British Academic Anaesthetists

1950-2000

Volume 1

Michael J Harrison

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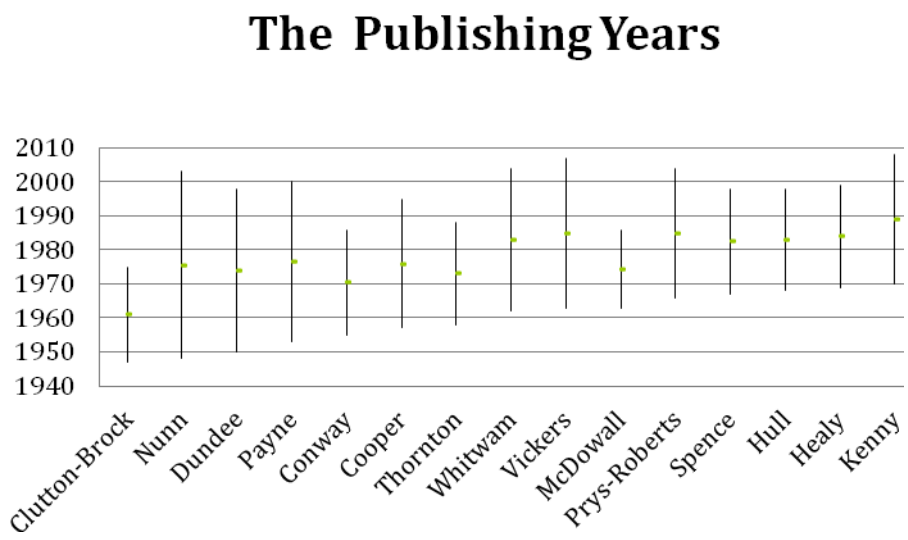
Preface

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 volume highlights the work of some of the British workers in anaesthesia and it is not complete. A second volume would still not be complete, and to put it all into an international context would be a daunting proposition. Life is too short…this can be left to someone else. Volume two may be a few years away and so those who do not appear here be reassured, you have not been forgotten.

Below are the individuals whose work, and that of their colleagues, is covered.

"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)



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

They include Tom Clutton-Brock, The Royal College of Anaesthetists, Trish Willis (Anaesthesia Heritage Centre, The Association of Anaesthetists of Great Britain & Ireland) and Alistair Mckenzie (History of Anaesthesia Society), Maureen Fortier (Magill Dept of Anaesthetics) and Neil Soni (Imperial College, London). Phil Hopkins, Academic Unit of Anaesthesia, Leeds General Infirmary; Gavin Kenny and Douglas Russell - Past President, the Society for Intravenous Anaesthesia; (www.siva.ac.uk); James Murray – Queen's University, Belfast; Judith Hall (University Department of Anaesthesia, Cardiff), David Smith (University Department of Anaesthesia, Southampton. Alan Craft (Department of Paediatrics, Newcastle) and Debbie Nolan (University Hospital of South Manchester NHS Foundation Trust) and Brian Pollard, University Department of Anaesthesia, Manchester.

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Michael Harrison 2011

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J Clutton-Brock
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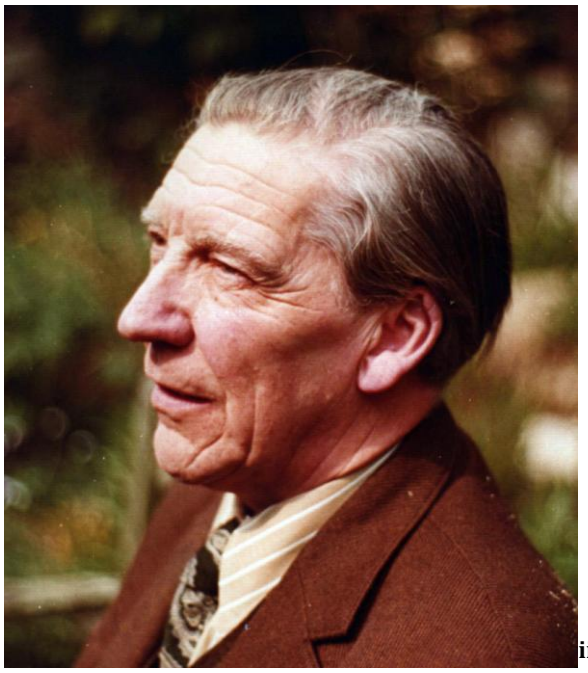 [ii]

