in 1993 [80]. In 2000, [124], a letter about the use of vasopressor vs. the use of fluids – arguments on both sides. The second, another letter, about the complex clinical scenario of management of hypotension, that resulted in a myocardial infarction, in a young patient; strongly argued positions presented. [175]

And…

[High] segmental spinal for cholecystectomy [158, 165]. The need for a laparoscopic cholecystectomy under regional anaesthesia was because of the patient's severe chronic pulmonary disease. The needle was inserted at the 10th

[vi] Foelschow et al. Regional Anaesthesia 1982;7:79
[vii] Tuominen M et al. Br J Anaesth 1992;68:136-8

thoracic interspace and bupivacaine and sufentanil was injected into the CSF, an epidural catheter was also inserted; the resulting block was between T3 and L2. Ephedrine and fluid were given and the circulation was stable following initial hypotension [158]. Following this case report a formal study was carried out where 20 patients had high spinals for laparoscopic surgery. None had to be converted to general anaesthesia. However, it was stressed that spinal anaesthesia above the level at which the spinal cord terminated has to be done with extra care [165].

Extradural/Epidural anaesthesia:

Epidural abscess [84, 90, 156]

The first is an editorial, the second also – about the risk of epidural abscess formation. Causal factors include poor asepsis, direct contamination from nearby bacteria, haematogenous bacteria and the presence of an epidural catheter. It is quite critical of the clinical practice described in an accompanying paper[viii] in which patients with infections had epidurals. However, at least the clinicians did not use the technique in patients on steroids and the blocks were at lumbar level – steroid therapy and thoracic blocks being other risk factors. Carson and JAWW made the point that "no risk is acceptable unless there is very clear benefit.

The third is a review article of 144 references.

Haematoma [79, 112, 162]

The second publication is one of two letters in the same journal – the Wildsmith team were obviously keen letter writers. They were commenting on the use of anticoagulants during epidural anaesthesia [ix]. The sort of dose they would recommend was in the range of 3–5000 units. A much higher dose was considered "*incautious*". Continuing the epidural into the second post-op day may also have hidden the diagnosis. Skilton and Justice strongly defended their position. The third publication is a similar situation seven years later, this time with the use of other agents with anticoagulant effects.

[viii] Jakobsen KB et al. Br J Anaesth 1995;75:536-540

[ix] Skilton & Justice. Anaesthesia 1998; 53: 691–701

Other complications [56, 78, 104, 172]

The first report was a case report: a spinal anaesthetic, following a failed epidural, with 1.6 ml of 0.5% heavy bupivacaine produced a sensory blockade to T2. Because of dyspnoea and distress general anaesthesia was necessary; intravenous ephedrine and fluids were given in response to severe hypotension. Eventually a healthy infant was delivered Caesarean section.

The third – an editorial on accidental intravenous injection of local anaesthetic when doing epidurals – an avoidable event

The fourth publication was the report of an audit carried out on behalf of The Royal College of Anaesthetists. A national audit over two weeks was carried out to determine the rate of all major complications. Symptoms lasting for more than six months were defined as permanent. The census produced a denominator of over 700,000 central neuraxial blocks. There were eighty-four major complications; "*Two-thirds of initially disabling injuries resolved fully*." The incidence of permanent injury was estimated 'pessimistically' as 4.2 (2.9-6.1) per 100,000 and 'optimistically' at 2.0 (1.1- 3.3).

Who might benefit from, or be harmed by, epidural anaesthesia and analgesia? [171]

This is obviously a crucial question. Although complications from the use of spinal/epidural blocks are rare they can be devastating and the risks have to be compatible with the benefits. This was another letter in response to a previous editorial and subsequent discussion. There is a lot of detail in the letter about the pros and cons and relative risks of epidural analgesia/anaesthesia. From the UK point of view it was thought that "*elderly patients undergoing emergency laparotomy are a group with the potential to gain most from epidural anaesthesia*" and it was suggested that if a cost benefit analysis of a suitable sized population was undertaken, the elderly might be the clinical population to study.

'Neuraxial':

The first two papers with this keyword were audits and the third about risk definition [167, 172, 177].

The first was the report of a two-week national audit of the use of neuraxial block. It involved 304 National Health Service hospitals, 90% of the responses were judged to be 'accurate'. The number of procedures reported was 27,533 equivalent to about 700,000 major blocks annually. These data

were to be used as denominators for the calculation of the incidences of complications.

The second determined the complication rate. There were 84 major complications and 52 met the inclusion criteria (see above). The data were considered reassuring central neural blockade had a low incidence of major complications.

The third publication was in response to a letter by Kirkham, Payne and Cooper[x]. Their audit results suggested that the incidences of complications were considered "*clinically useful by 64% of the anaesthetists surveyed and 38% had altered the statistics provided to patients in line with the audit findings*". However, further clarification was required. Cook, Counsell and Wildsmith responded by explaining the necessity for the complex nature of the presentation of the numbers. They also thought that the major problem was the dissemination of the message despite a multi-pronged effort. They thought that they had "*... done quite well compared with others (well, we would wouldn't we!)*". They did agree that a national survey of the impact of the audit was necessary and said that it was underway.

Brachial plexus block:

Axillary: "Axillary brachial plexus block: method of choice?" A review article [63].

Interscalene: Plasma concentrations of local anaesthetics after interscalene brachial plexus block [9].

Three methods: Plasma prilocaine concentrations after three techniques of brachial plexus blockade [47]. Axillary, perivascular subclavian and interscalene blocks were done with 35 ml of 1.5% prilocaine. There was no significant difference in the prilocaine concentrations.

Prolonged block: This was a supraclavicular brachial plexus block with 0.42% bupivacaine. The motor and sensory block lasted 26 hours but there was full recovery at 40 hours [52].

Nerve blocks: [40, 43, 59, 71, 146]

These papers are mainly about nerve conduction, the first about peripheral nerves and local anaesthetic drugs in a symposium on local

[x] Kirkham L, Payne S and Cooper R. British Journal of Anaesthesia 104 (5): 656–66 (2010)

anaesthesia in the Br. J. Anaesth. The second about differential nerve blockade: esters v. amides and the influence of pKa and the third about structure-activity relationships in differential nerve block at high and low frequency stimulation.

Differential nerve blockade is about how pharmacological agents affect the different types of nerve fibres, A B and C. This last study was in rabbits to determine their sensitivity to local anaesthetics. The A fibres were the most sensitive and the C fibres the least. Low pKa and high lipid solubility was best at blocking A fibres; high pKa and low solubility, C fibres. Local anaesthetics of the amide type have a high pKa and low lipid solubility and can produce differential C fibre block.

Only the last reference discusses a technique for a nerve block; in this case a sciatic nerve block

Toxicity of local anaesthetic agents:

This subject is addressed in three letters -

2000 [125]– natural killer cells are a type of cytotoxic lymphocyte that are known to kill tumour cells. This letter is in response to a research paper that suggested that local anaesthetics, by abolishing pain, abolished this activity. This could lead to wound infection and tumour spread. JAWW said that "*The battle to improve the quality of surgical pain relief is difficult enough without such unqualified statements.*" And "*Perhaps they [the authors] would revert to using no anaesthesia or analgesia at all!*" I like the following quotation –"*Observation is easy. Considering the relevance of the observation is altogether more difficult.*"

2006 [159]– local anaesthetic toxicity – prevention or cure.

This was all about the use of lipid for the management of bupivacaine cardiotoxicity and is a response to an editorial. There were some concerns about the "*somewhat over-enthusiastic advocacy*" of untested proposals. The main concern was the emphasis on 'curing' rather than 'preventing' the problem'. Care with dosage was of great importance.

2008 [170]– local anaesthetic toxicity – this is a further treatise on the management of local anaesthetic toxicity and JAWW emphasises first principles in the management of patient resuscitation before specific therapy. Responses by the Honorary Secretary, AAGBI, on behalf of the AAGBI Working Party on

Local Anaesthetic Toxicity ("*How refreshing to have to reply to a letter of support*!") and the author of the original case report are printed.

Allergy and anaphylaxis:

The first is a case report (1981). A patient with allergy to lignocaine was challenged with an intradermal injection of bupivacaine. This resulted in a systemic reaction. There was a decrease in complement C4 suggesting an immunological cause. It was reported as the first of documented by concurrent immunological changes [21].

1993: A letter disputing the cause of an anaphylactoid reaction [83].

1997: Another article disputing causes of allergic reactions during local anaesthetic procedures – this time the description of a reaction that may have been caused by latex rather than the local anaesthetic. Careful assessment is necessary [98].

In 1998 [110] there was a review of 25 patients diagnosed as having local anaesthetic allergy, the review included intradermal testing. Only one patient was genuinely allergic to an amide local anaesthetic. Reactions should be carefully assessed.

2009: JAWW was part of a team that had produced a set of guidelines from the Association of Anaesthetists of Great Britain and Ireland about Suspected Anaphylactic Reactions Associated with Anaesthesia [174]. In brief – morbidity may be reduced if diagnosis is early; initial management should use the ABC approach with the use of adrenaline given as early as possible. The patient should be investigated further - tryptase levels may help and specialist (allergy) referral advised. All cases should be reported to the national databases and all departments should identify a consultant anaesthetist with specific responsibility for anaphylaxis.

Local anaesthesia is associated with dentistry – no 1940s child could forget. Between 1998 and 2005 there were a series of communications on the subject of dental anaesthesia – however this was about sedation and general anaesthesia for dental surgery. Death in the dental chair was a catastrophe and had been highlighted and addressed since 1969, and was addressed again [108]. Conscious dental sedation in 1999 [118] (in the British Dental Journal) and a comment about another sedation technique in 2005 [154], and another comment in the European Journal of Anaesthesiology in 2002 [137]. The 2000 paper was an audit of paediatric dental anaesthesia in Scotland [121].

There were other publications on sedation: 1983 (midazolam vs. diazepam during spinal anaesthesia [29]), 2007 (an update on dental sedation [163]), 2008 (monitoring during sedation [169]) and 2011 (radiologists and sedation – do they follow their guidelines? [180]).

Before leaving the subject of local anaesthesia completely we must deal with the subject of carotid endarterectomy. The last publication first; "*Regional anaesthesia for carotid endarterectomy*" [117]. This is a letter about the difficulties associated with studies comparing general anaesthesia with local anaesthesia. JAWW's preference was for a combined approach – GA +LA. All the other papers were about carotid blood flow:

1991 Transcranial Doppler monitoring [70]
1992 Carotid endarterectomy: future perspectives [76]
1993 Middle cerebral artery blood flow after clamp release [81]
1993 Hyperaemic response after carotid endarterectomy [82]
1994 Extracranial Doppler ultrasonographic flowmeter [89]
1995 Cerebral oximetry [92]

Something different: Induced hypotension

Induced hypotension was a major facet of anaesthesia in the 1970s, the most non-specific, and less controllable, technique being a combination of curare and halothane; ganglion blocking agents were also used.

Nitroprusside became the short acting agent of choice that could be titrated to effect.

It was noted in this first paper [4] that there were "... *marked falls in arterial pressure, peripheral resistance and central venous pressure. Heart rate and cardiac output rose while stroke volume was little changed. All parameters returned quickly to control values on discontinuation of sodium nitroprusside administration.*" The perfect agent?

In 1975 the blood gas changes during induced hypotension with nitroprusside was presented at the Manchester ARS meeting [8], later published in full [7]. PaO_2 declined but returned to the previous values on cessation of the nitroprusside infusion. It was thought to be due to altered ventilation/perfusion ratios.

Nitroprusside did have the potential for toxic side effects and so a technique that could reduce the dosage was a good idea – the combination with trimetaphan was studied and seen to be satisfactory [17, 22, 33].

A letter in 1979 discusses the safe administration of nitroprusside – amongst other details it reminded the writer that during profound hypotension the cerebral function monitor that we used was the rate and rhythm of respiration – so no IPPV [16][xi].

In 1987 a study was performed in a further attempt to reduce doses by giving beta-blockers preoperatively – it was a step too far – too profound bradycardia – not recommended [41].

"*In 1994 my interest was sought in the new academic department of anaesthesia being established in Dundee. All three of our children were by then at University so the timing was good and the opportunity to widen my activities appealing. The members of the Dundee department were regional anaesthesia enthusiasts, but there were other research opportunities as well. Collaboration with the pharmacologist, JJ Lambert, on mechanisms of anaesthetic action was anticipated, but studies with a nursing lecturer, JE Rattray, on quality of life after intensive care, were not! A revision of the undergraduate medical curriculum allowed me to introduce the concept of Acute Care, duties in the Dental Hospital brought me back into contact with that specialty, and a pan-Scotland collaboration between academic departments led to the development of a simulation centre."*

Intensive care: [107, 147, 150, 164]
Janice Rattray and Marie Johnston were, apart from JAWW, common authors for these four papers that spanned a decade, 1998-2007. The first was about the quality of life of survivors of intensive care. According to this study quality of life did not change much (assessed retrospectively). It appeared that the main factors in quality of life were people, family and leisure activities.

In 2004 they attempted to assess the perceptions of patients' experiences in intensive care by the development of an intensive care experience (ICE) questionnaire. It was determined that there were four components: **'awareness of surroundings'**, **'frightening experiences'**, **'recall of experience'** and **'satisfaction with care'**. A year later another publication,

[xi] This monitoring concept shocked trainees in the 1990s and 2000s!

this time on predictors of emotional outcome. It would appear that the severity of the illness was not a factor but there were both objective (*length of stay*) and subjective (*patient characteristics*) factors that helped..

In 2007 a randomised study of post-discharge care was planned (multi-centre with a big team) to assess the emotional impact of the intensive care experience and to see what benefit a special set of clinic attendances might have on the final physical and psychological health of the patient. A pragmatic, randomised, controlled trial of intensive care follow up programmes in improving longer-term outcomes from critical illness[xii] .

Now to something more retrospective - History:

"On retirement (2007) I decided that someone who is 'history' should only pursue that aspect of his former discipline! I have been (2008-10) President of the History of Anaesthesia Society and am currently (2012-15) Honorary Archivist to the Royal College of Anaesthetists."

JAWW was interested in this retrospective aspect of anaesthesia from early on.

1984: Local anaesthetic drugs--an historical perspective [34]
1985: Horace Wells [36]
1985: Origins of local anaesthesia [37]
1987/88: A British footnote to the life of Horace Wells [44, 51]
1997: So just who was James "Young" Simpson? [99]
1999: Donald Bruce Scott, M.D., F.R.C.A., F.R.D.P.Ed. 1925-1998 [115]

2001: **No sceptic me, but the long day's task is not yet done**: the 2002 Gaston Labat lecture [138]. This was an eponymous lecture given to the American Society of Regional Anesthesia. As he says "... *the purposes of an eponymous lecture, an obvious one is to honor the subject*[xiii]*. A secondary purpose might be to honor the lecturer, and Dr. Winnie's introduction was most kind.* "

[xii] BMJ 2009;339:b3723: Not effective or cost effective in improving patients' quality of life.

[xiii] Gaston Labat 1876-1934

The following is included as it gives more of a personal view of JAWW:

"*I certainly wish that my parents had been alive to hear it. My father would have enjoyed it immensely, and my mother, bless her, would have believed every word. However, my wife, Fay, did no more than tolerate his kind words. If I do not keep my ego under control, she will certainly do it for me, so I must deny that this lecture is to honor me*."

There are 231 publications listed below; 65 are letters/comments (his "Disgusted of Dundee" publications[xiv]), 16 are editorials, 9 classified as historical articles and 14 as reviews. This still leaves 132 study reports.

The summaries above are an incomplete description of all the work undertaken but it will have given the reader an insight into the nature of the breadth of the studies. Here are some publications that may be of interest to the reader – you may wish to chase them for yourself [10, 15, 25, 75, 94, 101, 114, 133, 136, 141, 151, 161]!

JAW (Tony) Wildsmith has influenced the safety of local anaesthesia, addressed the problems associated with sedation for procedures and had forays into cerebral blood flow, intensive care and history; a significant body of work.

Addendum:
Searches of computer databases are never foolproof and many of JAWW's publications were missed. Tony Wildsmith has been kind enough to add further detail to the above description of his work. The main purpose of this book has been to highlight themes in an academic's life's work and to try and shed some light on the personality behind the publications and so his own words will help.

The text below is that supplied by JAW himself. A few paragraphs have been included above.

[xiv] Personal communication!

“My career can be divided into five, very different phases:

1. 1970-1977 - Training in Edinburgh;
2. 1977-1984 - Early consultant posts in Edinburgh, ending with a year in Boston;
3. 1984-1995 - Consultant to the Edinburgh vascular surgery unit;
4. 1995-2007 - Foundation Professor in Dundee; and
5. 2007-???? - Retirement.

Each phase had its influence on my clinical and academic interests, with the latter developing early through the combination of two factors. First, I was attracted to anaesthesia as a career while an undergraduate, and a four-week ‘elective’ attachment to the RIE department confirmed my choice of specialty. Thus, I went straight from pre-registration house jobs to training in anaesthesia and was off to a prompt start. Second, having passed the primary fellowship examination at the earliest opportunity, I was advised that I could not sit the final for another two years so that I had a year (assuming that it took a year to prepare) to broaden my experience in some way. My earliest mentor, AHB Masson, suggested research training as one option; it appealed, so what followed is as much his fault as anyone’s! The University of Edinburgh was kind enough to award me a research fellowship for this training, but I quickly realised that the best way to learn about any method is to use it, this resulting in the range of topics of my early publications[4, 6]. A key study was on the haemodynamic effects of induced hypotension with sodium nitroprusside, this involving collaboration with DB Scott (who had the necessary equipment) and WR MacRae (who used the agent clinically)[4]. They both joined Alastair Masson as long-term supporters, and SNP was the subject of my MD thesis. Also important during that year was spending one day per week in theatre with HWC Griffiths, pioneer of induced hypotension with high spinal anaesthesia.

A year later I became a registrar, widening my clinical experience and passing the final fellowship at the earliest opportunity. While gaining this wider experience I came to the view that regional anaesthesia was a much-underused solution to many anaesthetic problems, a decision not without longer-term significance! A full time clinical training post did not allow much research opportunity, but a lectureship (specifically in dental anaesthesia) became available in the University Department (head, Prof JD Robertson) in 1975. Contact with dentists triggered my interest in the history of anaesthesia, and

the post offered time for more research [7, 11, 13] as well as teaching dental students. During this period BG Covino, an American friend and collaborator of Bruce Scott, spent some time in Edinburgh, and they encouraged me in my enthusiasm for Alon Winnie's interscalene brachial plexus technique. Importantly, they also suggested using it for research so we devised a study of systemic concentrations of local anaesthetics after brachial plexus block, my first venture into regional anaesthetic research [9].