After working as a consultant anaesthetist in Lincoln (1943-52) and Birmingham (1952-3) John Clutton-Brock became a lecturer at the University College of Bristol and had consultant status there from 1953. He became head of department in August 1958, and professor in August 1966[i]. Collaborative research links were established with the Veterinary School (1967), and also with the Burden Neurological Institute (at Frenchay Hospital). John Clutton-Brock retired in 1975. Much of his work was associated with pain/clinical topics or equipment. The first two publications preceded 1950, one in 1947 [1] on skin temperature during anaesthesia as an aid to diagnosing shock, and in 1949[2] on the position of electrical anaesthesia.

A low blood pressure without a falling forehead skin temperature was considered of little significance but a falling temperature was of great note and could indicate compensation for shock [1]. The short review of electrical anaesthesia [2] is interesting in that it suggest that J C-B was involved with animal work which the present author has not found (possibly studying fish – personal communication from T C-B). In brief he describes electrical anaesthesia (which had been studied for the previous eighty years) as best with AC current (20-80ma at 2000-800cps) with electrodes in the fronto-parietal position. In primates and man paralysis, airway control and IPPV were necessary. In animal work it had been shown that unless a convulsion had occurred reversal of the anaesthesia was instantaneous on switching off the current with no tissue damage, even after 24h of anaesthesia.

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

[ii] Photographs courtesy of Tom Clutton-Brock, University of Birmingham

Equipment

There are a variety of equipment related topics, some of great simplicity and some of complexity; from bathroom hooks to hold gas pipes above head height [3], a cradle to hold the transfusion bottle [4] and a perforated face mask to accommodate a stomach tube [5], to custom made ventilators with different respiratory patterns [6,7], phonocardiography[8] and electroencephalography [9].

The custom made (in-house) ventilator had the ability to produce any respiratory pattern including negative phase. The ability to have a negative phase at this time was considered good as it increased venous blood flow and hence augmented the cardiac output, advocated by Hubay and Moloney[iii]. The different patterns of respiration were generated by cams acting on levers acting on a concertina bellow, a very Victorian type of engineering which was still prevalent at that time. A sample of gas could be extracted at any point in the respiratory cycle. The electric motor was controlled with a thyratron, a form of thermionic valve. The second ventilating device was a modified hand ventilator that would also allow negative pressure which was previously impossible using standard systems.

The phonocardiography paper [8], a presentation at the Association of Anaesthetists' Annual Meeting 1969, was an attempt to relate the power of the first heart sound to the blood pressure. A filter was used to isolate the study to a sound frequency of 40cps, the signal being integrated with a time constant of 0.1s. It was thought to be a qualitative measure of stroke work during isometric contraction. This work does not seem to have been followed up.

The work on electroencephalography is largely occult. An overview of the EEG [9] is published in 1961 and includes information about the flicker test and the use of 'scanning' cathode ray tubes to highlight whether the EEG is in synchrony with the flicker. There is a referral to work with W Walter, which is unpublished, but referred to in Trends in Anaesthesia by Evans and Gray, 1958. Referral to unpublished work has diminished over

[iii] Moloney JV jr. Et al. J Amer med ass 1953;152: 212
Hubay CA et al. Anesthesiology 1954;15;445

the last few decades. Another paper describes a new display system for display of the EEG [10].

The impression is that J C-B did much more than is obvious from the literature. The remaining equipment related publications refer to static in and outside rotameters [11], the bottom line being that an inaccuracy in gas flow was never seen if the rotameter was rotating, and a plea, in a letter, for simplicity in the design of anaesthetic machines[12].

Pain:

Apart from a paper on the use of xylocaine for caudal anaesthesia in 1951 [13] the three papers of note are those on pain assessment and pain and barbiturates[14-16]. The first paper's main subject is overventilation, but the topic is centred on the measurement of pain during normal breathing and during hyperventilation. At this time many anaesthetics involved minimal anaesthetic agents and a lot of ventilation. It was thought that overventilation increased the depth of anaesthesia. This was studied in volunteers, including the author (and his son).

A household spring balance (kitchen scales) was modified so that when (after removing the pan) the top of the scales could be pressed onto the tibia. The pressure exerted on the tibia could be read of the scale. Using this technique the pain threshold was between 3 and 4kg. During forced breathing it rose to 6-8kg. It was considered that this might be due to cerebral hypoxia induced by the overventilation[iv]. To clarify the physiology the experiments were repeated and the participants on achieving hypocarbia were given extra oxygen (to relieve any cerebral hypoxia) or amyl nitrate to relieve cerebral vasoconstriction. Pain thresholds returned towards 'normal'. The conclusion was that "cerebral vasoconstriction produced by overventilation may cause hypoxia and should be avoided." This is a significant paper.

The second publication is of the style of an abstract and is a preliminary communication about pain thresholds and premedication (referring to a previous

[iv] Kety, S. S., and Schmidt, C. F. (1946). The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output and blood pressure of normal young men. J. Clin. Invest., 25, 107.

publication [14]) but then goes on to describe the abolition of this effect by small doses of thiopentone (25-100mg). This was described as a transient phenomenon except in the situation where an induction dose of thiopentone had been given which then results in prolonged anti-analgesia because the blood barbiturate levels would be raised for at least two hours. The full version was published in 1961; "...it seems most likely that the explanation [*for the anti-analgesia effect*] will be found in the effects of the barbiturates on the reticular system of the brain stem[v]."

The device used for measuring pain thresholds was improved in 1964 [17]; the scale to be read was linear rather than circular and there was a modification that allowed the pressure to be recorded after the pressure was taken off.

Miscellaneous others:

There is a letter about hiccup during anaesthesia [18] in 1952 that demonstrates J C-B's early thoughts on hyperventilation as described above, a paper on the technique to achieve hypothermia, by surface cooling, for cardiac surgery [19]. There is some historical interest for clinicians in this paper, firstly the use of both the drug doses in grains and mgs, the use of only nitrous oxide and oxygen and muscle relaxant (with small doses of opiate) for the anaesthetic, and the use of the EEG to assure the anaesthetist of a light anaesthetic and "The electro-encephalogram has been found to be of more use than the electrocardiogram; changes in the electrocardiogram are not necessarily reflected in changes of the circulation to vital organs, whereas the electro-encephalogram is a most sensitive indicator of cerebral hypoxia."

An overview of the central nervous effects of anaesthetic agents [20] was published in 1961. Some comments may seem cavalier to modern anaesthetists.

> It can probably be agreed that the patient should be perfectly comfortable and must not be sufficiently aware of his surroundings to be frightened or upset by them. This upset may be caused by his overhearing what the surgeon has to say—for example, "Let's sew the old bag up now"—or by feeling the surgeon at work in his abdomen, even if there is no pain.

[v] Brazier, M. A. B. (1954). Brain Mechanisms and Consciousness. 163. Oxford.

There was discussion on the nature of consciousness, of neural pathways involved in consciousness and referral to his work on pain and anaesthetic agents. The assessment of depth of anaesthesia was a major problem and an example given of a patient conscious enough to respond to a question (during an aortic aneurysm repair) whilst not retaining the memory of this event.

> Amnesia surely is not an adequate substitute for anaesthesia!