At that time spinal anaesthesia was a technique used rarely in the UK, and even in Edinburgh considered only for very major abdominal surgery, primarily for its hypotensive effect. However, discussions with Griffiths, Scott and others (especially those who had done locums in Sweden where spinals were used widely) had convinced me that the reasons for its unpopularity in the UK (fear of neurological sequelae) were invalid. Thus, appointment as a consultant in 1977 gave me the clinical freedom to pursue this view, with Scott and Covino again being supportive. They not only encouraged me to use spinal anaesthesia clinically, but also to study it as if it were an entirely new method, and so began a series of publications[19, 24, 26, 29] which ended only once I had retired [172]. I continued the research into induced hypotension to complete my MD [17, 22, 33, 47], and later co-edited one of the very few texts on this subject [Induced Hypotension. MacRae WR, Wildsmith JAW (Eds). Amsterdam: Elsevier, 1991]. However, my interest in regional anaesthesia came to dominate, and widened to include early forays into alleged local anaesthetic allergy [21, 27] and the correct technique for intravenous regional anaesthesia [18], both becoming long term interests. Enthused to encourage others to use regional anaesthesia by the example seen at the 1979 ASRA meeting I instigated an annual local anaesthesia demonstration course in Edinburgh in 1980, and from that realized that a British book on regional anaesthesia was needed to guide its use in British conditions.

In 1982 I helped organize ESRA's original meeting [Regional Anaesthesia: 1884-1984. Scott DB, McClure JH, Wildsmith JAW (Eds). Sodertalje: ICM AB, 1984 (Proceedings of the first ESRA meeting)] also in Edinburgh, and this involvement had three important personal consequences. First, I undertook my first historical research project for a presentation at the meeting [185]. Second, in meeting EN Armitage I found both a like mind and a complementary collaborator for a British book on regional anaesthesia; Principles and Practice

of Regional Anaesthesia is now in its fourth edition. Third, Ben Covino was at the meeting and, by then, chairman of department at the Brigham & Women's Hospital in Boston where he had built an unequalled regional anaesthetic research group. He invited me to join him for a while, a huge opportunity which allowed me to extend my experience into laboratory work, learn much about the pharmacology of local anaesthetic drugs, pursue my interest in the history of anaesthesia, meet many more like minded individuals than were then to be found in the UK, and show that I could work successfully in another setting. The year was very enjoyable, immediately productive [36, 38, 39, 41, 43, 186-188] and had a long-lasting significance for my career. Several subsequent publications stemmed directly from the knowledge or expertise which I acquired during that year [37, 40, 41, 191] and the background influence lasted much longer.

Back in Edinburgh, AA Spence had succeeded JD Robertson as professor and, taking a much more pro-active approach to research, was very supportive, with expanded departmental accommodation allowing for a wider range of studies, including the technique I had used in Boston [61, 66]. My return also coincided with reorganisation of surgical services, and I elected to join the newly formed specialist vascular surgical unit, the first such in the UK. Staff included the research-orientated surgeon, CV Ruckley, and another consultant anaesthetist, JH McClure, with whom I had worked previously. The group settled down to a productive period of vascular related research [75, 76, 82, 86, 88, 92, 121], edited a book on postoperative analgesia [Conduction Blockade for Postoperative Analgesia] and published other related reviews [41, 42, 53, 69, 87]. The regional block studies also continued [39, 45, 46, 48, 106, 189, 190, 196], many supported by funding (originally started by Scott) from Astra for a clinical research fellowship, and a programme of epidural (single-use for surgery [54, 59] and continuous for post-operative analgesia [87, 157] research was added, leading to work on the new drug, ropivacaine [see below]. As an elected member (1986-90) of Council of the Association of Anaesthetists I chaired two groups: first, the Education & Research committee, organising larger postgraduate meetings and assessing research funding applications; and second, a working party on high dependency care, this stemming very much from my involvement with vascular surgery [Chairman of the Working Party: The High Dependency Unit - Acute Care in the Future. London: Association of Anaesthetists of Great Britain and Ireland, 1991]

In 1994 my interest was sought in the new academic department being established in Dundee. All three of our children were by then at University so the timing was good and the opportunity to widen my activities appealing. The members of the Dundee department were regional anaesthesia enthusiasts, but there were other research opportunities as well. Collaboration with the pharmacologist, JJ Lambert [148, 204, 205], on mechanisms of general anaesthesia was anticipated, but studies with a nursing lecturer, JE Rattray (she just appeared one day and asked for my help!), and a psychologist, M Johnston, on quality of life after intensive care, were not [107, 147, 150, 164]. My regional block research took longer to re-establish, but I was busy enough starting a new department, developing other research, and co-editing *Anaesthesia for Vascular Surgery*! When regional studies restarted they were along similar lines [128], but with some new topics and a focus on ropivacaine [67, 86, 126-128, 131, 142, 149, 153, 155, 168, 176], again with generous support from (by then) AstraZeneca. This collaboration with industry also involved writing the original Expert Clinical Report (and some later addenda) on ropivacaine for the European Regulatory process [Clinical Expert Report: Ropivacaine, 1995; Addendum to Clinical Expert Report: Ropivacaine, 1998 and Clinical Documentation on Ropivacaine: Intra-articular Administration, 2001]. As noted above, I had become interested in local anaesthetic allergy in Edinburgh, and this continued and broadened in Dundee [98, 110, 122], primarily by investigating (and usually refuting the diagnosis in) individual patients, but also contributing to a national guideline [174]. An unusual collaboration was advising some Dutch colleagues who were using intrathecal injection in the thoracic region in high risk patients [158, 165].

Research activity predominates in academic circles today, but I have always felt that the teaching of others is vital, if only to encourage the next generation of researchers. Most of my first-named co-authors were trainees and I hope that they gained more from the experience than just CV development! My duties in Dundee included contributions to the undergraduate medical and dental curricula, [*Dental local anaesthesia: Course workbook* and "Skilled task teaching and assessment" [210] and at postgraduate level I was involved in the establishment of the Scottish Computerized Simulation Centre ['A beginning, not an end' A Report from the Royal College of Anaesthetists Simulation Working Group, 2005]. The emphasis placed on research (especially grant

income) during the 1990s led many to take a very pessimistic view of the future for academic anaesthesia, a view which I found disappointing. Indeed, one of the reasons I took the chair in Dundee was to show that the future is not totally bleak, but it is challenging, and the specialty has to recognize and meet that challenge. Thus, while a member of Council (1998-2008) of the Royal College of Anaesthetists and chair of its Academic Committee, I persuaded the College to undertake a review of academic anaesthesia, [A National Strategy for Academic Anaesthesia. London: Royal College of Anaesthetists, 2005 and "A national strategy for academic anaesthesia: an overview" [224] this resulting in the formation of the National Institute of Academic Anaesthesia to provide a focus for all those interested in the issues.

My other major area of activity as a member of College Council started at my very first meeting when I disagreed with a motion relating to the teaching of dental students, this resulting in an immediate invitation to chair the dental anaesthesia committee! General anaesthesia was still used in many 'high street' dental practices in the UK then, but not always to modern standards in spite of previous attempts to improve matters, so a report making recommendations agreed by all the relevant organisations (i.e. dental and anaesthetic) was produced [Standards & Guidelines for General Anaesthesia for Dentistry. London: Royal College of Anaesthetists, 1999]. Unfortunately, individuals do not always adhere to published standards, with those in working with general anaesthesia in dentistry seemingly prone to ignore such advice [121]. Almost inevitably, disasters (usually the death of a healthy young child) continued to occur, and these attracted increasing media attention until the Department of Health decreed that general anaesthesia should be restricted to the 'hospital' setting. Only techniques of 'conscious sedation' were to be used in dental practices, a sensible recommendation in itself, but these methods are used widely across medicine, as well as dentistry and are not without their own risks if not used correctly (too often they aren't). Thus I chaired another group, formed under the auspices of the Academy of Medical Royal Colleges, to look at these technique in all settings [Implementing and Ensuring Safe Sedation Practice for Healthcare Procedures in Adults. London: U.K. Academy of Medical Royal Colleges, 2001], and was involved in the production of a number of related publications [8. Conscious sedation in termination of pregnancy: Report of the Department of Health Expert Group. London: Department of Health, 2002, 10. Guidelines for Conscious Sedation in the Provision of Dental

Care. National Dental Advisory Committee. London: Department of Health, 2003, 12. Standards for Conscious Sedation in Dentistry: Alternative Techniques. Joint Working Group, Faculties of Dental Surgery & General Dental Practice, RCSEng and Royal College of Anaesthetists, 2007 and "Sedation in a radiology department - do radiologists follow their own guidelines?" [180].

From my earliest involvement in regional anaesthesia research I was keen to promote the view that the techniques used should be both safe and effective. That was the specific reason for the study of systemic concentrations of local anaesthetics produced by the very large dose needed (in the pre-ultrasound era) for brachial plexus block, and the insistence on an exact technique for IVRA mentioned earlier. When regional anaesthesia was used rarely in the UK, those of us prepared to do so recognised that there were colleagues prepared to cry 'foul' if something went wrong so we were very aware of complications and how to avoid them. As the benefits became known and usage increased, knowledge of complications perhaps lagged behind, yet the introduction of anti-thrombotic therapy into surgical practice added another risk factor, particularly for central neuraxial blocks. There are perhaps too many to reference specifically here, but a large proportion of my editorials and review papers address the issues surrounding complications, but some examples are worth highlighting [60, 73, 80, 138, 156]. I also feel that persuading those who produced the earliest authoritative UK guideline on antithrombotic therapy that they should include 'anaesthetic' issues was important [Prophylaxis of Venous Thromboembolism. Edinburgh: Scottish Intercollegiate Guideline Network, 2002]

My final contribution in this area was to persuade the Royal College of Anaesthetists to devote one of its national audits to assessment of the exact scale of the problem after central neuraxial blocks in the UK [Major Neuraxial Complications of Central Nerve Block in the United Kingdom: The 3rd National Audit Project of the Royal College of Anaesthetists. London: Royal College of Anaesthetists, 2009, [225], However, these were not the end of written contributions on this subject; against my better judgement (I believe that retired clinicians should stop speaking about their former interests) I was persuaded to give a presentation to a College meeting (and write an editorial), essentially on the relative indications for postoperative epidural analgesia [227]. My strictures did stir up a member of the audience to object, and I am

glad to be out of it now, but I will never accept that performing an epidural on an anaesthetized yet healthy child was an appropriate technique for analgesia after laparoscopic surgery. That the child was rendered paraplegic does, sadly, rather prove my point.

After my year in Boston I had little time for researching the history of anaesthesia, but a number of subsequent publications were based on my existing knowledge -

> [History and development of local anaesthesia, The history and development of induced hypotension, Recognition from Britain: The Horace Wells Testimonial Fund, History of Pain Relief in Childbirth, Memorabilia of Wells and Morton in New England: The Relics of Injustice and So just who was James 'Young' Simpson?]

As retirement approached, and my other activities lessened or were assumed by others (see below), I had time once again to go searching ancient publications for forgotten people and events, with the focus on local anaesthetic drugs and those who use them -

> [So just who was James 'Young' Simpson?, British Pioneers of Regional Anaesthesia, Lidocaine: a more complicated story than simple chemistry suggests [226] Some (mostly Scottish) local anaesthetic heroes [228], European Society of Regional Anaesthesia and Pain Medicine (1982 2012): Thirty years strong [229], From cocaine to lidocaine: great progress with a tragic ending [231]].

Such historical activity continues, and for the last three years I have been Honorary Archivist to the College in London, with the launch of a biographical project on our early fellows (of the then Faculty of Anaesthetists) due later this year.

In the above I have focused on publications related to my major interests, and named my significant mentors and collaborators. I have made reference to encouraging trainees, and they are mostly the first named authors in many of my papers, with me last as leader of the research group, not as head of department! The joy of that role is bringing others up to the status of independent workers, and I am delighted to have supervised the higher degrees of Janice Rattray (quality of life after intensive care), Cameron Weir (now the

primary anaesthetic collaborator with Jerry Lambert) and Graeme MacLeod (a growing authority in regional anaesthesia). My successor is a pharmacologist, but at least there is still a department (not the case everywhere in the UK), with Cameron, Graeme and Paul Fettes (who took on supervision of the undergraduate teaching) as integral parts of it.

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Rajinder K Mirakhur

MD PhD FRCA

R K Mirakhur worked with Professor John Dundee and Dr RS Clarke (Reader in Anaesthetics) in Belfast. He was appointed senior lecturer in 1990 and to a personal chair in 1996[i]. He is well known for his work on drugs that work at the neuromuscular junction. The neuromuscular junction is the point at which the South American 'arrow poison' curare works, and changed anaesthetic practice for ever. Curare competes with acetyl choline (ACh) at the junction between the motor nerve and the muscle. ACh facilitates the electrical impulse from the nerve to the muscle that causes a muscle to contract – curare blocks this and causes paralysis which makes surgery easier and means that anaesthesia can be 'lighter'.

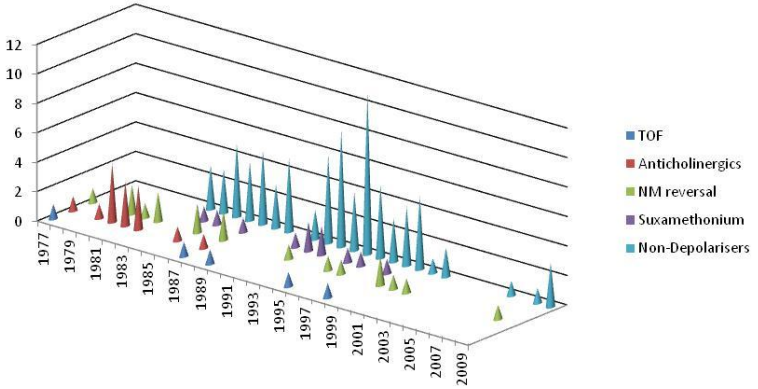
The following drugs cause paralysis – suxamethonium (depolariser) and the rest (non-depolarisers) pancuronium, vecuronium, atracurium, doxacurium, mivacurium, pipecuronium, rapacuronium and rocuronium.

The following are antidotes to non-depolarisers – neostigmine and edrophonium (the author has never seen this used in clinical practice, nor pyridostigmine), and now sugammadex. Atropine and glycopyrrolate prevent bradycardia and salivation secondary to neostigmine.

Mirakhur studied all these drugs, and more, and the technique used for studying the degree of neuromuscular blockade is the electrical stimulation of the nerve and the assessment of either the electrical effect on the muscle (EMG) or the physical movement of the muscle. The most commonly used patterns of electrical stimulation are the 'so-called' Train-Of-Four (TOF) or a tetanic stimulus. The former is a series of four electrical shocks which

[i] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916

produces different patterns of muscle contraction, the greater the degree of paralysis the larger the difference between the 1st and the 4th muscle twitch, the T1-T4 ratio. A tetanic stimulus is a continuous series of electrical shock that cause a continuous muscle contraction.



This represents the number of papers published each year for the five different categories. 1987, 1993 and 1995 were the busiest years with 10, 10 and 14 paper respectively – an extraordinary rate of publication.

Monitoring the Neuromuscular Junction

Mirakhur's first publication was in 1972; his first publication about neuromuscular blockade was in 1977, and the first specifically on the TOF ten years later in 1987. We will address the monitoring of the neuro-muscular junction first as it will create a foundation for the understanding of the other work.

The 'Train-of-Four' (TOF)

"*Four consecutive stimuli are delivered along the path of a nerve, and the four responses of the muscle (T1, T2, T3 and T4) is measured in order to evaluate stimuli that are blocked versus those that are delivered*" [ii]

The first in 1987 [74] was to determine the TOF value that might indicate that another dose of muscle relaxant was necessary. The TOF

[ii] http://medical-dictionary.thefreedictionary.com/train-of-four

responses were measured during recovery of neuromuscular block (paralysis) from atracurium, vecuronium, pancuronium and tubocurarine in order to quantify the height of T1 at which T2, T3 and T4 reappear. The 4th response (T4) appeared at approximately 30% height of T1 (previously thought to occur at 25%). It was recommended that the appearance of T3 (at about 25% of T1) be used as the trigger for a further dose of muscle relaxant.

In 1989 [90] fade in the TOF responses during onset of neuromuscular block was studied following administration of atracurium, vecuronium, pancuronium and tubocurarine. TOF ratios (T1:T4, fade) were measured at heights of T1 of 75, 50 and 25%. Fade increased as the height of T1 decreased; maximum fade at T1 of 25%. Vecuronium showed the least fade and pancuronium, atracurium and tubocurarine showed increasing fade. I'm unsure of the significance of these results.

Again in 1989, the fade in response to tetanic stimulation was studied [89]. Patients received atracurium, vecuronium, pancuronium and tubocurarine and tetanic fade was measured either at maximum block or at 10% recovery depending on the dose given. They stated that "*If fade in response to tetanic stimulation represents a prejunctional effect ... that neuromuscular blocking drugs cannot be differentiated with respect to their relative prejunctional effects by measurement of tetanic fade...*"

This was followed six years later by "*Nondepolarizing neuro-muscular blocking drugs and train-of-four fade*" [144]. Again, the aim was to assess differences in prejunctional effects of different relaxants but this time by measuring the TOF fade. It was concluded that the relative prejunctional effects of the relaxants were similar.

In the same year they assessed a new TOF monitor [141]. The TOF-Guard (it incorporated an accelerometer) was compared to a standard mechanomyographic (Myograph 2000). When the data were analysed using the Bland and Altman technique the 95% limits of agreement were not so close. They recommend that results from the TOF-Guard and the Myograph 2000 should not be considered equivalent but that the TOF-Guard was an improvement on tactile evaluation of the TOF.

Once again, in 1998, fade associated with TOF stimulation was examined [167]. The fade, which was thought to be due to a prejunctional

effect[iii], was assessed after doses of cisatracurium, atracurium, vecuronium, mivacurium or rocuronium. The TOF fade (during onset and offset of the block) was greater with a low dose of cisatracurium compared with all other relaxants. Cisatracurium, a stereoisomer of atracurium, had a slower onset of action than all the others but the duration of action was similar.

In 2001 Mirakhur wrote an editorial in the European Journal of Anaesthesiology on "*Current developments in anaesthesia and neuromuscular transmission*" [190].

We will now examine some of the muscle relaxants, many occur in various combinations in the same study.