Electroencephalography seemed to be a possible method of monitoring anaesthesia, however....

> With nitrous oxide the author has failed to find any constant relationship between the depth of anaesthesia and the e.e.g. pattern.

The report on the poisoning of patients with the higher oxide of nitrogen is of interest, the appearance of methaemoglobinaemia and the management with methylene blue[21].

The final paper of comment was that of *Scientific Measurements in sociology* [22]. This is an amusing short 'article' first published in 'Anaesthesia Points West'[vi] and reproduced in the Bristol Medico-Chirurgical Journal. It describes a unit of beauty (the Helen [of Troy]), of strength (the Herm [Hermes]) and when you combine these (1 herme / 1 helen) you get 1 Preg! A milli-helen, by the way, only launches one ship.

John Clutton-Brock was working in the first half of this 50 yr epoch; technology was starting to have an influence on anaesthesia and his investigation of the use of the e.e.g. , the effects of hyperventilation and the measurement of pain are of importance[vii].

John Clutton-Brock in his workshop in Bristol

[vi] Journal of the Society of Anaesthetists of The South Western Region

[vii] Obituary: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1342091/pdf/bmjcred00262-0060.pdf

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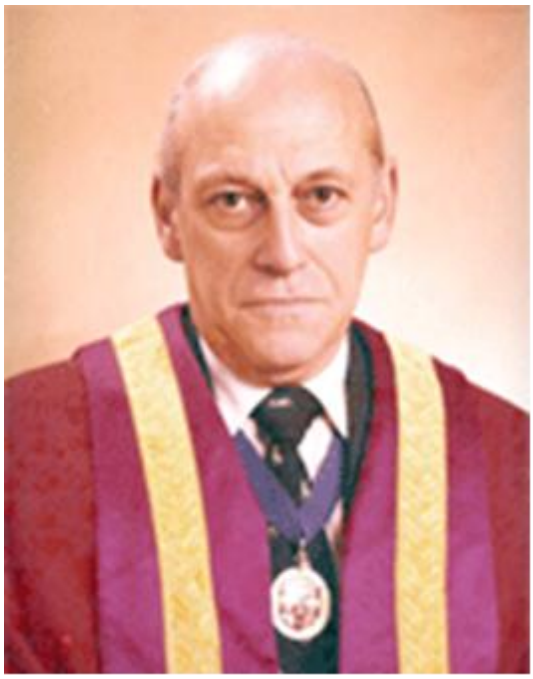
John F Nunn

PhD MD FRCA

 [i]

John Nunn is most well known, amongst anaesthesia trainees working for exams, for his book on Applied Respiratory Physiology. He started his academic career as a research fellow in Birmingham (1955-56) and then at the Royal College of Surgeons (1957-64). He was the foundation professor in Leeds from 1964 until1968, when he returned to London to become head of the Division of Anaesthesia of the Clinical Research Centre. Permanent accommodation was completed in 1972 at Northwick Park, Harrow; Nunn retired in 1991.[ii] John Nunn's publications start before, and finish after, the epoch this series of reviews cover. He started in 1948 and finished in 2003. The journals that accepted his work are of the highest reputation, Nature [4], Journal of Applied Physiology [8], Lancet [9], BMJ [7], British Journal of Anaesthesia [89], Anaesthesia [20], Anesthesiology [16] and Respiration Physiology [4], in no particular order.

His first publication is an article on mountain sickness in the Queen's Medical Magazine[1], a student production of the University of Birmingham. It was another six years before an anesthetist's look at Malaya was written in the Lancet[2]. He was the first author of 103 papers and the sole author of 62.

There is no disputing his contribution to the understanding of respiratory physiology as the vast majority of his publications are in this area, either dealing with the physiology itself or the devices used to study it.

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[i] http://www.rcoa.ac.uk/index.asp?PageID=1460

[ii] Development of academic anaesthesia in the UK up to the end of 1998
J F Nunn. British Journal of Anaesthesia. London: Dec 1999. Vol. 83, Iss. 6; pg. 916, 17 pgs

Measuring devices

The first was a time-phased end tidal sampler [3]; it is hard to imagine in the 21st century how difficult it was to measure respiratory gases. This paper describes how with a relatively simple differential pressure device an electronic circuit could be triggered which would then start a small suction pump that would aspirate gas through a magnetically controlled valve [controlled from the same circuit]. This enabled a selected portion of gas from the circuit to be analysed using a colorimetric method. Its performance was studied during both spontaneous and controlled ventilation. Following on from this, a year later was a description of the Dräger carbon dioxide analyser [4]. From Nunn's account this device was devised during WWII for use in submarines. This device, in retrospect, is so simple/crude. A known volume of the gas to be analysed (a ten ml syringe) pushes the sample gas into a sodium hydroxide chamber where the CO_2 is absorbed and the volume of gas is then re-measured. There were, as one might expect, lots of careful preparation for accurate results, temperature, humidity of the gas, nitrous oxide and so on but in 1958 this was leading technology. An overview of the problems of gas analysis, storage of gases, absorption of gases in chemical reagents and so on were also examined in detail and modifications to Haldane's apparatus were made in the light of their findings [5]. Nunn worked with Andrew Thornton at this time a produced a paper on the "Accuracy of determination of pCO_2 by the indirect method." [6]

The next equipment/measurement paper was on the coiled cathode oxygen polarograph [7], with co-workers RA Butler and S Askill. This was published in Nature, a short report on an improvement in design that overcame the disadvantages of previous devices – the total volume of the cuvette was 0.2ml. This is accompanied by an overview of the measurement of blood oxygen tension in the Brit. J. Anaesth. also in 1962 [8]. In the opening paragraph he describes how there is a dearth of measurements of pO_2 during anaesthesia because a) anaesthetists think they can detect hypoxia and b) its measurement has been so difficult. This article contains all you would wish to know about the handling of specimens and the measurement of oxygen.

1962 was a busy year, another paper assessed the accuracy of two respiratory flow meters [9]. The respirometer (the Wright Respirometer) turned

out to be less accurate at low and high flow rates but all the forces of error evened out during anaesthesia; as the authors point out, the errors exaggerate a departure from normality which one could perceive as a good thing. The ventigrator, being something similar to a pitot tube, measures the difference in pressure on either side of a constricting 'throat' in an air conduit. The sensitivity changed markedly with flow and, more importantly during anaesthesia, with the density of the gas. It was not considered suitable for routine use as, although the device itself is robust, the paraphernalia required to make the measurements were unlikely to "withstand dropping on the floor."

Over the next thirty years a variety of instruments were assessed, paramagnetic oxygen analysers [10, 11], refractometers [12, 13], anaesthesia related equipment – a new halothane vapouriser [14], the Quantiflex machine [15], and a modification to the Brompton Manley ventilator to facilitate intermittent mandatory ventilation [16], another ventilator tested was the Ohmeda CPU-1 ventilator – a very sophisticated device at the time [17]. Later 1988 and 1990 there were a further two papers, one on the oesophageal detector device [18] and one assessing three indirect calorimetry devices for assessing metabolism in critically ill patients [19]. These devices are used during artificial ventilation and were tested on a lung model where butane was burned in a gas-tight combustion chamber. The combustion of oxygen and production of carbon dioxide characteristics are known. They investigated the effect of oxygen concentration on the accuracy of the instruments with fixed set ventilation parameters. It would appear from their results that the Datex Deltratrac Metabolic Monitor came out best. This is a far cry from a clinical study [which would be extremely difficult] but it demonstrates the ingenuity of the team effort. In 1984 they had developed a lung that could represent spontaneous breathing (as well as being able to be artificially ventilated) and it had the ability to trigger ventilators as patients do in the real world [20]. There are other equipment/measurement related papers [21-26]

Lung Perfusion and ventilation

Nunn is known internationally for his work on respiratory physiology, particularly relating to the practice of anaesthesia. In 1962 there were papers

on the topics of predictors for oxygen and carbon dioxide levels during anaesthesia [27] and hypoxaemia after anaesthesia [28] .