Curare was first prepared in 1832
Suxamethonium was discovered in 1906 but the neuromuscular blocking properties were not described until 1949
Pancuronium was synthesised in 1964
Vecuronium was synthesised in 1973
Atracurium was synthesised in 1974
Rocuronium was introduced to clinical practice in 1994

The 1970s and 80s were a great time for NMB investigations.

Suxamethonium
The aspects of this depolarising agent that were investigated were its duration of action, the muscle pain that followed its use and associated biochemical changes, the pretreatments aimed at reducing this side effect, the management of associated bradycardia and the speed of onset compared with other agents. The latter is described in the following section on nondepolarisers.

Bradycardia occurs subsequent to administering a second dose and the effect is minimised by the use of antimuscarinic agents. In 1979 they wished to determine the efficacy of a new agent, glycopyrrolate, and compared it with the standard drug atropine, and so they studied patients who received intermittent doses of suxamethonium [16]. There were 28 patients in each group. "*Although no statistically significant differences were seen, clinically,*

[iii] Bowman WC. Anesthesia and Analgesia 1980; 59: 935–43.

glycopyrrolate seems to afford better protection against the cardiac changes resulting from intermittently administered suxamethonium." Considering the lack of statistical significance the following statement of efficacy seems unsupported.

Another early paper, in 1984, [49] was a report of the investigation of how long suxamethonium's effect lasted in children, and the plasma cholinesterase activity. There was no difference in cholinesterase activity between children and adults but the apnoea was of shorter duration in children; it was suggested that this might have been due to their larger volume of extracellular fluid.

Suxamethonium is well recognised clinically by the muscle fasciculations that occur before paralysis, by the cellular release of creatine kinase (CK) and by the subsequent muscle pains, myalgia. Myalgia, although an unwanted, unpleasant side effect, was never considered a contraindication to the use of suxamethonium in clinical situations where its use was considered necessary. However a variety of measures were tried to reduce its severity: In 1983 pretreatment with vecuronium and neuromuscular blocking agents [42], in 1985 pretreatment with benzodiazepines [52] and in 1992/93 there were two papers on the biochemical changes associated with myalgia with various pretreatments [113, 119].

Pretreatment with nondepolarisers [42]: Patients were assessed for muscle pain on the 1st and 2nd postoperative days. Vecuronium, gallamine, tubocurarine or pancuronium were given one or two minutes before the suxamethonium. The incidence of pain was halved with pretreatment (from 40% to 20%).

Pretreatment with benzodiazepines: Several studies investigated these phenomena. Diazepam and midazolam failed to reduce the myalgia but tubocurarine was effective as a pretreatment; it virtually abolished fasciculation but it also reduced the intensity and duration of the neuromuscular block [52]. Changes in serum potassium, creatinine phosphokinase and aldolase were clinically insignificant..."..... *although 5 out of 47 showed an atypical rise in creatinine phosphokinase.*"

The release of creatine kinase was increased if suxamethonium and halothane were used together in chicks [100], this did not occur to a significant degree when the drugs were used individually. The release of CK was thought to be due to muscle damage, possibly by the involvement of phospholipases because it was prevented by chlorpromazine. In a clinical study [113] myalgia

was reduced by tubocurarine, chlorpromazine and alphatocopherol but only those who received tubocurarine and chlorpromazine had reduced CK efflux. As expected intubation conditions were not as good with the pretreatment with tubocurarine. A further study examined the effect of hypnotic induction agents [119], propofol or thiopentone. It was concluded that they had no effect on myalgia or CK release.

How did the pretreatments affect the neuromuscular blockade produced by suxamethonium [124]? Those pretreated with chlorpro-mazine, alpha-tocopherol or aspirin had no significant difference in time to maximum block or time to recovery of twitch response compared with those receiving no pretreatment. Those pretreated with d-tubocurarine took longer to achieve maximum block and the duration was shorter compared with those receiving no pretreatment. It was considered that chlorpromazine was the better drug in the prevention of the side effects of succinylcholine.

A relatively uncommon clinical scenario with suxamethonium is where it is necessary to re-intubate a patient after a non-depolarising agent has been 'reversed'[iv] with an anticholinesterase. The speed of onset of and duration of action of suxamethonium was assessed after the use of edrophonium or neostigmine (both anticholinesterases)[145]. Both the onset and duration were prolonged and plasma cholinesterase activity was reduced after neostigmine.

Non-depolarising muscle relaxants

Combinations:

Some of the earlier Mirakhur studies compared all three commonly used agents – pancuronium, vecuronium and atracurium [57, 66, 81, 86]. It was a great time for NMB investigations. Many other drugs were studied but few survived – rocuronium was a survivor. (*see below*)

Quickness of onset and duration of action of muscle relaxants are of clinical significance. In 1985, in a group of patients over 65 years of age, pancuronium, vecuronium and atracurium were assessed. The intubating conditions were similar but the time to complete block was shortest with vecuronium at 4.3 minutes, the differences were not significant. Atracurium and vecuronium, however, lasted a significantly shorter time, 35 vs. 99 minutes.

[iv] 'Reversed': a colloquial term for the administration of an antidote for the termination of the action of a non-depolarising muscle relaxant.

Other clinically significant factors were the effects on the cardio-vascular system. In 1986 the heart rate, rhythm and systolic, diastolic and mean arterial pressures were measured after giving atracurium, vecuronium or pancuronium in the presence of a standard anaesthetic. Pancuronium caused an increase in blood pressure and heart rate (and a junctional rhythm). Vecuronium caused a fall in diastolic blood pressure and some patients had signs of histamine release after atracurium.

To try and reduce the time from the patient going to sleep and the time to intubation the idea of a small 'starter' dose followed by a later dose was considered. In 1988 this was studied with the three agents. Ten percent of the total dose was given four minutes before the second dose. There were no significant differences between the single and divided dose groups.

Dose-response curves are a mainstay of pharmacokinetics and in 1989 were constructed for atracurium, vecuronium and pancuronium in another set of elderly patients. There appeared no significant differences between elderly and young adult subjects.

From the table below it can be seen that the main interests were vecuronium, atracurium and rocuronium with mivacurium a runner up.

	Panc	**Vec**	**Atrac**	**Cisa**	**Dox**	**Miv**	**Pip**	**Rap**	**Roc**
Panc	2	7	4	0	0	0	2	0	0
Vec		13	8	0	0	0	0	0	1
Atrac			8	2	0	1	0	0	0
Cisa				0	0	0	0	0	1
Dox					1	0	0	0	0
Miv						9	0	0	1
Pip							1	0	0
Rap								4	1
Roc									21

The comparison studies will be left for the reader to examine but some of the more interesting studies will be described.

Plasma cholinesterase [45]

Plasmacholinesterase (aka pseudocholinesterase) is produced in the liver and found in the plasma. Levels may be reduced in advanced liver disease but only a reduction to <25% of normal will result in significant prolongation of neuromuscular blockade with suxamethonium. Levels can be affected by various anaesthetic agents and so plasma cholinesterase levels were measured following pancuronium and vecuronium. Pancuronium produced a significant reduction in the enzyme levels but vecuronium was without any significant effect. Vecuronium was always considered a 'clean' drug.

Drug interactions: these are always important. The following were studied: doxapram, H2 receptor blockers, beta-blockers, calcium channel antagonists and anticonvulsants.

Doxapram is a respiratory stimulant and it may be used at the end of anaesthesia to improve ventilation and therefore increase the elimination rate of volatile agents without affecting analgesia. There was some evidence that it enhanced neuromuscular block and so the rates of spontaneous and neostigmine-induced recovery were studied; the time from 25% recovery of T1 to 75% (RI). It was significantly longer after vecuronium in the presence of doxapram but there was no significant difference after atracurium or when neostigmine was administered. This suggested that only if neo-stigmine reversal was incomplete, a prolonged recovery might result [105].

H_2 receptor blockers, cimetidine and ranitidine, are used to reduce gastric acid production. At the time there was "*conflicting evidence about the occurrence of interactions between H2-receptor blocking agents and neuromuscular blocking drugs.*" So a study of single oral doses of cimetidine or ranitidine on the neuromuscular blocking effects of vecuronium and atracurium was undertaken. With vecuronium the times following cimetidine were prolonged significantly but there were no significant differences in any of the variables following ranitidine pretreatment. Cimetidine pretreatment had no affect on atracurium [99].

Beta-blockers, calcium entry blocking drugs and anticonvulsants: The affects of these agents had been well studied on the neuromuscular junction and rocuronium at this time was a new drug and their effects with this agent needed to be assessed. Neuromuscular block was monitored during a fentanyl, propofol infusion and nitrous oxide anaesthetic. There were no differences in onset times. Apart from chronic therapy with anticonvulsant drugs, which

reduces the duration of action of rocuronium, there were no other significant changes [162].

Intra-ocular pressure: The effect on **intra-ocular pressure** was of importance as it is necessary to avoid excessive pressure if the globe is damaged or open during surgery. In all there were eight studies [64, 65, 79, 80, 84, 85, 91, 96].

The first, in 1985, was a comparison of the effects of Diprivan (propofol) and thiopentone. The next, in 1986. determined the effects of atracurium or succinylcholine during nitrous oxide-oxygen-fentanyl anaesthesia. Intra-ocular pressure was stable with atracurium but succinylcholine caused a significant increase. Thiopentone was associated with a decrease in pressure but it increased in both groups as a result of laryngoscopy and intubation [65].

In 1987 the effect of vecuronium was assessed during a normal induction of anaesthesia sequence (thiopentone + vecuronium) and during a rapid induction sequence (vecuronium + thiopentone). Vecuronium was associated with a decrease in intra-ocular pressure and even though tracheal intubation caused an increase it never exceeded pre-induction levels [80].

A year later a report was published in ***Anaesthesia*** where intra-ocular pressure was measured during induction of anaesthesia with propofol or thiopentone followed by vecuronium. The results were similar to previously [84] and in the same year in the ***BJA*** something similar again [85]. Post-intubation, intra-ocular pressure in the propofol group remained significantly less than the baseline value.

Infusions: Muscle relaxants are very suitable for use as infusions as their pharmacological effect is easily measured and therefore the dosage easily titrated.

In 1984 [50] it was shown that when vecuronium was given as a continuous intravenous infusion the dose required to maintain a steady state at 90% block was, on average, 0.083 mg kg^{-1} h^{-1} (5.8 mg h^{-1} for a 70kg patient). Although there were large variations recovery was quick when the infusion was stopped. Five years later prolonged infusions (15-68h) in an intensive care unit were studied [88]. Recovery on cessation of the infusions took almost half an hour. No adverse affects were noted. A similar study was reported in 1991, this time in a paediatric intensive care unit [97]. Eleven infants and children and

four neonates received an infusion to maintain a 90% block for between 9.5 and 179 hr. The mean doses were in the region of 0.1 $mg.kg^{-1}hr^{-1}$. The recovery times were in the region of 50 minutes. Again no adverse effects were noted.

Mivacurium and rocuronium were the subjects of subsequent infusion studies.

Thirty patients were infused with mivacurium during thiopentone, fentanyl and halothane anaesthesia [129]. Reversal was with either neostigmine or edrophonium, or spontaneous recovery was allowed. A significant negative correlation ($r = -0.81$, $p < 0.001$) was shown between time to recovery from the initial bolus dose.

In the same year rocuronium infusions were used [132]. Following a bolus dose of 0.45 mg kg^{-1} an infusion was adjusted manually to maintain T1 at 10%. Again neostigmine or edrophonium, or spontaneous recovery was allowed. Inter-patient dose requirements varied. Reversal with neostigmine and edrophonium was about four times quicker than spontaneous recovery which took about 36 minutes. Because of variable recovery rates neostigmine was considered a more reliable antagonist.

The final study was a pharmacokinetic study of rocuronium infusions [156]. The average rocuronium infusion rate for a steady state 90% block of T1 was about 0.5 mg kg^{-1} h^{-1}. Spontaneous recovery time was about 30 minutes. Blood samples collected over six hours post infusion were analysed for concentrations of rocuronium and metabolites using HPLC. The pharmacokinetic data "were not significantly different from previously published data for a single bolus dose of rocuronium".

Reversal of neuromuscular blockade

Reversal of neuromuscular blockade can be left to nature (spontaneous recovery) or can be stimulated by overcoming the existing competitive block between the neuromuscular blocking agent and acetyl choline (Ach). This is achieved by increasing the levels of ACh by decreasing its rate of breakdown by using an anticholinesterase. However an antidote is required for the antidote because anti-cholinesterases also have unwanted side effects: bradycardia and salivation. To oppose these effects atropine (old) and glycopyrrolate (relatively new, patented in 1960) are used. To complete the picture the newest, most expensive, and novel agent, sugammadex was also investigated.

The first four papers (1977-81) [10, 23, 24, 32] were comparative studies of atropine and glycopyrrolate. In the first a glycolpyrro-

late/neostigmine ratio of 0.2 mg /1.0 mg was thought safe and effective, heart rate was stable but the antisialogogue action of glycopyrrolate was superior. Arrhythmias were similar in both groups. The second paper was similar but they added another anticholinergic, antimuscarinic drug hyoscine. The third was a study in children (atropine vs. glycopyrrolate) and the fourth was a study where the effects were assessed if the neostigmine was given with, or after atropine and glycopyrrolate. If the drugs have different onset times then the overall effect could potentially be different. Given first, both anticholinergic agents produced an increase in heart rate which decreased after the administration of neostigmine. The bottom line was that anticholinergic drugs should be administered with neostigmine and that glycopyrrolate, 10 μg kg^{-1} produced a stable heart rate.

The second set of papers [37, 40] was about the effect of neostigmine and pyridostigmine on serum cholinesterase activity. Acetyl-cholinesterase is considered the target but there was evidence that they also inhibited serum cholinesterase (pseudocholinesterase). Serum cholinesterase activity was measured after reversal of pancuronium blockade and the enzyme activity was significantly depressed. The clinical importance is that a subsequent dose of suxamethonium could be prolonged; if a non-depolariser were to be given for further neuromuscular blockade an increased dose would be required. In 1986 [67] a similar study was done with edrophonium; this was after atracurium, there was no inhibition of enzyme activity. It was suggested that in previous studies the use of pancuronium may have been partially responsible for the depression of enzyme activity.

There were other comparative studies [56, 76, 77, 145]. However, one non-depolarising drug that is different to the others is mivacurium. It is metabolised by the action of plasma cholinesterase. In this study [160] it was given after the reversal, with neostigmine or edrophonium, of an atracurium induced block. As might be expected the action of mivacurium was prolonged by neostigmine but not by edrophonium.

We must now address the novel drug sugammadex [194, 198-200, 202, 204]. The action of this agent is akin to the way an antibody attaches itself to an antigen. The drug attaches itself to rocuronium (and less efficiently) to vecuronium and the pharmacological action is terminated, almost

immediately[v]. Prior to this agent the early reversal of a non-depolarising neuromuscular blocking drug was virtually impossible. Attempting to reverse the block early caused problems and increasing the dose of the anticholinergic can cause an increase in the neuromuscular block!

2006: [194] Sugammadex, Org 25969, a cyclodextrin, was studied to determine its efficacy. After a profound block with rocuronium various doses of sugammadex were given. The time to achieve a TOF ratio to 0.9 was recorded and there was a dose-related decrease. It was determined that the fastest time possible to get to a TOF ratio of 0.9 to be 1:35 minutes and that a dose of 2-4 mg kg^{-1}would be effective.

2008: [198] This study compared the reversal of rocuronium-induced neuromuscular block with sugammadex with that of neostigmine for reversal of cisatracurium. The reversal agent was administered when T2 appeared and it was shown that recovery to a TOF ratio of 0.9 was 4.7 times faster with sugammadex than with neostigmine. [The author would like to ask: Why not compare rocuronium reversal with neostigmine with rocuronium reversal with sugammadex?]

2009: [200] This was a review article. It described how the neuromuscular block of both rocuronium and vecuronium can be reversed by sugammadex; for a shallow block 2mg kg^{-1}, for a deep block 4mg kg^{-1}, for a really deep block (16 mg kg^{-1}). Using 1-1.2 mg kg^{-1} of rocuronium produces a rapid block which raised "*the possibility of using rocuronium as a replacement for suxamethonium*". Sugammadex was said to have an "*acceptable safety profile*".

[v] The author was fortunate in being the recipient of both the first box of rocuronium in New Zealand, and the first box of sugammadex. Sugammadex is, simultaneously, both an exciting and boring drug. It works extraordinarily well and has virtually no side effects (apart from a few drug interactions). The first time he used it the rapidity and completeness of recovery appeared almost miraculous. A reflection, perhaps, of 30 year's experience of slow and less than 100% recovery; the cognitive recovery of the patient also seemed enhanced (an impression and, of course, anecdotal).

2009: [202] This was a phase IIIA study to explore the efficacy and safety of sugammadex in infants, children, adolescents and adults. All was well, it rapidly, effectively and safely reversed rocuronium neuromuscular blockade in all patients.

2011: [204] Rescue reversal refers to the situation where a neuromuscular blocking drug has been and the airway cannot be secured. The quick return of spontaneous breathing is required. This letter pointed out some facts in previously reported studies including that by Hogg et al. Journal of Anaesthesia 2010; 105: 726–727P. Return of diaphragmatic movement was recorded about 40seconds after a 16 mg kg^{-1} dose of sugammadex. With pre-oxygenation this should maintain oxygen saturation It was pointed out in the letter that the storage place for the sugammadex should be widely known so that it should be available within one minute, and the dose should be known: 3 vials of 500 mg[vi].

Anticholinergics

There are 25 papers involving atropine, or glycopyrrolate or hyoscine [10-12, 14, 16, 20, 23-26, 28-33, 35, 38, 39, 43, 58-60, 78, 135]. Excluding those already mentioned which ones are of particular interest?

Hypersensitivity to atropine [11]

This is a 10 line letter – *"...We were interested in the case report of hypersensitivity to atropine by Giala and Tzovairi-Tsakona (1978). A safer and appropriate alternative to atropine is glycopyrronium."*

Gastric acidity and glycopyrrolate premedication [20]

This letter was making comment about a paper by Baraka et al (Anesth Analg 1977; 56:642- 645). They make the point that the doses of the two anticholinergics studied were not comparable. Their observations showed that 0.2 mg of glycopyrrolate and 1.0 mg of atropine were indistinguishable regarding the effects on pH of gastric contents. They also criticised the statistical tests used and the data presented They said that anticholinergic

[vi] At this time (2011) the cost of sugammadex in New Zealand was about 1$ / mg. This was not a cheap exercise.

agents reduced the opening pressure of the cardio-oesophageal sphincter and in addition they reduce the motility and "*perhaps*" delay gastric emptying. They believed that obstetric anaesthesia would be safer with cimetidine and metoclopramide. Glycopyrrolate they considered better than *"the dubious and unproven attribute of raising the pH of gastric contents."*

Atropine premedication and respiratory complications [29]

This was a letter in response to an article by Jones and Drummond[vii] who showed that atropine did not change the frequency of postoperative respiratory complications. Mirakhur and Clarke were questioning why atropine was used routinely for premedication when it had no obvious benefit [19, 21] and left the patient with a dry mouth. Routine anti-cholinergic medication has not been used in routine anaesthetic practice for several decades; coinciding with a move against intramuscular premedication.