The 'hypoxaemia' paper was a joint effort with Jimmy Payne [see his bibliography], they were both Lecturers at the time at the Postgraduate Medical School, Hammersmith Hospital. "All patients undergoing minor operations under general anaesthesia were found to be hypoxic for several hours after operation….The cause of the hypoxaemia appears to be a disturbance of ventilation/perfusion relationships within the lung." This is the crux of all the work, the avoidance of hypoxia and hypercarbia. There are many interrelated papers and so only a selection will be described.

Much of the work started in the late 1950s.

"A comparison of artificial ventilation and spontaneous respiration with particular reference to ventilation-blood flow relationships." 1958 [29]

"Anatomical subdivisions of the volume of respiratory dead space and effect of position of the jaw." 1959 [30]

"Gaseous exchange during halothane anaesthesia: the steady respiratory state." 1959 [31]

"Ventilation nomograms during anaesthesia." 1960 [32]

"Respiratory dead space and arterial to end-tidal carbon dioxide tension difference in anesthetized man." 1960 [33]

"The respiratory effects of resistance to breathing in anesthetized man." 1961 [34]

"Factors Influencing the Arterial Oxygen Tension during Halothane Anaesthesia with Spontaneous Respiration." 1964 [35]

"Ventilation-perfusion relationships after haemorrhage." and "Problems of Oxygenation and Oxygen Transport during Haemorrhage." 1963 and 1964 [36, 37]

"Influence of Age and Other Factors on Hypoxaemia in the Postoperative Period." 1965 [38]

"Factors influencing the arterial oxygen tension during anaesthesia with artificial ventilation." 1965 [39]

"The influence of cardiac output on arterial oxygenation: a theoretical study." 1967 [40]

"A comparison between the effect of nitrous oxide and nitrogen on arterial PO2." 1967 [41]

"Influence of duration of hyperventilation on rise time of P-CO2 after step reduction of ventilation." 1968 [42]

"Influence of anaesthesia on the regional distribution of perfusion and ventilation in the lung." 1969 [43]

"Influence of anaesthesia on the regional distribution of perfusion and ventilation in the lung." 1970 [44]

"Distribution of gas and airway closure." 1971 [45]

"Expiratory muscle activity and changes in functional residual capacity during anaesthesia." and "Factors influencing the development of expiratory muscle activity during anaesthesia." 1973 [46, 47]

Functional residual capacity during anaesthesia, I, II and III 1974 [48-50]

This is a fraction of all the papers on this aspect of physiology as it relates to anaesthesia; a huge body of work from a wide range of team workers; Alagesan K, Bergman NK, Campbell EJ, Coleman AJ, Ezi-Ashi TI, Freeman J, Hewlett AM, Hill DW, Hulands GM, Kelman GR, Matthews RC, Peckett BW and Webb SJ. My apologies to any I have missed.

There are another 41references in this section. 51-92]. [21, 22, 27-30, 32-40, 42-92]

The cellular effects of anaesthesia

Another interest was that of the cellular effects of anaesthesia, this work started in 1968 and over 20 years was carried out in collaboration with many people, Alison, Bottiglieri, Chanarin, Chapple, Deacon, Dixon, Jones, Keeling, Kimball, Konieczko, Lovis, Lumb, Monk, O'Morain, Pope, Rostain, Royston, Sharp, Skacel, Snape, Sturrock, Wardley-Smith, Webster and Wiklund (apologies to any I have missed).

The first was on the possible mechanism of anaesthesia by a study of cellular microtubules [93]. This was a review article – a good way to start an investigative project. Microtubules are found in many cellular sites that are affected by anaesthetics. Cold, high hydrostatic pressure and colchicine can produce narcosis and they also reversibly depolymerise the microtubules . How

the depolymerisation caused narcosis was unknown but the abundance of microtubules in neurons may suggest a role in neurotransmission. The authors were hypothesizing that anaesthetic agents may also reversibly depolymerase the microtubules.

The first presentation of an experiment was at the Anaesthetic Research Society held in London in November 1968, with JA Sharpe and K Dixon. They studied the movements and mitosis of cells cultured from mouse lung and thymus. They filmed the cells for a control period and then exposed them to 2% halothane. Of the different cell types cultured only the lymphocytes exhibited significant loss of motility – mitosis also took twice as long. It was speculated that it was a direct effect on microtubules as they had been implicated in both motility and mitosis[iii].

They then moved from cell culture to living organisms, protozoa with spherical bodies, Actinosphaerium [94]. These organisms have thin cytoplasmic projections called axopods and their inner cores are axonemes which can cause the axopods to bend. These protozoa were exposed to a number of anaesthetic agents, chloroform, diethyl ether, divinyl ether, methoxyflurane and halothane. They discovered that the effects were proportional to that found in man; evidence for the site of activity had been strengthened.

There were another three papers in 1970 [95-97]; “Effects of halothane on the single cell”, “Reversible effect of an inhalational anaesthetic on lymphocyte motility." (a letter to Nature) and "The effects of halothane on bacterial division rate." The Nature letter – this described how the mobilization of neutrophils was suppressed by halothane. And the BJA article (ARS) bacterial growth rate was inhibited in a dose dependent manner by halothane but only if it was in a concentration greater than 3%, this led on to other aspects of the effects of anaesthetic agents on cellular division – see below.

There were a variety of publications over the next few years [98-102] but we will now jump to 1974 [103]. They studied the effect of six anaesthetic agents on the swimming velocity of Tetrahymena pyriformis (a ciliate protozoon). The concentrations resulting in a 50% reduction in motility were of the same order

[iii] Hirsch, J. G., and Fedorko, M. E. [1968].. J. Cell Biol,38, 615.

as in man (cyclopropane was an exception). No cellular damage was seen at these 'clinical' concentrations but was at 10x the normal dose, but even this was reversible after time.

In 1975 a further study [104] using halothane on the contraction and relaxation of Spirostomum ambiguum and Vorticella sp. were studied. In these animals, contraction was stimulated; two sites of action were postulated, the microfilaments of the myonemes or the stimulatory system that controlled contraction. It wasn't until 1978 that another 'cilia related' paper was published, this time it was an investigation of the effect of ambient pressure on the depression of cilia activity by halothane [105]. It was a test of the critical volume hypothesis of anaesthetic action[iv]. Simply put, the hypothesis was that high ambient pressure could reverse the actions of anaesthetic agents. The swimming speed of Tetrahymena pyriformis was studied at high pressure and at different concentrations of halothane. The results were contrary to expectations of the critical volume hypothesis and it was suggested that the pressure reversal of the narcotic effect of anaesthetic agents must be different to the effect on cilia. A study in 1986 [106] also studied the effect of pressure 'reversal'. Rats were compressed in a helium-oxygen mixture until they convulsed. The rats were given either saline or barbituric acid (a non-anaesthetic), those with the barbituric acid infusion remained convulsion free to higher pressures. Again the results suggested that anti-High Pressure Nervous Syndrome activity involved "at least one site which is different from that responsible for anesthetic activity." The critical volume hypothesis was soon replaced by another, and then by another, time and time again.

There were other studies on motility, now of neutrophils [107-109]; in brief, halothane did not seem to reduce motility, nitrous oxide did.

This just about completes this aspect of their work on anaesthetic agents and cellular mechanisms but another aspect was the effect of anaesthetic agents on DNA synthesis and cell division and mainly the effects of nitrous oxide.