Antiemetic effects [31, 135]

This [31]was also a letter but a very detailed one – a mini-paper! The message from this was that glycopyrrolate does not have an anti-emetic action and this was thought to be due to its inability to cross the blood-brain barrier.

This was revisited in 1995 [135]. Children having squint surgery, who are prone to vomiting, were studied to assess the effectiveness of anticholinergics as antiemetics. The incidence of the intra-operative oculocardiac reflex was also recorded. Glycopyrrolate and atropine reduced the incidence of the oculocardiac reflex by over 90%. There was no significant difference in emesis between the placebo group and the anticholinergics.

Now for the non- neuromuscular studies:

Propofol

Propofol was studied with regard to intraocular pressure [64, 79, 84, 85], propofol-opiate anaesthesia [126, 134, 158, 188, 193] and propofol and cellular function [138, 197]. The last two are of interest.

[vii] Jones GC and Drummond GB. Br J Anaesth. 1981;53:441

Delayed hypersensitivity reactions and T lymphocyte proliferation were studied. Thiopentone and propofol were given to volunteers as an infusion on two occasions. Skin antigen tests were carried out before and after administration. The results showed that the reactions were depressed but there was no effect on T lymphocyte proliferation [138].

The second study was about the protective effect of propofol on myocardial contractility during ischaemia. Rat ventricular cardiomyocytes were made ischaemic for two hours. Under normal conditions, propofol decreased the contraction of cardiomyocytes by approximately 37%. However, during ischemia, propofol was associated with responses where ischaemic values were equal to normal values. This showed that propofol can offset the effects of free radical compounds on cardiomyocytes undergoing oxidant stress and actually improve contractility [197].

Remifentanil

Remifentanil was studied with regard to cardiovascular effects [177, 180, 183], recovery from anaesthesia [184, 188] and case reports of three adrenalectomies [191].

Remifentanil can suppress the cardiovascular effect of laryngoscopy/intubation [177] and so its use for adrenalectomies seemed appropriate. There were no adverse events during resection of an adrenal cortical tumour but there was hypotension and bradycardia. It did not prevent increases in blood pressure or plasma catecholamine levels during excision of the two phaeochromocytoma, even with alpha and beta blockade [191].

The elderly

The elderly were also studied – seven related to neuromuscular blockade but another two were about pre- and post-anaesthesia oxygenation.

In brief - [98] It was decided that, in those over 65 years of age, at least two minutes preoxygenation was necessary to give the maximum apnoea time before oxygen saturation dropped to 93%.

[111] This study was in patients over 70 years of age having eye surgery. Oxygen saturation was recorded on the pre-operative night, immediately postoperative, within the first 60 minutes, and then on the first postoperative night. The percentage of time during which the patients had an oxygen saturation of less than 90% was less than 0.15%. There were no

differences between general and local anaesthesia for this minimally invasive surgery.

Laryngoscopes

Finally, a series of five studies about a new laryngoscope [123, 143, 147, 157, 192].

The first four are about the McCoy designed laryngoscope – McCoy is a co-author in each paper. The McCoy laryngoscope had a modified Macintosh blade; it had a hinged tip that was activated by a lever on the handle. It enhanced the ability to elevate the epiglottis and it was claimed to reduce the difficulty of larynx visualisation associated with an anterior larynx [123]. The second [143] was a technical paper on measuring the forces exerted at laryngoscopy which was then used to compare laryngoscopy with the Macintosh and McCoy blades [157]. The year before a comparison was also made by assessing the cardiovascular changes, at laryngoscopy, with the two blades.

The final one in the series [192] was a modification of the modification – an adjustable mirror was added to the blade. Using in-line neck stabilisation to simulate difficult intubation, the mirrored laryngoscope out performed both the McCoy and the Macintosh. It was concluded this new laryngoscope offered "*considerable advantages over the Macintosh and the McCoy laryngoscopes*"; McCoy was not involved in this study.

Mirakhur was the first author in 79 of these studies. He had many co-authors. A number were RS Clarke, involved in 32 publications, Elliott P 21, Gibson FM 21, McCoy EP 20, Maddineni VR 17, Lavery GG 16, McCarthy GJ 15, Cooper RA 13, Ferres CJ 10 and Reid J 10.

After 34 years studying neuromuscular blockade I think I might have become a bit jaded with train-of-four ratios. However, it all ended with sugammadex, a very interesting exciting and stimulating endgame.

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Brian J Pollard

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Brian Pollard was a MRC research scholar at the Clinical Research Centre, Harrow, in Middlesex, from 1971-72, after qualifying BPharm; MB. ChB in 1977, FFARCS in 1981. After anaesthesia training in Nottingham, he became senior lecturer in Manchester in 1985[i]. He was appointed to a personal chair in 1996 and became head of department in 1997[ii].

His first paper, published in 1973, was as a MRC research scholar and was a study involving the rat phrenic nerve-diaphragm preparation, a commonly used animal model that was used in Nottingham in the same period. It was used to study the effects of inhalational anaesthetic agents. Diethyl ether, methoxyflurane and trichloroethylene caused depression; cyclopropane just potentiation and chloroform and halothane potentiation followed by depression. Halothane caused the least depression. Studying the preparation with tubocurarine, direct stimulation of the muscle and denervation of the muscle suggested that the effects of the inhalational agents were a non-junctional process [1].

Further work was done using this technique in 1983, *"Interactions between tubocurarine, pancuronium and alcuronium demonstrated in the rat phrenic nerve-hemidiaphragm preparation"* [8]. They found that mixtures with tubocurarine were synergistic; alcuronium mixed with pancuronium was not. This type of work was continued later in Manchester

Nottingham: 1973 – 1985

Brian and the author shared time in Nottingham and therefore the names of the co-authors are very familiar.

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[i] Studies Concerning the Interactions between the Neuromuscular Blocking Agents. MD Thesis, University of Sheffield, 1991

[ii] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916

1976: This was a description of the efficacy of nasogastric feeding, with a group of physicians interested in metabolic processes, for patients in intensive care; they used a constant drip method [3].

A series of case reports followed. 1982/'83/'85:

1. A baby born with a paralysed hemidiaphragm and congenital hypothyroidism [5].
2. Reversal of biliary sphincter spasm with glucagon [7].
3. Fatal pulmonary embolism due to limb exsanguination [9].
4. Subtotal tracheal resection: a case report and review of airway, anaesthetic and post-operative problems [12]. An intrathoracic tumour required tracheal resection; the 'gap' was replaced with a musculocutaneous flap[iii].

Manchester 1987 -

Tom Healy, ex-reader Nottingham, was professor in Manchester and BJP followed in '87.

The major theme in BJP's work was neuromuscular blockade, particularly the combination of agents:

Neuromuscular Blockade

1987: "*The neuromuscular blocking effect of trimetaphan alone and in combination with different non-depolarizing muscle relaxants in the rat*". Trimetaphan produced potentiation of neuromuscular blockade when given with tubocurarine, metocurine and pancuronium but produced an all-or-none block when the concentration exceeded a threshold value [21]. Trimetaphan (Arfonad) was commonly used during anaesthesia to induce hypotension and thus knowing its effect on the neuromuscular junction was important.

1988: "*Differing interactions between hexamethonium and tubocurarine, pancuronium or alcuronium at the neuromuscular junction*". Hexamethonium in low concentrations opposed the neuromuscular blockade produced by tubocurarine, pancuronium and alcuronium. Higher doses produced a dose-

[iii] The author was the lead anaesthetist and needed a very competent trainee to assist; BJP was the one. In retrospect this procedure should probably have been done using cardiopulmonary bypass. The tracheal airway was maintained using a rigid bronchoscope and the patient oxygenated using a venturi injector. Anaesthesia was maintained with intravenous agents.

dependent block. The inhibition of cholinesterase in the tissue of the preparation only occurred at concentrations higher than that that resulted in antagonism and therefore could not explain the results. The possible mechanisms were discussed [30].

1988: "*Prolonged neuromuscular blockade with vecuronium in renal failure"* [32]. A case report: the title speaks for itself – full recovery took 90 hours.

1988: "*Interactions of vecuronium and atracurium in an in vitro nerve-muscle preparation*" [33]. In this study atracurium and vecuronium were combined and the combination's log dose response curves indicated an increased potency. This synergy was considered consistent with multiple receptor site and different modes of action hypotheses.

1989: "*Concentrations of atracurium and laudanosine in cerebrospinal fluid and plasma during intracranial surgery*" [34]. Atracurium was given by infusion for up to four hours during neurosurgery. Atracurium and laudanosine concentrations were measured in the cerebrospinal fluid and plasma. It was apparent laudanosine accumulated in both plasma and CSF; laudanosine is known to predispose to convulsions.

1989: *"The effect of acutely administered phenytoin on vecuronium-induced neuromuscular blockade"* [35]. Phenytoin administered intravenously during steady state neuromuscular blockade caused a significant increase in the neuromuscular blockade; possible mechanisms are discussed.

1989: "*Use of atracurium or vecuronium to prolong the action of tubocurarine"* [37]. When atracurium or vecuronium was given after some recovery from tubocurarine, the first dose always had a more intense effect and lasted longer than subsequent equal doses.

1989: "*Priming with alcuronium and tubocurarine accelerates the onset of neuromuscular block"* [38]. Priming[iv] accelerated the onset of neuromuscular block.

1989: "*Should vecuronium be used in renal failure?"* [40] A letter.

1989: "*Use of continuous prolonged administration of atracurium in the ITU to a patient with myasthenia gravis*" [41]. A case report - muscular relaxation was with atracurium 5 mg h^{-1} and on cessation power recovered rapidly.

[iv] Priming is where a sub paralyzing dose of the drug is given prior to the main dose.

1989: "*Doxapram and the neuromuscular junction*" [43]. This was another rat phrenic nerve-diaphragm study. Doxapram enhanced neuromuscular transmission. Cholinesterase inhibition was excluded as an underlying mechanism. However, dose-related depression occurred if there was a partial neuromuscular block. Using agents with known presynaptic activity it was suggested that doxapram had a presynaptic facilitatory effect and in the presence of partial neuromuscular block an inhibitory action, post-junctional. It was pointed out that these effects were at concentrations much greater than those used in clinical practice.

1990: "*Concentrations of atracurium and laudanosine in cerebrospinal fluid and plasma in three intensive care patients*" [51]; a follow-up paper to a similar report in 1989. There were no adverse effects attributable to laudanosine.

1992: "*Atracurium block prolonged by low dose tubocurarine*" [68]. This was a detailed letter about the potentiation of atracurium by tubocurarine and could be used to reduce the dose of atracurium required and possibly avoid the use of anticholinesterases at the end of surgery. Presynaptic inhibition may be the cause; it would enhance agents acting on post-synaptic receptors.

1992: "*Effect of doxapram on neostigmine evoked antagonism of vecuronium neuromuscular block*" [70]. Recovery was prolonged in the presence of doxapram, but it was not statistically significant.

1992: "*Neuromuscular blocking drugs and renal failure*" Editorial [71].

1993: "*Neuromuscular blocking drugs in the intensive care unit: introductory remarks"* [77] and "*Neuromuscular blocking agents in intensive care*" [81] and were leading articles in an 'Intensive Care Medicine' supplement, followed later by "*Which drug - steroid or benzylisoquinolinium?*" [80].

1993: "*The onset of alcuronium and tubocurarine: alone and in combination*" [85]. The rate of block onset with the 50% combination was faster than the agents given alone. However, the small effect was considered unlikely to be of clinical use.

1993: "*Extending a pipecuronium neuromuscular block. Increments of atracurium or vecuronium as an alternative to pipecuronium*" [86]. A dose response relationship was constructed for pipecuronium. Further patients then received a dose to produce a >90% block. Small repeated doses of atracurium, vecuronium or pipecuronium were then given on recovery to 90% block. The

block with pipecuronium was constant but the duration of the blocks with atracurium or vecuronium became less with subsequent increments.

1995: *"Molecular mechanisms of neuromuscular blocking agents: is the increased understanding of importance to the practising anaesthetist?"* [91] This was a review article which explained that the precise mode of action of muscle relaxants remained unclear. It reviewed the ways in which other drugs used during anaesthesia "*may modify this system*".

1995: "*Prediction of infusion rates of vecuronium using the bolus test dose technique*" [94][v]. Neurosurgical patients were given a loading dose of vecuronium (0.1 mg kg^{-1}). On recovery of the first twitch in response to the train-of-four electrical stimulus various boluses were given. The duration of 2mg and 4mg boluses were capable of predicting the required infusion rate. They suggested the initial dose could also be used for prediction.

1995: "*The role of muscle relaxants in total intravenous anaesthesia*" [95]. This describes the use of muscle relaxants during total intravenous anaesthesia and does emphasise the need to monitor neuromuscular function.

1995: "*Intubation conditions and time-course of action of low-dose rocuronium bromide in day-case dental surgery*" [97]. Rocuronium, relatively new, was compared with atracurium and vecuronium. They used relatively small doses and so full relaxation was unlikely at 60s. The rocuronium group had the better conditions for intubation and the duration was of the order of 22 minutes.

1995: *"Pulmonary function and head lift during spontaneous recovery from pipecuronium neuromuscular block"* [93].

1996: "*The infusion requirements and recovery characteristics of cisatracurium or atracurium in intensive care patients*" [106]. Cisatracurium is an isomer of atracurium and makes up a small proportion of the atracurium formulation.

[v] The author is somewhat biased about this paper as it reproduces some work he had published in the Br J Anaes 1990;64:287-293. He is not sure about the statement that a prediction can be made using the first dose as the first dose is in mg kg^{-1}. It was shown in 1989 that weight determined dosage of vecuronium bromide can result in different durations depending on whether the patient is fat or slim. Anaesthesia 1989;44:692.

Both drugs were administered as an infusion for a minimum of 24h, the mean infusion rate of cisatracurium was a third of the atracurium rate. The recovery time was the same and there were no side effects and so it was considered a satisfactory drug for this use. The following report in 1997 is similar.

1997: "*A comparison of cisatracurium (51W89) and atracurium by infusion in critically ill patients*" [109].

1997: "*Rocuronium and cisatracurium*" [111]. This is an overview of rocuronium and cisatracurium, the most recent additions to the anaesthetic armamentarium.

1997: "*Mivacurium or vecuronium for muscular relaxation in day-case surgery*" [112]. Day case surgery is for relatively short procedures thus the muscle relaxants used need to be of short duration and recovery. The other agents used were propofol, fentanyl, nitrous oxide and isoflurane. The maximum block and ease of intubation was similar with the two test drugs but recovery was much faster in the mivacurium group; all the patients given vecuronium were given neostigmine. It was considered that mivacurium was possibly the better agent for day-case surgery.

1999: "*Antagonism of rapacuronium using edrophonium or neostigmine: pharmacodynamics and pharmacokinetics*" [117]. Half of the patients were given 1.5 mg kg^{-1} rapacuronium and the others 1.5 mg kg^{-1} rapacuronium plus three further doses of 0.5 mg kg^{-1}, all were given neostigmine or edrophonium. The results suggested that a three-compartment pharmacokinetic model was justified. Clearance was 4.4 ml kg^{-1} min^{-1}, initial volume of distribution 94.8 ml kg^{-1}. Clearance in females was 38.5% less and V1 was 25% less for those over 65 years of age.

The result of all this work demonstrated the effects of drugs used in anaesthesia on the pharmacodynamics of muscle relaxants, on the interactions between muscle relaxants, confirming the ability to predict infusion rates in individual patients and, hopefully, enhancing the likelihood of improving the frequency with which neuromuscular monitoring is used.

Heart rate variability (HRV)

HRV is the variation in the interval between heartbeats. The variations are largely due to vagal modulation; the parasympathetic tone normally exceeds the sympathetic effects. The vagal activity is the major contributor to the high frequency (HF) component; the low frequency (LF) component includes both sympathetic and vagal influences.

Previous work in the Manchester Department had revolved around the assessment of sinus arrhythmia as a depth of anaesthesia index[vi], CJ Pomfrett being a common co-author.

1998: "*The influence of premedication on heart rate variability"* [114]. This is an interesting collaboration with anaesthetists and cardiologists from the University Hospital, Iraklion, Crete. They used HRV to study the autonomic effects of midazolam, morphine and clonidine as premedicants. The patients were studied 60 mins before and after premedication using a Holter device. The low-frequency and high-frequency components were calculated. A ratio of <1 signified parasympathetic dominance. Power decreased with premedication whereas it did not with the placebo. Morphine and clonidine caused the low- to high-frequency ratio to decrease suggesting parasympathetic dominance.

2004: "*Perturbation of heart rate variability in cattle fed BSE-infected material*" [133]. The highest concentration prions that cause BSE are found in the brainstem, particularly nuclei in the medulla oblongata which are involved in the modulation of HRV. The level of high-frequency HRV was significantly different between control cattle and those exposed to BSE.

Another interesting collaboration.

2007: "*The vagus nerve as a conduit for neuroinvasion, a diagnostic tool, and a therapeutic pathway for transmissible spongiform enceph- alopathies, including variant Creutzfeld Jacob disease"* [139]. This is obviously a follow up to the 2004 paper and it is a little unusual as it is published in the journal called Medical Hypotheses. To quote from their website – **"***Medical Hypotheses* is a forum for

[vi] Pomfrett CJ, Barrie JR, Healy TEJ Br J Anaesth. 1993;71(2):212-7

ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives."

It was hypothesised that the vagus nerve is an important conduit for infective neuroinvasion during the incubation of certain transmissible spongiform encephalopathies. They proposed that HRV analysis of vagal function may indicate early functional signs of infection and may be used to measures the effect of new therapies.

2001: "*Delta sleep-inducing peptide*" [121]. DSIP is a delta sleep-inducing peptide which can cross the blood-brain barrier. Its effect is similar to natural sleep.

2009: "*Delta sleep-inducing peptide alters bispectral index, the electroencephalogram and heart rate variability when used as an adjunct to isoflurane anaesthesia"* [144]. It was thought that it might be useful as an anaesthetic supplement and so was studied using BIS, the EEG and HRV. Half of the subjects were given a placebo and the other half DSIP – all had a standard anaesthetic. The results were counterintuitive. The active group developed a tachycardia, increased BIS, reduced delta activity on the EEG, and decreased HRV (reduced parasympathetic tone). It lightened rather than deepened anaesthesia. It just reinforces the need for physical experimentation rather than thought experiments.

Day case surgery

There were four publications that audited and discussed anaesthesia for day case surgery.

2002 "*Anaesthetic agents in paediatric day case surgery: do they affect outcome?"* [124] The aim of day case surgery is to minimise post-operative morbidity, most commonly postoperative delirium, nausea and/or vomiting. The induction of anaesthesia, cardiovascular effects, recovery and postoperative nausea and vomiting were all addressed. The use of sevoflurane, halothane, propofol, desflurane and nitrous oxide, and combinations of them were all assessed.

2002/3 *"Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial"* and *"Clinical and economic choices in anaesthesia for day surgery: a prospective randomised controlled trial"* [123, 126]

2003 "*Anaesthesia for day case surgery: a survey of adult clinical practice in the UK"* [127] In 2000 a national postal survey of the range and variation of anaesthetizing patients for day case surgery was carried out, particularly urology and orthopaedic day cases. They used a structured postal questionnaire. Premedication was used by between 6 and 12% of practitioners, propofol was the preferred induction agent and isoflurane the preferred maintenance agent. Prophylactic antiemetics were only used in between 32 and 41% of patients and a laryngeal mask was used by between 86 and 93%.

2003 "*Anaesthetic agents in adult day case surgery".* [128] This was a meta analysis of "*all comparative published studies of adult day case anaesthesia in the English language up to December 2000*". One hundred-and-one studies were analysed. Propofol was found to be equal to sevoflurane and desflurane and better than methohexital, etomidate and thiopental. Isoflurane and halothane were considered the worst for maintenance. Propofol was the induction and maintenance agent of choice and avoiding nitrous oxide might help reduce the incidence of postoperative nausea and vomiting.

2008 "*The effect of anaesthetic agents on induction, recovery and patient preferences in adult day case surgery: a 7-day follow-up randomized controlled trial."* [141] This was a study of the longer term effects of day case anaesthesia. It was a randomized controlled trial of four standardized techniques. "... *propofol induction and maintenance, propofol induction with isoflurane/N_2O, or sevoflurane/N_2O maintenance, or sevoflurane/N_2O alone*". The bottom line was that the differences in outcome were transient and patients base their preferences on the method of induction; it is, after all, that which they are most aware of.

Cardiac output

1987: "*The effects of calcium-blocking agents on sympathetic responses to acute haemorrhagic shock in dogs"* [19]. Verapamil, nifedipine and diltiazem were studied to determine their effects on the cardiovascular in response to

haemorrhagic shock; this study was in dogs. Cardiac output, mean pulmonary artery pressure, mean right atrial pressure and pulmonary capillary wedge pressure all fell; adrenaline and noradrenaline activity increased; and the calcium antagonists did not make a difference. However patients receiving the higher doses of verapamil or nifedipine had a greater rise in renin levels.

1991: "*Bioimpedance versus thermodilution cardiac output measurement: the Bomed NCCOM3 after coronary bypass surgery"* [62].
The gold standard for cardiac output measurement, thermodilution, was compared with measurements using bioimpedance (Bomed NCCOM3) after coronary artery bypass surgery. Cardiac output measured by bioimpedance was significantly lower than with thermodilution during their time in intensive care. The limits of agreement were also large. Later measurements, with all patients breathing spontaneously, there was no difference.

1991: "*Measurement of transthoracic electrical impedance"* [65] This letter highlights some of the problems with bioimpedance measurement. It is affected by both intra- and extravascular fluid and the packed cell volume. As they stated, it "*may explain why a technique that was well described more than 20 years ago has yet to find its way into routine clinical use.*"

1991: "*Non-invasive measurement of cardiac output during induction of anaesthesia and tracheal intubation: thiopentone and propofol compared."* [66]. In this paper they investigated haemodynamic changes during standard anaesthesia with the bioimpedance monitor. The cardiac index decreased after induction and decreased further after tracheal intubation. There was no difference between the two groups. Mean arterial pressure and systemic vascular resistance were stable after thiopentone but both increased after tracheal intubation. Propofol caused a decrease in both mean arterial pressure and systemic vascular resistance.

Cerebral Function

BIS asymmetry [125, 130, 135]

It has been shown that there is an asymmetry in BIS recording between the left and right brain in children. It has been thought that it was immaterial which side of the head was used for measurement. These three studies investigated the pnenomenon.

Functional electrical impedance tomography by evoked response (fEITER) [146, 148-150]
These describe the use of a portable new non-invasive device for brain imaging. The aim was to study "sub-second mechanisms underlying consciousness". A sinusoidal current was passed between electrode pairs; non-current electrodes were used for voltage measurements. The sub-second responses to single flashes enabled construction of 3D maps of conductivity. Large changes in trans-cerebral impedance occurred during propofol induction[vii].

Case reports

1982: Paralysis of the right hemidiaphragm. [5]
1983: Reversal of biliary sphincter spasm with low dose glucagon during operative cholangiography. [7]
1983: Fatal pulmonary embolism secondary to limb exsanguination.[9]
1985: Subtotal tracheal resection: a case report and review of airway, anaesthetic and post-operative problems. [12]
1988: Prolonged neuromuscular blockade with vecuronium in renal failure.[32]
1989: Use of continuous prolonged administration of atracurium in the ITU to a patient with myasthenia gravis.[41]
1989: Anaesthesia in the testicular feminisation syndrome.[39]
1989: The use of flumazenil (Anexate, Ro 15-1788) in the management of drug overdose.[42]
1989: Anaesthesia in myotonia dystrophica.[44]
1989: Renal transplantation and diabetic autonomic neuropathy. [45]
1989: Obstructive sleep apnoea.[47]
1989: Failure to cannulate the epidural space.[49]

1989 was obviously the year for the reporting of clinical problems. Brian Pollard was involved at this time with the writing of the manuscript for "*Anaesthesia for Uncommon Diseases*" with the author. In fact 1989 was a very busy year – there were at least fourteen publications.

[vii] See http://www.wellcome.ac.uk/News/2011/News/WTVM051674.htm

He was the Editor-in-Chief of *Current Anaesthesia and Critical Care* (1989 to 2003–13 editorials), was involved with the *European Journal of Anaesthesiology* from 1997-2009 (Editor-in Chief 2004 to 2009) and Editor-in-Chief, "*Trends in Anaesthesia and Critical Care*" 2010 to 2014 (10 editorials). There were many more invited articles for a variety of non-indexed publications.

He was president of the Section of Anaesthesia of the Royal Society of Medicine, Council member of the Association of Anaesthetists and an Executive Committee member of the Anaesthetic Research Society. He was also a Senate Member of the European Academy of Anaesthesiology.

Books:

Anaesthetic Management: A Rule-Based Guide. 1986 BJ Pollard, MJ Harrison and R. M. Jones. Butterworths (1986).

Anaesthesia for Uncommon Diseases. 1989 BJ Pollard, MJ Harrison. Blackwell Scientific Publications, (1989)

"Aids to Anaesthesia" Second edition.T.E.J.Healy and B.J.Pollard Churchill Livingstone, 1999

Edited books

Applied Neuromuscular Pharmacology (1994), The Muscle Relaxant Handbook, (1995) and Handbook of Clinical Anaesthesia, three editions 1996 – 2011 and twenty-five chapters in various books,

Odds and ends:

Nasal CPAP: [47, 63, 75, 76], Assisted conception: [58, 113, 115] and the QT interval: [104, 105]

And ... to finish:

"Beards, academia and anaesthesia: a controlled study" [103]. This was published in the pre-Christmas edition of the BMJ, usually a jocular publication. It's worth a read!

"*Anaesthesia acronyms and abbreviations*" [132]

"The impact of increasing oximetry usage in India: A pilot study" [147]

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

 [i]

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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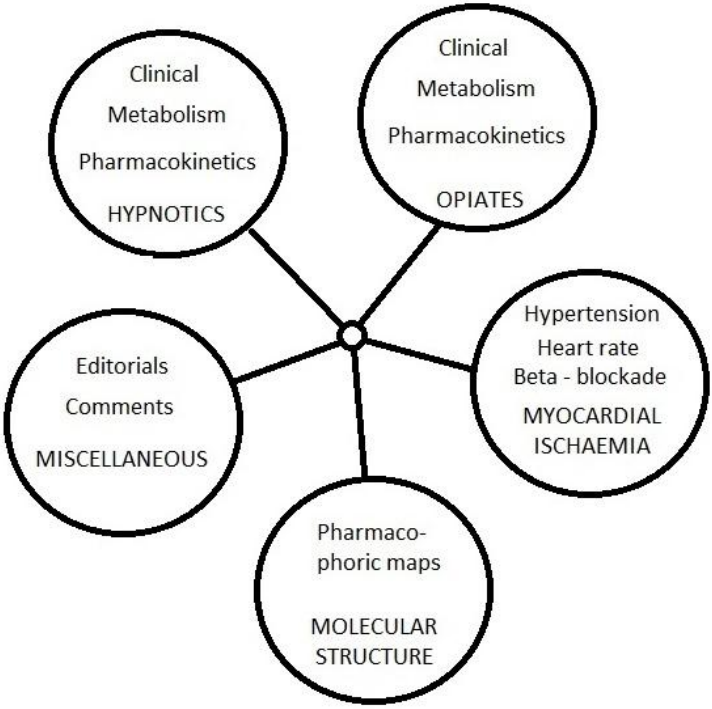
[i] Courtesy of Dr Douglas Russell

[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]

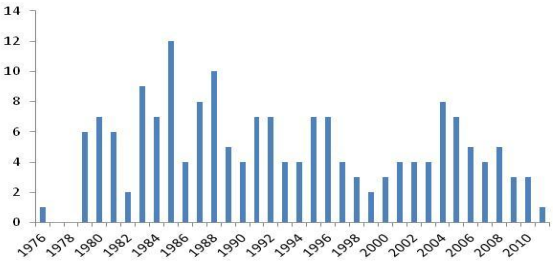
9. [The results were] "*...at variance with other published data, but* [they concluded] *that monitoring for peri-operative silent myocardial ischaemia does not aid the prediction of long-term [1 year] cardiovascular complications."* [127]
10. [It was concluded] "*...that, with the possible exception 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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Alan R Aitkenhead

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 [ii]

Alan Aitkenhead was a research fellow in Oxford in 1978-79 and then became senior lecturer in Leicester. He remained there until 1988 when he was appointed professor of anaesthesia in Nottingham[i].

At least a third of his publications were from his time at Leicester and a specific interest was that of colon blood flow.

This is rather a niche topic but the rationale is the answer to the question "*Can anaesthesia affect blood flow to the bowel and therefore influence the healing of anastomoses*?"

Colon blood flow

The first paper (1977) highlighted by the Medline Database was "*The effect of changes in arterial pCO_2 on colonic blood flow in the dog*" [1] which was published in the Scottish Medical Journal. Following this was "*The effects of subarachnoid spinal block on colonic blood flow in the dog"* [2]. This was presented at an ARS meeting in London in October 1977. The blood flow was measured by injecting Xe-133 into the superior mesenteric artery and determining its clearance through the main marginal vein of the colon. Blood flow increased by 22% and this was associated with a marked decrease in colonic vascular resistance, 44%.

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[i] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916

[ii] http://www.thestar.com/news/crime/2013/05/02/dr_george_doodnaught_trial_hospital_engaged_in_coverup_prosecution_alleges.html

This was followed by a full paper on "*High spinal nerve block for bowel anastomosis....*" [3]; a retrospective clinical study of neuraxial block vs. general anaesthesia. There was a threefold incidence of dehiscence in the general anaesthesia group compared with the neuraxial block group. The size of the study was such that this was not statistically significant. Morphine also appeared to have an increased risk of anastomotic failure.

A further dog study ensued – "*Effects of subarachnoid spinal nerve block and arterial pCO_2 on colon blood flow in the dog"* [6]. Spinal nerve block caused a significant increase in colonic blood flow irrespective of pCO_2. It was considered to be of some clinical importance.

Highlighting the 'niche', another paper in 1980 was published in the British Journal of Surgery [8]; the subject was certainly of surgical significance. This dog study showed that a 10% loss in blood (over 20 minutes), with no change in blood pressure and very little in heart rate, was associated with a 26% fall in cardiac output. Colonic blood flow and oxygen availability fell by a quarter; all these changes were significant. Retransfusion of shed blood resulted in a slow and incomplete return to pre-bleed status. It was advised that the "*slightest degree of hypovolaemia should be avoided*" and that systemic blood is inadequate indicator of need for transfusion.

The third publication on this topic was reported in '*Cardiovascular Research*', "*Colon blood flow in the dog: effects of changes in arterial carbon dioxide tension"* [9]. It describes the use of 133Xenon for the determination of colonic blood flow. Hypercapnia increased the blood flow by 50% and hypocapnia a 25% fall; "*...there was a straight line relationship between colon blood flow and arterial pCO2."* However, hypercapnia also caused a significant increase in colon oxygen consumption. This again may be significant in anaesthetic practice.

This work covered the two major anaesthetic 'side effects'; hypotension and hypocapnia; the latter very popular at the time as it was considered to be useful in reducing the need for analgesic supplements.

Two review articles were written in 1984 on the subject of "*Anaesthesia and/for bowel surgery*" [12, 13].

In 1988 there was a prospective study of "*High spinal nerve block for large bowel anastomosis*" [29]. Dehiscence of the anastomosis was of equal incidence in both the spinal and general anaesthesia groups but the transfusion rate in the general anaesthesia group was twice that in the spinal group.

Moving from the colon to the oesophagus: "*Lower oesophageal contractility as an indicator of brain death in paralysed and mechanically ventilated patients with head injury"* 1987 [24]. [Oesophageal sphincter pressure had been studied as an indicator of depth of anaesthesia] All patients with no spontaneous lower oesophageal contractility were invariably diagnosed as brain dead. Non-propulsive oesophageal activity requires an intact connection between the brain and oesophagus. It was suggested that oesophageal contractility might be useful in identifying brain death.

Another review on the wide topic of *"Anaesthesia and the gastro-intestinal system"* [26] was published in 1988.

The final GIT related paper was in 1990, *"Relationship between lower oesophageal contractility and type of surgical stimulation"* [36]. The two stimuli were those of hysterectomy and those of varicose vein surgery. Spontaneous oesophageal contractions and provoked contractions were greater during hysterectomy. The use of surrogate measures of depths of anaesthesia faded when the bispectral index (BIS) and evoked brain stem potentials became mainstream.

Awareness

Awareness and depth of anaesthesia was a constant food for thought during the 1970s and 80s. In 1983 Aitkenhead wrote a review on awareness in the *Annals of the Royal College of Surgeons of England* [10]. It was a general overview. What should a patient be told after experiencing awareness and, preoperatively, about the risk? He addressed this problem in an editorial in 1990 [34]. It was a comprehensive advisory. The anaesthetist should always be informed of the possibility of awareness; lack of communication would be overcome if anaesthetists talked to their patients after recovery and the patient's account should be believed. Awareness can occur without fault (this should be explained to the patient) and account should be recorded in the hospital notes, alerting future anaesthetists to the

problem. If an error had occurred it was Aitkenhead's view the error should be admitted "*...as this may serve to reduce the patient's fears about awareness during subsequent operations*" [the author concurs with this]. He believed that awareness should be discussed at the pre-operative visit especially for the patient at high risk, such as before Caesarean section.

A year later an audit involving 1000 patients was reported [40]. The patients were interviewed between 20 and 36 hours after surgery. Using a standard set of questions the incidence of recall and dreams were 0.2% and 0.9% respectively. This was much lower than similar studies.

An editorial in 1996, "*Awareness during anaesthesia: when is an anaesthetic not an anaesthetic*?" appeared in the *Canadian Journal of Anaesthesia* [61] and finally, in 2014, the "*Personal and medicolegal implications of awareness*" [81], an editorial.

Intensive Care

The earliest foray into this area was with Ledingham et al. at the Western Infirmary, Glasgow, and concerned the "*Movement of the critically ill within hospital*" [4]. It described a "*mobile intensive care unit (MICU)*"; a patient trolley with appropriate attachments for all the usual monitors and pumps.

The next was with Willis and Barnes, Oxfordshire Area Health Authority (Teaching) Ambulance Service staffing officer and senior technician at the John Radcliffe Hospital respectively. It describes the design of a patient trolley to facilitate the transfer of intensive care patients between hospitals with minimal disruption [7].

An editorial with Graham Smith was published in 1986 on "*Aspects of intensive care*" [22]. It is an introduction to the Postgraduate Issue devoted to advances in intensive care.

In 1989 there was paper, "*Comparison of propofol and midazolam for sedation in critically ill patients*" [32] in the Lancet, followed by a letter about propofol and intensive care [30]. This was a short letter about the quick time of recovery from propofol compared with midazolam and was answering a comment[iii] about the use and

[iii] Standing,V. And Leach, F. Lancet 1989;2:975

expense of using propofol for long term sedation. There was also a review article in the British Journal of Anaesthesia [31] on the same subject, "*Analgesia and sedation in intensive care*" [30]

Four years later Aitkenhead was a member of the team developing "*International standards for safety in the intensive care unit. Developed by the International Task Force on Safety in the Intensive Care Unit*" [45]. This was endorsed by the World Federation of Societies of Intensive and Critical Care Medicine. It covered staffing, design, services, equipment, monitoring, records, drugs and infection control.

Respiration/Simulation

"*Quantitative effects of respired helium and oxygen mixtures on gas flow using conventional oxygen masks*" [11]. A mixture of 79% helium/21% oxygen was administered via a conventional, disposable face mask to a resuscitation dummy. The greatest flow was at tracheal concentration of 40% helium which, with fresh gas flows in excess of eight litres per minute, all masks delivered.

1994: "*Effect of three different surgical prone positions on lung volumes in healthy volunteers*" [51]. The knee-chest position was compared with the prone position using an Eschmann frame and a standard prone position. The study was done in awake volunteers – it was shown that the knee-chest position caused the least respiratory restriction.

1998: "*A physiology simulator: validation of its respiratory components and its ability to predict the patient's response to changes in mechanical ventilation*" [65]. The computer simulator was supplied with a wide variety of parameters from patients receiving intensive care. Values calculated by the simulator for PaO_2, SaO_2, PvO_2, SvO_2, $PaCO_2$, $PvCO_2$ and arterial pH, when compared with measured values, were accurate. Subsequent changes in the patient were simulated in the simulator and the 95% limits of agreement were good. It was suggested that it could be used to predict the effects of change in ventilation in stable intensive care patients.

1999: *"Estimation of alveolar deadspace fraction using arterial and end-tidal CO_2: a factor analysis using a physiological simulation"* [67]. Alveolar dead space can be used to monitor pulmonary disease and predict the ability to wean from mechanical ventilation. As in the previous study the simulator used was the Nottingham Physiology Simulator (NPS). Read the original paper; VDalv/VTalv = 1.135 x (Pa-E'CO_2)/PaCO_2-0.005 during normal physiological conditions. The equation could be used clinically to determine the alveolar dead space.

In 2000 there were two papers published in the same issue of *Anesthesia and Analgesia, "Investigating hypoxemia during apnea: validation of a set of physiological models*" [69] was the first. It was to further validate the NPS. They reproduced the methodology of previous clinical studies. The results were within 2% in most cases and within 13% of all cases.

The second was *"Factors determining the onset and course of hypoxemia during apnea: an investigation using physiological modelling"* [68]. Using the NPS, hypoxemia caused by apnoea after pulmonary denitrogenation was studied*. A wide range of respiratory parameters were altered to examine their influence on the onset of hypoxaemia.* Airway obstruction was bad -reducing the time to 50% oxyhemoglobin saturation to 8 minutes (vs. 11minutes). One hundred percent oxygen was good; prolonging the time to 66 minutes [that's why it was used in the testing process for brain death]. This did highlight the value of good simulation as this study could not be performed in volunteers or patients.

2002: *"Effect of videotape feedback on anaesthetists' performance while managing simulated anaesthetic crises: a multicentre study*" [71]. "*Those trainees exposed to videotape feedback had a shorter median 'time to solve' and a smaller decrease in chart error when compared to those not exposed to video feedback*". This type of study is intrinsically difficult and these results, as in other similar studies, were not statistically significant.

2003: *"Estimating alveolar dead space from the arterial to end-tidal CO_2 gradient: a modeling analysis"* [73]. This seems to be very similar to the 1999 paper in Anaesthesia and Intensive Care.

2003: *"Validation of an original mathematical model of CO_2 elimination and dead space ventilation"* [74]. Data from previous clinical investigations were used to validate a new mathematical model. The first used low-dead space, the second examined dead space during anaesthesia. This validation against previously published clinical data was such that it could be used in theoretical investigations where data is not available.

A subject not much studied is that of the cough. Aitkenhead did author a few papers on the topic[iv]. The first three were all in 1994 and obviously the result of having bought a tussometer.

"*The tussometer: accuracy and reproducibility*" [54]. This was a new technique for measuring laryngeal function. It analysed the airflow waveform during a maximum effort voluntary cough. Cough peak flow rate and peak velocity time "…*were found to be reproducible; the within-subject variability for CPFR was found to be 23.9% and for PVT 9%*." There was no inter-observer variation.

"*Effect of topical anaesthesia on the motor performance of vocal cords as assessed by tussometry*" [52]. The measured variables remained unchanged and it was concluded that topical anaesthesia did not impair the motor performance of the vocal cords.

"*Relationship between expired lung volume, peak flow rate and peak velocity time during a voluntary cough manoeuvre*" [53]. Tussometry was used during voluntary cough manoeuvres at a variety of lung volumes. Peak velocity time varied with *cough peak flow rate* which had a direct relationship to expired lung volume. These

[iv] The subject is of interest to the author as, coincidentally, whilst working in Nottingham he had a project based on the mechanics of the cough. As an aside, the one really pertinent publication happened to be in Russian and the author spent a few interesting hours with a Russian/English dictionary translating it.

relationships should be taken into account when interpreting the results of tussometry.

The final paper using the tussometer was in 1995: "*Relationship of peak flow rate and peak velocity time during voluntary coughing*" [59]. This was a study of the cough dynamics of men and women. "*There was a positive correlation between peak velocity time and cough peak flow rate in both..."* Height and sex were determinants of the peak flow rate/peak velocity time relationship. Anatomical differences "*may have implications*" when interpreting tussometry.

Pharmacokinetics

1984: "*Pharmacokinetics of single-dose i.v. morphine in normal volunteers and patients with end-stage renal failure*" [14]. There was considerable variation but plasma concentrations in the patients with renal failure were higher for the first quarter of an hour. Pharmacokinetic parameters were significantly different between the two groups apart from the terminal elimination half-life and total body clearance, which were similar.

1984: "*Pharmacokinetics and analgesic effect of slow-release oral morphine sulphate in volunteers*" [16]. The mean peak plasma concentration occurred at a mean time of 142.5 minutes and analgesia was maximum about 40 minutes later.

1988: "*The pharmacokinetics of oral and intravenous nalbuphine in healthy volunteers*" [27]. A three compartment model was used to derive pharmacokinetic parameters.

1991: "*Simple method for the determination of morphine and its active glucuronide metabolite in human plasma by high-performance liquid chromatography with electrochemical detection"* [41]. A simple method based on the method of Svensson [J. Chromatogr., 230 (1982) 427 and 375 (1986) 174].

Consent

1999: "*Anaesthetists need consent, but not written consent*" [66] A letter. This was in response to an article by R Dobson which said that

"*...consent from patients specifically for a general anaesthetic is not needed*". Aitkenhead was making the point that this was an inaccurate reflection of what the AAGBI guidelines advised. A signed consent did not guarantee that the patient understood the risks and that it was more important to accurately record what was discussed about the procedure and to what the patient had agreed.

2006: "*Informing and consenting for anaesthesia*" [78]. The paternalistic actions of doctors were no longer acceptable and this had been highlighted in the courts. Aitkenhead made it clear that anaesthetists should be aware of current requirements regarding patients' need for information and obtaining appropriate consent for anaesthetic procedures.

Other miscellaneous publications of interest

1986: *"Does anaesthetics research need training?"*[21] The first line reads "*Anaesthetics research in the UK appears to be thriving*." This was because of the increase in publications and submissions for presentation at the Anaesthetic Research Society meetings. However adverse comments had been made on the quality and the need for education in scientific methodology. It was said that it was important to recruit the academic teachers of the future, to enhance the finances (both personal and for research[v]), and for the consideration of training of non-clinical scientists.

1987: *"Clinical investigation - why we must keep control"*[23]. The 'control' referred to here is the control group of patients in comparative studies and highlights some of the problems of historic 'controls' and placebos and such like.

1991: *"Comparison of contemporaneous and retrospective assessment of postoperative pain using the visual analogue scale"*[39] Although there were significant correlations between contemporaneous scores and the

[v] At about this time the annual capital available to the academic department in Nottingham was of the order of £3000. No wonder it was hard to recruit a new professor.

retrospective scores there was a wide scatter of results. The two sets of measurements were not interchangeable.

1993: *"The effect of the anaesthetist's attire on patient attitudes. The influence of dress on patient perception of the anaesthetist's prestige"*[48]. This was the difference between formal or casual wear. In brief the mode of dress did not make a difference. The preferred preference was for name tags, white coats and short hair.

1994: *"The pattern of litigation against anaesthetists"*[50]. This appeared in a Postgraduate Educational issue following a Symposium on Mishap or Negligence. The symposium actually occurred about eighteen months earlier. The 'pattern' of litigation described covers all the usual suspects – airway management, hypoxaemia, cerebral damage, drug errors, anaesthetist's failures, etc.

1997: *"Anaesthetic disasters: handling the aftermath"*[62]. This is a "Special Communication" on the management of the situation following a major adverse event – severe injury or death of a patient.

Books

Textbook of Anaesthesia, 1985, by G. Smith and A. R. Aitkenhead (multiple editions 1985 -2013)

Clinical Anesthesia, 1996, by J. S. Gravenstein and A. R. Aitkenhead

Quality and Risk Management in Anaesthesia (Bailliere's Clinical Anaesthesiology), 1996, by A. R. Aitkenhead

Pharmacology of the Critically Ill, 2001, by Gilbert Park, Maire Shelly, Ronald M. Jones and Alan R. Aitkenhead

Fundamentals of Anaesthesia and Acute Medicine, 2001, by Ronald M. Jones and A. R. Aitkenhead

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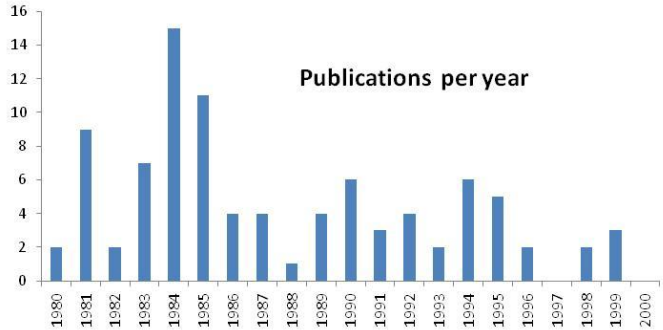
MD FRCA

As an anaesthetic trainee Ron Jones went to the University of Michigan and wrote his first paper whilst there; he was first author, "*Narcotic-induced chole-dochoduodenal sphincter spasm reversed by glucagon*" [1]. This was followed by another on the
same topic [5]. He maximised his opportunity as there was a third paper published on the topic of "*Use of pentolinium in postoperative hypertension resistant to sodium nitroprusside*" [6]. His experience of working there is described in the journal *Anaesthesia* in 1981 [12].

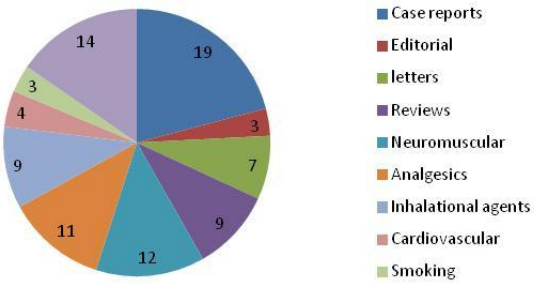
He returned to the UK and worked in Nottingham as a senior registrar. With Tom Healy he wrote a review on the subject of "*Anaesthesia and demyelinating disease*" [2]. He soon became a consultant and was determined on an academic career.

Jones became senior lecturer at Guy's in 1982 and became the foundation professor of anaesthesia at St Mary's Medical School in 1990, a college of Imperial College. The rearrangement of the various London establishments was complex[i].

In the years 1981, 1982 (a quiet year), 1983 and 1984 thirty three papers were published; a prodigious amount and indicative of his determination. This was to be the peak of his productivity.



[i] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916



Types / Subjects of publications

Neuromuscular (excluding case reports)
1983: [20] The rat phrenic nerve diaphragm was a common preparation used in the Nottingham academic department. This study was with Brian Pollard. The synergism of mixtures of tubocurarine and pancuronium and tubocurarine and alcuronium were demonstrated but a mixture of alcuronium and pancuronium was not synergistic. Synergism would become a significant feature of Pollard's work.

1983: [19] This letter pointed out an error of interpretation by Donati, Ferguson and Bevan[ii] of a paper published by Williams, Webb and Calvey[iii]. An interesting start to the study of neuro-muscular blockade; at least it demonstrated their understanding of the physiology. Jones was at Guys Hospital when this was published.

1984: [30] Edrophonium reversed atracurium neuromuscular blockade more rapidly than neostigmine when 21 patients were studied. "*A T4 ratio of 0.5 was confirmed to be compatible with the reliable and safe reversal of atracurium - induced neuromuscular blockade*". A sustained 5s

[ii] Donati F, Ferguson A, Bevan DR. Anesth Analg 983;62:3146
[iii] Williams NE, Webb SN, Calvey TN. Br J Anaesth 1980

head lift was one parameter of adequate recovery. More recently 0.7 or even 0.9 have been recommended.

1984: [33] "*Atracurium for short surgical procedures in day patients*"; a straightforward assessment of dose/onset/duration and recovery.

1985: [46] "*Factors affecting train-of-four fade*". This study suggested that a fixed T4 ratio (a measure of fade) may have different consequences with different drugs; it was said that it was the absolute height of the fourth twitch that determined sustained muscle power.

This was the opening article that preceded a series of studies on fade; fade being the difference between the magnitude (height) of the first twitch of the train of four and the fourth [38, 54, 55].

1985: [38] This was about the onset of neuromuscular block with pancuronium, tubocurarine and a mixture of them. Four indices of onset were defined. "*The mixture had the most rapid total onset time (100.3s), tubocurarine the slowest (135.1s) and pancuronium was intermediate (124.0s)*".

1987: [54] "*Relationship between single twitch depression and train-of-four fade: influence of relaxant dose during onset and spontaneous offset of neuromuscular blockade*." This study demonstrated that during block onset there was "*a variable and dose-related relationship between the ratio of height of the initial twitch, T1, and fourth twitch, T4.*" During recovery the same T1 values were associated with similar degrees of fade. The T4 ratio during recovery bore a fixed relationship to the initial T1 depression. (Does this mean that only T1 needs to be monitored?)

1988: [55] "*Fade profiles during spontaneous offset of neuromuscular blockade: vecuronium and gallamine compared*". They studied the onset and the spontaneous offset of neuromuscular blockade using vecuronium and gallamine. Gallamine produced significantly more fade than vecuronium but there was less fade during onset than offset.

What was the clinical significance of these results?

The remaining studies of neuromuscular blockade are of a heterogeneous mixture.

1985: [41] This review covered the new agents atracurium and vecuronium and highlighted the importance of calcium and calmodulin in neuromuscular physiology.

1986: [47] The reversal of neuromuscular blockade due to atracurium with edrophonium or neostigmine was measured. Edrophonium produced a significantly faster reversal than the small dose of neostigmine but a larger dose produced a reversal time close to edrophonium. So much research was done using edrophonium but, in the author's experience, it was rarely if ever used clinically.

1986: [48] The onset of neuromuscular block with vecuronium was quicker with doses up to ED95 x 3; higher doses did not. The pharmacokinetics was discussed.

1986: [49] A case report on the use of vecuronium during surgery for phaeochromocytoma.

1989: [58] A review of "*The priming principle: how does it work and should we be using it?*" followed by "*The priming principle: early development*" in 1990 [62].

1989: [56] "*Atracurium recovery: prediction of safe reversal times with edrophonium*". Safe reversal at this time was thought to be when the T4 ratio was greater than 0.5; this is very low by today's standards[iv]. The study demonstrated the ease of reversal of atracurium as long as the procedure lasted 30 minutes. It was said that *"if no monitoring equipment* [was] *available, at least half-an-hour should elapse after administration of atracurium ... before rapid and reliable reversal* [could] *be anticipated."*

[iv] Kopman AF. Residual neuromuscular block and adverse respiratory events. Anaesth Analg 2008;107:1756

Nerve stimulators were rarely available and if they were they were of a hand-held type, operated manually and usually when recovery was not as anticipated..

1990: [60] "*Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function*". The maximum block and time to achieve it were similar in the two groups but the duration of action of doxacurium was longer in the renal failure group (not significant considering the size of the study). Spontaneous recovery was not significantly different.

1991: [67] A case report: "*Resistance to atracurium in a patient with an increase in plasma alpha 1 globulins*". It was thought that this was due to binding of the drug to the protein.

1992: [72] "*Mivacurium chloride: a study to evaluate its use during propofol-nitrous oxide anaesthesia*".

1994: [78] "*Safety and potency of ANQ 9040 in male volunteers*". This was a collaboration with Donati whose interpretation of previous work was criticised ten years earlier. ANQ 9040 was an experimental non-depolarizing neuromuscular relaxant. It was thought to have a quick onset time similar to suxamethonium. The estimated ED95 of ANQ was 1.3 mg/kg. No important adverse occurred but there was an increase in plasma histamine associated with a decrease in mean arterial pressure and a significant increase in heart rate. The onset time to neuro-muscular block was 51.3s. The histamine release suggested that it would not be clinically useful.

Let's go now to the studies of cardiovascular content.

Cardiovascular (excluding case reports)
"*Rate pressure product"* [3] 1980 (a letter): The RPP was one of the earlier indices used in anaesthetc clinical practice – the goal was to avoid the systolic blood pressure x heart rate exceeding a certain value – for the

patient with ischaemic heart disease it could be as low as 12000. So a blood pressure of 120mmHg x heart rate of 100 bpm would be border-line.

"Cardiovascular responses and changes in plasma cation levels associated with infusion of hyperosmolar urea solutions" [11] 1981 (1981 was a very busy year). A hyperosmolar urea solution used to decrease brain volume caused hypotension and decreasing levels of ionized calcium. This was studied using dogs. There were significant reductions in arterial pressure, systemic vascular resistance, hematocrit, and levels of plasma sodium and ionized calcium. Cardiac output, right atrial pressure, arterial pO_2 and pCO_2 and plasma potassium all increased. These were considered important effects.

"*Anaesthesia in first-degree atrioventricular block"* [15]; letter. This was a strong criticism of the anaesthetic used for a patient with first-degree atrioventricular block – and, this was in 1983 – Jones still thought it necessary to advocate the routine use of electrocardiography during anaesthesia.
"*Renin-angiotensin activation is not primarily responsible for the changes in mean arterial pressure during sternotomy in patients undergoing cardiac surgery"* [23] 1984. The bottom-line was that giving an angiotensin converting enzyme inhibitor did not change the cardiovascular response to sternotomy.

"*Nifedipine and cardiopulmonary bypass. Post-bypass manage-ment after continuation or withdrawal of therapy*" [24] 1984. One group of patients had nifedipine withdrawn prior to cardiac surgery, another continued therapy, and there was a control group. Vasodilator intervention was required more in the 'withdrawn' group. This reduced the need for inotropic support but systemic vascular resistance was increased. It was recommended that nifedipine should be continued.

"*The anaesthetic management of the Eisenmenger syndrome*" [26] 1984; a review.

"*Calcium antagonists*" [28] 1984; an editorial.

"Cardiac rate and rhythm during anaesthesia for dental extraction. A comparison of halothane, enflurane and isoflurane" [39] 1985. Halothane had the highest rate of arrhythmia. Heart rates were highest in those patients given isoflurane, lowest with halothane.

Inhalational agents

1984: "*Clinical comparison of inhalation anaesthetic agents*" [16]. This is a lengthy review-type article[v].

1985: "*Anaesthetic carrier gases. Their effect on middle-ear pressure peri-operatively*" [45]. The middle ear pressure was measured with a self-calibrating device fitted into the external auditory meatus. The anaesthetic carrier gas was oxygen, oxygen-enriched air or nitrous oxide. Only nitrous oxide caused pressure change and it was recommended that oxygen-enriched air was the carrier of choice.

1990: "*Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers"* [64]. An early study of desflurane; inhalation of the anaesthetic was accomplished without coughing, breath-holding or salivation. Respiratory and cardiovascular parameters were recorded and it was noted that after 90 minutes of anaesthetic exposure there was a rapid and clear-headed recovery.

1990: "*Kinetics and potency of desflurance (I-653) in volunteers"* [63] . It was predicted that desflurane should cause rapid induction and recovery from anaesthesia. The MAC was estimated at 5%. In the study it was shown that after 10-minutes the alveolar to inspired concentration was 0.82. Ten minutes after cessation of desflurane the alveolar concentration fell 89%. Recovery was such that response to commands occurred about 2.7 minutes after cessation. MAC-awake was 2.42% and MAC 4.58%.

[v] The reference year in the Medline database was incorrect.

1990: "*Biotransformation and hepato-renal function in volunteers after exposure to desflurane (I-653)*" [65]. Volunteers were exposed to (on average) inspired concentration of 3.6% for (on average) 89 minutes. A huge array of tests were carried out but there "were no significant changes in any measured haematological or biochemical variable".

1990: "*Desflurane and sevoflurane: inhalation anaesthetics for this decade?"* [61]; a review.

1991: *"Induction and recovery characteristics of desflurane in day case patients: a comparison with propofol*" [68]. Sixty patients were allocated to receive either desflurane or propofol. Loss of consciousness with desflurane induction occurred in approximately two minutes. Psychomotor scores were worse in patients given propofol which suggested that desflurane would be suitable for day case anaesthesia.

1991: "*A prospective study of liver function in infants and children exposed to daily isoflurane for several weeks*" [66]. Daily radiotherapy was the reason for the daily anaesthesia. There were no measurable changes in the liver function tests.

1992: "*Inhalational agents - an update*" [71]; a review.

1992: "*A national database on hepatitis after exposure to inhaled halothane*" [69];a letter. The idea of having a database, which Kenna and Jones would create, of patients suffering from 'halothane hepatitis' was to enable a study of the genetic make-up of those susceptible.

1992: "*Recovery characteristics using isoflurane or propofol for maintenance of anaesthesia: a double-blind controlled trial*" [70]. One hundred and fourteen patients were studied; anaesthesia being induced with propofol. Atracurium was given and nitrous oxide in oxygen. Some patients received isoflurane and alfentanil (bolus + infusion). Other patients received propofol with alfentanil as an infusion. There was a control group of subjects who did not have an anaesthetic. "*There were no significant differences in awakening or orientation times*" or psychomotor

testing during recovery. There were significant differences with the control group. The techniques used were all acceptable.

1995: "*Is there a need for a new inhalational anaesthetic agent?"* [82]; this is a discussion on the development and merits of new agents which, in this case, is really about the properties of desflurane. Its sympathetic autonomic effect makes it less than perfect.

1995: "*The organ toxicity of inhaled anesthetics*" [83]. This was in an *Anesthesia and Analgesia* supplement devoted to the pharmacology of sevoflurane; it has 143 references and covers all aspects of the subject. Sevoflurane compared favourably, it was thought that there was a low rate of metabolism because of its low tissue solubility and that the metabolic processes did not produce reactive metabolites.

1995: "*Serum fluoride concentration and urine osmolality after enflurane and sevoflurane anesthesia in male volunteers*" [84]. The study involved giving the anaesthetics for a variety of MAC hours (minimum alveolar concentration x duration). There was an 18-h post-anaesthesia period of fluid deprivation during which the serum fluoride concentration was measured. Sevoflurane resulted in the greatest serum fluoride concentration which reached a peak in the 9-MAC-hour group. There were no significant differences between enflurane or sevoflurane anaesthesia and it showed that prolonged administration of enflurane or sevoflurane is not associated with impaired renal function.

And finally, the 'thorn in the foot' of sevoflurane -

1996: "*Sevoflurane degradation by soda lime in a circle breathing system"* [85] Compound A, a vinyl ether, is the end product sevoflurane degradation by soda-lime. Using gas chromatography and a flame ionisation detector Compound A concentration was measured. "*It ranged between 10 to 32 ppm in the inspiratory limb and 7 to 26 ppm in the expiratory limb*." The temperature of the soda lime and the end-tidal concentration was positively correlated with the amount of Compound A.

Smoking

1984: "*Smoking and anesthesia: preoperative abstinence and perioperative morbidity*" [32]. This seems like a discussion document. What are the risks of stopping smoking in the short period before operation? Carbon monoxide and nicotine elimination, improved ciliary beating and reduction in sputum volume may enhance well being. "*There are no proven disadvantages to the respiratory system from stopping smoking in the short term, and it seems unwise to sacrifice proven advantages for a theoretic consideration that sputum may become "stickier" and more difficult to clear*."

1985: "*Smoking before surgery: the case for stopping*" [42]. This was an editorial type article. Its conclusion was that "*...roughly six weeks after stopping smoking patients may expect an improvement in pulmonary function, a reduction in postoperative respiratory morbidity, and a return towards normal immune responses. If, however, patients cannot be persuaded to stop smoking for this period (or permanently) considerable benefit will still accrue from the improvement in cardiovascular function brought about by even 12 to 24 hours of abstention from smoking - a factor of particular importance in patients with ischaemic heart disease."*

1993: "*The effectiveness of preoperative advice to stop smoking: a prospective controlled trial*" [74] The advice was ineffective. However, it did reduce the amount of tobacco consumed. But more than a sixth of all patients smoked within an hour of surgery.

Analgesics

1981: *"Prevention of rigidity during fentanyl-oxygen induction of anesthesia*" [4]. Patients undergoing coronary artery surgery were given 2500μg of fentanyl for induction of anaesthesia and rigidity occurred (hampering manual ventilation) but was ameliorated if pancuronium was given at the same time.

1984: "*Naproxen pharmacokinetics in the elderly*" [34]. Plasma clearance/bioavailability was found to be less in the elderly than in a

younger group and the fraction unbound was doubled; this relates closely to the toxic effect. Significant dose reduction was advised.

1985: "*Parenteral aspirin for pain relief in day-case dental anaesthesia. A randomised double blind placebo controlled trial*" [40]. Patients received either lysine acetylsalicylate intravenously or a placebo. Patients given lysine acetylsalicylate had better recovery overall but there were no statistically significant differences in pain scores. This was accompanied by a "*Comparison of infusions of morphine and lysine acetyl salicylate for the relief of pain after surgery*" [37] and "*Comparison of infusions of morphine and lysine acetyl salicylate for the relief of pain following thoracic surgery*" [44]. Lysine acetyl salicylate provided analgesia equal to morphine. There was less drowsiness, nausea and vomiting. There were no untoward side effects.

1994: "*Comparison of desflurane and fentanyl-based anaesthetic techniques for coronary artery bypass surgery*" [79]. This was a comparison between desflurane and fentanyl vs. high dose fentanyl. With desflurane the mean arterial pressure was maintained during incision and sternotomy but decreased afterwards. Fentanyl maintained arterial pressure during induction but it increased at incision. Heart rate was lower with desflurane than fentanyl prior to cardiopulmonary bypass. Vasodilators were needed more in the fentanyl group.

1998: "*Comparison of remifentanil in combination with isoflurane or propofol for short-stay surgical procedures*" [87]. Two hundred and fifty patients were studied; they were given either a remifentanil with isoflurane, or remifentanil with a propofol infusion. There were differences but the differences were clinically insignificant (author's interpretation).

1999: "*Alpha-2 and imidazoline receptor agonists: Their pharmacology and therapeutic role*" [88]; another *dexmedetomidine on isoflurane requirements in healthy* discussion document; a review. This was the opening for the "*Effects of volunteers. 1:Pharmacodynamic and pharmacokinetic interactions*" [89]. Dexmedetomidine is an alpha 2-

adrenoceptor agonist. Volunteers were given isoflurane preceded by an infusion of dexmedetomidine on three occasions. The high dose dexmedetomidine group responded to a tetanic stimulus at half the isoflurane concentration at which the placebo group responded. Dexmedetomidine also decreased the heart rate and arterial pressures. Cognitive dysfunction persisted for several hours after anaesthesia.

1999: "*Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 2: Auditory and somatosensory evoked responses*" [90]. Auditory and somatosensory evoked responses were measured after doses of dexmedetomidine at various end-tidal isoflurane concentrations. Some evoked parameters increased as isoflurane concentration decreased, some increased. The changes seen suggested that dexmedetomidine has a different action to that of volatile agents "*...at least for effects on the cortex*". It could have other potentiating effects such as N_2O and opiates, or indeed an isoflurane-like activity at subcortical levels.

2001: "*Effect of dexmedetomidine on propofol requirements in healthy subjects*" [91]. Dexmedetomidine or a placebo was infused and forty-five minutes later propofol was infused, both in a systematic way. Dexmedetomidine reduced propofol requirements, as measured using behavioural endpoints, and therefore the dose should be reduced when using dexmedetomidine.

Review or review-type articles

"*Anaesthesia and demyelinating disease*" [2]
"*Clinical comparison of inhalation anaesthetic agents*" [16].
"*The anaesthetic management of the Eisenmenger syndrome*" [26]
"*Neuromuscular transmission and its blockade. Pharmacology, monitoring and physiology updated*" [41]
"*The priming principle: how does it work and should we be using it*?" [58]. This was followed by a letter ("*The priming principle: early development*") [62] explaining that the earliest indication of the possibility of 'priming' was by the Nottingham team of Hussain, Healy and Birmingham in 1979.
"*Desflurane and sevoflurane: inhalation anaesthetics for this decade?"* [61]

"*Inhalational agents - an update*" [71]
"*The organ toxicity of inhaled anesthetics*" [83]
"*Alpha-2 and imidazoline receptor agonists: Their pharmacology and therapeutic role*" [88]

Case reports
1981: "*Severe hypertension associated with pancuronium in a patient with a phaeochromocytoma*" [7] (not surprising!).

1981: "*Cardiovascular and hormonal responses to electroconvulsive therapy. Modification of an exaggerated response in an hypertensive patient by beta-receptor blockade"* [9]. Propanolol attenuated the marked rise in blood pressure, heart rate and plasma catecholamines. The latter increased 15x, three times more than that expected to produce a cardiovascular response. The RPP was 16000 with β-blockade, 35000 without, and so attenuation with β-blockers was recommended with heart disease.

1981: *"Termination of cardiopulmonary bypass facilitated by insulin*" [10] 1981. The positive inotropic mechanism of insulin was unclear. In animal experiments it had been shown that glucose-insulin-potassium mixtures enhanced subendocardial perfusion and so this may have been a factor.

1981: *"Cardiovascular responses and changes in plasma cation levels associated with infusion of hyperosmolar urea solutions"* [11]. A hyperosmolar urea solution used to decrease brain volume caused hypotension and decreasing levels of ionized calcium. This was studied using dogs. There were significant reductions in arterial pressure, systemic vascular resistance, hematocrit, and levels of plasma sodium and ionized calcium. Cardiac output, right atrial pressure, arterial pO_2 and pCO_2 and plasma potassium all increased. These were considered important effects.

1982: "*Severe hypertension and flushing in a patient with a non-metastatic carcinoid tumour. Hypertension and flushing with a solitary carcinoid tumour"* [14].

1983: *"Reversal of biliary sphincter spasm with low dose glucagon during operative cholangiography"* [18].

1983: *"Fatal pulmonary embolism secondary to limb exsanguination"* [21].

1984: "*Vasomotor disturbance at unilateral cordotomy*" [25].

1984: "*Anaesthetic considerations in patients with paroxysmal supraventricular tachycardia*" [29]; case reports of three patients.

1984¨"*Sleep apnoea following cervical cord surgery*" [35] .

1985: [43] a case report summed up by its title "*Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium*".

1986: [49] A case report on the use of vecuronium during surgery for phaeochromocytoma.

1986: "*Generalized grand mal seizure after recovery from uncomplicated fentanyl-etomidate anesthesia"* [50].

1989: "*Postoperative hypotension associated with enalapril*" [59].

1991: "*Resistance to atracurium in a patient with an increase in plasma alpha 1 globulins*". It was thought that this was due to binding of the drug to the protein [67].

1993: "*Sinus arrest during cholecystectomy*" [73].

1994: "*Spontaneous oesophageal haematoma: a review of the difficult diagnosis*" [75].

Books

Anaesthetic Management: A Rule-Based Guide, 1986, by BJ Pollard, MJ Harrison and RM Jones

Clinical Cardiovascular Medicine in Anaesthesia: Fundamentals of Anaesthesia and Acute Medicine, 1997, by Pierre Coriat and Ronald M. Jones

Fundamentals of Anaesthesia and Acute Medicine, 2001, by Ronald M. Jones and A. R. Aitkenhead

Pharmacology of the Critically Ill, 2001 by Gilbert Park, Maire Shelly, Ronald M. Jones and Alan R. Aitkenhead

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At least a third of Ron Jones' publications were reviews, letters, comments or case reports. The substantial work was about fade during neuromuscular blockade and the early work on desflurane and dexmedetomidine.

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Epilogue

To understand a patient, one listens, looks, touches and measures – and using that knowledge and experience, and the experience of others, a diagnosis is made. Only with the correct diagnosis can the correct treatment be started. The rest is just fine-tuning – but let's start at the beginning.

"Medical training in the 1960s was still, almost completely, rote learning – primarily because the mechanisms of many pathologies and pharmacological agents were only crudely known, so the ability to deduce, for example, the action of a drug from its structure was limited. The anatomy of many drug receptor sites was unknown. Or, to put it another way, the only receptors taught were the α and β adrenergic receptors and the acetylcholine receptor. Rote learning is not everyone's preferred method of learning – memories fail and mnemonics multiply.

As a young house surgeon having to make diagnoses I decided I needed some help – the memory is weaker now but the first diagnostic algorithm related to determining the likely nature of breast lumps. From the past experience of others it was possible to use age as a differential piece of evidence, together with mobility and size – no need to go into greater detail but it gave me a method for systematically giving an order to the possible diagnoses. This was for personal use only.

After a digression, twelve months vocational training as a general practitioner, I realised that general practice was not for me and that I had to search for another specialty. Anaesthesia was an option but a vacancy was also advertised with ICL – a large computing company, they were looking for a medical developer/advisor – I was fresh out of the shell but I applied for it. Fortunately, I believe, the interview for the training post in anaesthesia in Nottingham came first; I took it.

Being in the right place at the right time is good; Nottingham had just acquired a medical school and the academic departments were expanding fast. At interview, I was bold enough to ask if I could be involved in research. In retrospect this was an extraordinary request; that had to wait until examinations had been passed.

Feeling a bit of a dropout, after 'failing' general practice, the books were hit hard and the first exams passed within six months. Some

studies were undertaken under the tutelage of Tom Healy – an enthusiastic, ambitious and very amusing raconteur – a good introduction to scientific methodology, basic statistics on computers and paper writing. Computing didn't really come to have importance until consultant status was achieved, closely followed by a senior lectureship in Nottingham."

The professors of anaesthesia that have been the subjects of the two volumes of "*British Academic Anaesthetists*" have been instrumental in many aspects of the development of anaesthesia in the UK and abroad (and provided me with textbooks and examination experience). This is only one way of telling the story and it must be remembered that there were a large number of other researchers behind the 'head' of the departments.

The references appended to each section name many of these people and their contribution should not be underestimated. Others are not included in the references; these are the multitude of laboratory workers, technicians, pharmacologists, statisticians, graphic artists and not forgetting the secretaries. Before word processors existed all submitted papers were typed and retyped and retyped. Cut and paste and auto-correction did not exist.

In the writing of these stories I have had the privilege of communicating with many of these researchers and without exception they have always been helpful and very interested in the 'stories' of their contemporaries. "I was too busy to know what everybody else was doing".

It has been suggested that I should have integrated the work completed by A in the UK, with similar work by B in USA or C in Germany. Life is too short and I will leave that to someone else.

Other names have been suggested as subjects for the book; again, life is too short. I have no doubt that there are really important productive, innovative, highly knowledgeable people that I have omitted, I can think of a couple at least, but the line has been drawn and here it is.

Volume 3 is left to someone else. One advantage of writing a history based book is that it is less likely to become out of date than a book on pharmacology! **Michael Harrison 2015**

ADDENDUM

Harrison MJ

MD FRCA FANZCA

Michael Harrison trained in anaesthesia in Nottingham, starting in 1971; mentored by Tom Healy. In 1975 he was lecturer in anaesthesia in Sheffield under Prof. Andrew Thornton. He became a consultant in Nottingham in 1977 and a senior lecturer in 1978.
When Tom Healy became professor of anaesthesia in Manchester Harrison became the acting head of department in Nottingham. After five years Harrison resigned his position and emigrated to New Zealand in 1987[1].

He was appointed senior lecturer in the Department of Anaesthesiology in the University of Auckland and again became acting head of the department, and Associate Professor, when Stephan Schug was appointed to the chair in Perth. He continued to work in this department when Alan Merry was appointed to the chair. In 2009 Harrison moved to Wellington.

Like so many others his first publication was a case report; "*Inhaled foreign body*" [1]. The foreign body was a spring from a Biro; tricky to extract but caused no respiratory distress.

Tom Healy encouraged 'bench' research and at that time the laboratory was a converted bathroom in the Nottingham General Hospital; the University Hospital was being built. It was fortunate that it was a bathroom as the first studies were significantly wet [2, 3]. The first assessed intravenous administration sets for particulate contamination,

[1] John Nunn actually got that wrong! J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916.

requiring litres of saline for flushing, and the second tested some blood warmers and required a steady flow of water at 4°C. No matter what care was taken water always seemed to find the floor.

The next bench study was one using an automatic flow interruption bronchoscope [4]. A venturi device was used to ventilate a model lung and the 'oxygenation' was assessed when the model lung was altered by varying resistance and compliance. The more difficult it was to ventilate the lung the higher the oxygen concentration in the ventilated gas – there was less entrainment.

These were relatively easy studies to perform whilst still having significant clinical duties.

In 1975 Harrison moved to Sheffield as lecturer which was a natural progression but it was not a very productive one [5, 7]. It did, however, introduce him to the art of writing – the lecture notes prepared for the primary examination course became the backbone of the "*Aids to Anaesthesia; the Basic Sciences*"[2].

An innovation was published in 1976 "*A double-lumen tube connector*" [6]. This was a simple device that allowed the isolation of one lung and suction access with a simple slide mechanism[3].

One clinical study in Sheffield was a dental sedation study; "*I.v. flunitrazepam and i.v. diazepam in conservative dentistry. A cross-over trial*" [10]; this was not published until 1980.

Back in Nottingham in 1980 an unexpected opportunity arose. A team of engineers and physicists had produced what was considered the first nuclear magnetic resonance imaging machine for humans. Harrison was asked to supervise the first patients through the device - "*Just in case*..." The research space looked like a ship's engine room with cooling pipes, a large Faraday cage and, of course, a very large magnet. The utilitarian appearance was softened with a few mobile patient screens borrowed from a ward. Of course nothing happened but the experience of seeing an ECG trace traversing the screen diagonally in response to the

[2] This was before the AIDS epidemic!

[3] It was taken up by a manufacturer – a more sophisticated prototype was made, a cylindrical valve mechanism. The core when warmed up by exhaled gas expanded and completely froze the mechanism.

magnetic field was intriguing [11]. This may be the first anaesthetic communication about MRI scanning.

That same year was the first of a multifaceted theme on the development of a decision support system for anaesthesia and the use of artificial intelligence system to enhance anaesthesia monitoring. The story is outlined below**.**

In 1978, or thereabouts, two Zenith (Heathkit) computers were bought with 64K of RAM – magnificent! They cost about £2000 each. Once they were turned on there was a green screen and a c:>! What next!? Harrison had no idea how to drive the machine but 'playing' with it and learning Basic – a very linear simple language – eventually allowed programs to be written – these were clumsy but over time became more and more complex.

Using the computer to assist decision making was an early goal and with the help of Frank Johnson (computer whiz and physicist in the orthopaedic department on the opposite side of the corridor) started to create an algorithm for an advisory program to create an anaesthetic recipe for different types of patients with different co-morbidities and surgery. Frank wrote in FORTRAN, which was really frustrating because Harrison was unable to tweak it – and with its complex IF-THEN rules it really needed a lot of tweaking. The answer was a parallel program in Basic, with a simpler structure. These both eventually worked well [12, 13]. The first was presented at an ARS meeting (and was met with some scorn by Prof. Jimmy Payne).

The computers were taken to Sheffield for others to use, for evaluation. In 1980 computer crashes were common. An aluminium 'mask' was put over the keyboard to restrict the keys that could be used. One important point from this evaluation was that the users wanted (needed) explanation for the advice being offered. With two colleagues (Ron Jones and Brian Pollard) the skeleton of the algorithm was turned into a book – *A Rule Based Guide to Anaesthesia Management*.

At that time there was a great upsurge in work on expert systems – de Dombal had published his paper on diagnosing appendicitis

with the intention of reducing the incidence of negative laparotomies[4]. Shortliffe's book on identifying bacteria and the treatment of infection[5] was out and the Edinburgh artificial intelligence unit headed by Michie were marketing a software package called ExpertEase[6] – a workshop was held in London - Harrison attended – the only medic there.

The government of the day was promoting artificial intelligence development and a specialist department in Nottingham was set up. The language used was Prolog – a programming language whose structure gobbled up memory at a phenomenal rate. Projects were needed to use as test beds – Harrison was approached and they used a part of the anaesthetic 'recipe' algorithm from the FORTRAN program to use with this language. They only used the premedication section but this turned out to be quite a feat –Harrison was just the medical advisor [14].

The situation at this time was that programming was a specialist activity, that computer memory was a significant factor (and speed – the FORTRAN program took two minutes to run). Computer hardware was still 'brittle' for routine use and I/O errors and floppy disc incompatibility common.

At this time, the 1980s, interested anaesthetists were writing their own programs on the basic home computers then available, BBC, Sinclair and so on. The journal *Anaesthesia*, for a short time, carried a description of programs that anaesthetists had written; Harrison was the editor for that section but this didn't last long – the fad faded.

Monitors for anaesthesia were also under investigation – each physiological variable had its own measuring device and these devices were festooned on the anaesthetic machine – commonly referred to as a Christmas Tree. The user interface, which is the appearance of the monitor screens, of the values of the different variables was investigated with a variety of different layouts and icons. Some were good, some not

[4] de Dombal FT, Leaper DJ, Staniland JR, McCann AP, Horrocks JC. Br Med J. 1972;2(5804):9–13

[5] MYCIN was developed in the 1970s at Stanford University; a doctoral dissertation of Edward Shortliffe

[6] Professor Donald Michie, MA, D Phil, D Sc, FZS, FRSE, FBCS, FAAAI 1974 - 1984 Director, Machine Intelligence Research Unit, Edinburgh.

so good. Understanding some of them was not intuitive and required varying degrees of relearning.

The concept may have had its origin in the medical bay of Starship Enterprise and it was this - for each variable there would be three zones, high, normal and low. These three zones were of uniform size, completely independent of the scales. For example the scale for blood pressure went from 40 – 200 mmHg, temperature from 34-42˚C but the high, normal, low zones were all the same size [23].

This had the advantage that if any variable was high, or low, they were easily spotted above or below the normal zone. In the computerised form, 3D histograms were displayed for each variable and as time passed the histograms receded into the background as new values appeared in front. Imagine an anaesthetic where all variable were within the normal range, the top surface of the histograms would resemble a plateau, any high or low values become mountains or valleys. In one 3D diagram, all the variables were displayed over the whole duration of the anaesthetic – an integrated display.

However, this was the only integration – the screen or printout – all the monitors were separate so each had to have cabling from their output sockets to an A-D converter. This was complex and a professional company did the job – not exactly charlatans but they certainly made a meal of it. It worked – this was the first time that real-time data collection and processing had been achieved in his studies. Lessons learnt – displays must be intuitive and programmers essential for real-time analysis.

Harrison's move to New Zealand was completed in 1987 and, being ignorant of NZ geography, both national and local, he was extremely pleased to see the medical school with its facilities just across the road from the hospital.

Around this time HP programmable calculators were popular and it was thought that the collecting of blood pressure data could be automated and, through a network of connections Harrison was put in touch with an engineer who was working for Trutest, and later Fisher and Paykel. He helped programming the device. The idea was that basic statistics for the collected data would be updated automatically as new data came in. This would be good for specialist units – for example

neurosurgical patients might have a different data set to orthopaedic patients. When the engineer moved to F&P, contact was lost and the HP hand-held computer ended up in a drawer.

This however started a connection with the Auckland University Department of Engineering – one of their previous graduates had gone on to do medical training and it was through this link that the next big step took place. Harrison had once again reached a point where his computing skills were quite inadequate for what he wanted to do and was about to 'throw in the towel'. Andrew Lowe wanted to do a medical based PhD and had been told about Harrison's work on monitoring – in engineering terminology 'fault detection'. Lowe changed everything and started a very productive era of research, development and publications.

For the next three years, on and off, afterwards the duo worked together, with Lowe's engineering supervisors Brian Mace and Richard Jones. During that time Harrison was introduced to fuzzy logic, neural networks and belief and plausibility, and the rules of evidence.

A major part of Lowe's work[7] was to write a program to connect a desktop computer to a GE/Datex-Ohmeda anaesthetic monitor. Between 1980 and 1987 the 'Christmas Tree' of monitors had largely disappeared and had been replaced with monitors that presented all the variables (most variables) in one box and on one screen. There were waveforms (ECG, arterial and carbon dioxide) and digital values as well. Lowe's software was made slightly more complex because of the need to pass on the data to an automated record keeping system.

With ethics committee and patient approval, many sets of data were captured and processed off-line.

Lowe's thesis covers the scope of this work that involved the theory of fuzzy logic, fuzzy courses (like navigation channels through which the variables pass for certain adverse events), determination of membership functions and rules of evidence – some very complex logic concepts intertwined with maths.

Papers were written about these concepts as applied to anaesthesia monitoring and, for the first time, using rules of evidence and

[7] Lowe A. Evidential inference for fault diagnosis – Application to anaesthesia monitoring. PhD thesis, University of Auckland.

Mu values, different diagnoses were contemplated by combining the various parameters in different ways. These were primarily conceptual and the clinicians' assessments of events were used to correlate the diagnosis with the changes. As the medical advisor for the PhD work Harrison was the one to describe the interrelationships of the variables to, hopefully, detect the events. Fortunately, it is a feature of fuzzy logic systems that 'experts' are used to do this modelling of a system [40, 43-45, 47-49, 51-53, 59].

One triumph of this period was the modelling of malignant hyperpyrexia (MH). It is a rare condition and, after searching for all clinical descriptions of the onset of the condition, a relatively simple model was created using membership functions of fuzzy courses for blood pressure, heart rate, carbon dioxide concentrations and temperature, although temperature was not essential. Physiological variables were taken from a hand-drawn anaesthetic record[8]. The values were widely spaced in time so there had to be some interpolation. The software worked but the data were crude. A simulator centre provided further data but this was also crude.

A chance meeting with Neil Pollock a Palmerston North anaesthetic specialist with a major interest in MH, resulted in the receipt of an almost complete data set for a 'virgin' case of MH in Australia, neither the patient nor the anaesthetist was aware of the susceptibility to MH. The data came as several metres of print out, some interpolation was necessary but not much. Temperature was not recorded initially and so it was clear when the anaesthetist considered the diagnosis because temperature values suddenly appeared. The software worked perfectly, the diagnosis was made about nine minutes before the first temperature measurement [43].

Following the completion of Lowe's PhD there was some limited collaboration.

There were several projects underway at the same time but one is pertinent – what blood pressures were recorded during anaesthesia? Together with a colleague (Phil Guise) blood pressures were collected at five-minute intervals – they had to be recorded anyway for the

[8] Rampton AJ et al. Br. J. Anaesthesia. 1984; 56:1443-1444

anaesthetic record. After collecting from many patients of all ages and a wide variety of surgery, a distribution curve for blood pressure under anaesthesia was created – *had this been done before – not sure*? A distribution curve for changes in blood pressure was also created [46]. This had been inspired by John Gleick's book *Chaos*, the plotting of the value of a variable against the next value. These were valuable data because it was then possible to 'predict', with some certainty, the range of blood pressure where the next blood pressure should lie and this would be the basis for future work.

Further progress was made when Harrison became a supervisor to a Master's student, Bhupendra Gohil, at the Auckland University of Technology (AUT). Fuzzy logic was used to diagnose hypovolaemia.

The aim, or one of the aims, of his work was to get a system working in real time; all Lowe's work had been done off-line. With Lowe's help, data was collected, as before, and there should have been an automated diagnostic alert system with the ability for the user to agree or disagree – unfortunately this did not eventuate. Gohil spent a huge proportion of his time developing artefact rejection mechanisms, an essential prerequisite to data processing. At the end of the day the program diagnosed acute onset hypovolaemia with an acceptable degree of agreement with clinicians [66-68, 73].

Age also is of importance in diagnostics – this was addressed [62]. The expectation was that both BP and HR would increase with age – counter intuitively the older person's HR, on average, went down probably due to the widespread use of beta-blocking drugs. This was presented at a meeting in Australia [62].

Whilst work continued with Auckland University of Technology and the University of Auckland other ideas were maturing in parallel. A conference in Plymouth in 2005, however, was really rewarding and resulted in four publications, and they were significant to the ultimate goal. The conference was on 'Pattern Recognition'.

There was a presentation by Paolo Lisboa about generating rules from the output of neural networks, the work of Terence Etchells who happened to be sitting next to Harrison. After discussion Etchells offered to analyse some data and the following day the kernel of a paper about rules governing the transfusion of blood, based on an audit of

anaesthetists in the Department of Anaesthesia at Auckland Hospital [60]. A paper on this topic had been accepted for publication in Transfusion Alternatives in Transfusion Medicine [63] but after a dialogue with the editor of *Anaesthesia*, explaining that this was a completely different approach, the paper was accepted. This was not 100% pertinent to the monitoring software but contact with Etchells was to prove very useful.

During the conference Chris Connor, a trainee anaesthesiologist in Boston, USA, made contact and it was arranged that he, and his wife, would visit NZ for Christmas and attend a research meeting there.

Another concept highlighted at the Pattern Recognition conference was about normalisation of data. After leaving the conference, a few days in the country allowed some consolidation on ideas regarding the application of normalisation methodology to alarm systems; there was a definite Eureka moment.

Connor was an engineering graduate from Cambridge in the UK, who went to the USA, worked for NASA and then completed an engineering PhD on a medical topic. With this experience he decided to cross credit and did medicine. After meeting for the first time at the pre-Christmas conference in Queenstown (NZ) they returned to Auckland. Connor enhanced the normalisation technique using Principal Component Analysis. With much editorial and reviewer support, it was published [69]. A subsequent paper extended the concept [73].

A belated MD thesis was accepted in 2007 "The enhancement of intra-operative diagnostics and decision-making using computational methods" [9].

During this period other 'mini' projects were underway and formed part of the infrastructure for the final diagnostic software. Two anaesthetic trainees, Amber Chisholm and Dan Faulke, needed to complete projects for their College accreditation. Chisholm's project was significant in that it led to a major component of the final program although the subject matter of her project was completely unrelated.

Faulke's project was aimed at one particular piece of knowledge the software depended on – was the patient being ventilated (or to put it

[9] http://hdl.handle.net/2292/74

more pedantically – were the patient's lungs being artificially ventilated?) or was the patient breathing spontaneously?

Chisholm: The death of a trainee by opiate overdose stimulated the search for some way of detecting the change in opiate usage in the operating room. Like units of alcohol, the various opiates used were converted to a common unit and data were collected from a set of colleagues; the historical data were collected from the dead trainee's records. A variety of statistical tests were unsuccessful but once again serendipity occurred in the contact with Davis Balestracci (a run chart guru). Using an 'adulterated' methodology it worked and was published [72] and a new technique for time series analysis was now available.

Faulke: To determine whether the respiration was 'spontaneous' or 'controlled' using only the respiratory rate, $EtCO_2$, and $FiCO_2$ was the goal. This information was needed because physiological responses are significantly different in these two modes of ventilation and for one index of blood volume status it was essential that the lungs were artificially ventilated. This being a classification problem, Etchell's skill was needed once more. In a diagnostic system an incorrect output is undesirable and so, to minimise this risk, the system tested separately for both 'spontaneous' and 'controlled' ventilation. If the two algorithms agreed, the output was accepted; if they did not agree the mode of ventilation was "unsure" [74].

During the collaboration with Lowe, an anaesthetic advisory system was created, and, as an aside, with the computer science department at the University of Auckland, a user interface was designed that could have been the public face of the diagnostic system [71]. However, user interfaces are like wallpaper – they could be of almost any design, but some are more user-friendly and intuitive than others.

The concept of 'change', rather than absolute values, brought a new direction to the fuzzy logic and a new Master's student – Mirza Baig [76-78].

What was wanted to know was: *When is a trend a trend*? *How many falls in BP are needed to be convinced that a true change is taking place?* When this question reached 'conscious' level the concept of using runs analysis surfaced, as in Chisholm's paper. The beauty about this technique is that the 'next' value has a 50:50 chance of going up or down,

two down in a row is 1:4, then 1:8 and then 1:16, for subsequent values in the same direction. This not only gave the probability of change but it was completely independent of units of measurement and, with time, reset itself to new values because of the moving window for the 'baseline' median value.

The clinical problem is that of the balance between the early and late notifications – data came through at 10s intervals. Instead of taking a single variable (BP), as above, but two variables in parallel (BP and HR) as in an organised physiological response, the likelihood of four changes consecutively in two variables was 1:16 x 1:16 which is 1:256. This was seriously good. With three variables (BP, HR and pulse volume (PV, amplitude) the odds are 1:4096 that it would happen by chance, with four variables (BP, HR, PV and $EtCO_2$), 1:65000.

It could still be argued that these trends could take place but the actual changes could be very small. Blood pressure is the final product of many physiological factors – heart rate, heart contractility, blood volume, peripheral resistance – and this is why it is the primary monitored variable; if the blood pressure hasn't changed significantly the anaesthetist is unlikely to worry very much. To check for clinical significance of the automated diagnoses it was decided to detect for trending (combined runs analysis) and then check for a significant change in BP (using normalisation). Not only could acute onset hypovolaemia be detected but by using appropriate combinations of BP up, BP down, HR up, HR down, PV up, PV down, $EtCO_2$ up, $EtCO_2$ down a whole range of diagnoses were open to investigation.

The established 'alarms', or alerts for hypotension on monitors was 'crisp' rather than fuzzy. There were 30 definitions of hypotension in the literature. With Stephen Lo, another trainee, a survey was devised where the aim was to capture the blood pressure values at which the anaesthetists would intervene to prevent the blood pressure falling further. It took into account various pathologies and ages [86].

The software was modularised and had the potential capacity to diagnose hypovolaemia, a decrease in cardiac output secondary to hypovolaemia, a sympathetic response, the Cushing response, malignant hyperpyrexia and, as a highly specialised extra, the ability to detect failure to ventilate post cardiopulmonary bypass. The ability to detect the

failure to ventilate post cardiopulmonary bypass was assessed with David Cumin [80], the sympathetic response and hypovolaemia was assessed by Vincent Bonhomme (Belgium)[81, 88] and the ability to detect a fall in cardiac output secondary to hypovolaemia with Mathew Zacharias and Ross Scott-Weekly [89].

Publications of interest: (in Harrison's view!)

1979: Nasotracheal intubation [9]. A very clean and atraumatic technique – a bit fiddly but very clean.

1984/1990: [17, 30, 31] Maintenance of drug levels at the therapeutic threshold; Prediction of infusion rates: computer study and Prediction of infusion rates: Validation of a computer simulation using vecuronium.

This was the result of an insight that was developed with the help of Prof. Chris Hull's pharmacokinetic program and subsequent patient studies. The pharmacokinetic modelling saved the necessity for many interim patient studies.

1986: Remote monitoring using an induction loop [25]. This is the description how a patient's variables could be remotely monitored using hearing aid technology - decades before Bluetooth!

1989: Weight determined dosage of vecuronium bromide [28]. A simple study of how the duration of action of a muscle relaxant is far more consistent if the dosage is based on the fat free mass.

1999: Personality traits of anaesthetists and physicians: an evaluation using the Cloninger Temperament and Character Inventory (TCI-125) [42]. An interesting exercise; the one question that still remains unanswered is whether the personality determines the choice of specialty or the specialty moulds the personality.

Books:

1 Aids to Anaesthesia, Basic Sciences

2 Aids to Anaesthesia, Clinical practice
Harrison MJ, Healy TEJ, Thornton JA, Churchill Livingstone.

3 A Rules Based Guide to Anaesthesia
Harrison MJ, Jones RM, Pollard BJ, Butterworths

4 Anaesthesia for Uncommon Diseases
Pollard BJ, Harrison MJ. Blackwell scientific.

5 So you're going to have an operation
(A patient information book on anaesthesia)

6 Diagnostic alarms during anaesthesia. Harrison MJ, Low A, and Gohil B. VDM Verlag 2009

6 British Academic Anaesthetists 1950-2000 Vol 1
ISBN 9780473200497

7 British Academic Anaesthetists 1950-2000 Vol 2
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