[iv] The Pressure Reversal of General Anesthesia and the Critical Volume Hypothesis Miller K. W. Paton W. D. M. Smith R. A. and Smith EB. Molecular Pharmacology March 1973 vol. 9 no. 2 131-143

Following on from Wardley-Smith's ARS presentation on the effects of halothane on bacterial division rate [97] Allison followed up with a general article on the cellular effects of anesthesia [98] and Nunn with a paper in the Annals of the Royal College of Surgeons on anaesthesia and cell division [99]. Over the next decade there were other such 'general' articles [102, 107, 110-112].

Further cellular effects

The research:

This can be divided into the effects of the 'aromatic' anaesthetic agents, those of nitrous oxide (particularly on bone marrow) and those showing the bad side of oxygen.

Aromatic agents

The effects of halothane on mitosis was published in 1969 [113] and the arrest of mitosis by halothane [100] in 1971. These papers were on plant-based experiments where changes in the chromosomes were likened to the effect of colchicine; after four hours exposure the chromosomes had contracted to about 50% of their normal length and were twice as thick, the ED50 was within the range 0.5-0.9%. Unpublished work by Forer, Allison and Nunn had shown a similar effect of mitotic spindle dispersal in the sea-urchin egg. It was also suggested that halothane may interfere with DNA synthesis. They mentioned the work by Ostergren 20 years previously as being extraordinarily far-sighted[v]. The effects were completely reversible and they commented that although this may occur in Man the duration of a standard anaesthetic was much shorter than the cycle of mitosis.

Two other points were made, a. the possibility of teratogenesis and b. the use of anaesthesia to synchronise cell division for cell cultures.

The full paper on the effect of halothane on bacterial growth [101] appeared in 1971. In essence there was no significant effect of clinically used concentrations and the effect that did occur at higher concentrations was reversible.

[v] Ostergren, G. [1944]. Colchicine mitosis, chromosome contractions, narcosis, and protein chain folding. Hereditas [Lund], 30, 429.

From plant s and bacteria the team moved on to animal preparations. DNA synthesis in hamster fibroblasts [114] , an ARS presentation. The cellular cycle has a pre-DNA-synthetic phase (G1), a DNA-synthetic phase (S) and a post-synthetic phase (G2) followed by mitosis. This study was designed to see at which point the effect of halothane occurred. The conclusion of several experiments was that something happened in the G1 phase in response to low, clinically relevant, concentrations and resulted in a delay in mitosis.

In 1975 there was a study on mitosis in mammalian cells following exposure to anaesthetics [115] . This was a more comprehensive study (methoxflurane, trichloroethylene, chloroform, halothane and diethyl ether) of the effects of these agents on the Chinese hamster fibroblasts. All agents caused dose-dependent inhibition of cell multiplication that seemed to be related to the oil-gas partition coefficient. In this study effects in the G2 phase were also noted. It was commented that the pollution of operating theatre air by anaesthetic agents was of too low a concentration to cause problems but chronic exposure to long-lived products of metabolism could have potential side effects.
"Effects of halothane on DNA synthesis and the presynthetic phase (G1) in dividing fibroblasts" [116] came out in 1976 and seems to be a full account of the 1974 ARS presentation.

In '76, in the last of this series of studies, Sturrock demonstrated that nitrous oxide alone had no significant effect on the production of abnormal cells in the Chinese hamster cell fibroblast preparation. However, when combined with halothane, which had a dose dependant effect (1% halothane caused 12% abnormalities in cells undergoing mitosis) the percentage of abnormal cells increased to 22% [117, 118]; a synergistic effect, whereas the effect on growth rates was additive.

Nitrous Oxide

To paraphrase Deacon et al's introduction to the subject… in 1956 four out of six patients who were given nitrous oxide during the management of tetanus developed megaloblastic red cells[vi]. It was thought that cobalt-ligand complexes

[vi] Lassen, H. C. A., Henriksen, E., Neukirch, F., Kristensen, H. S. Lancet, 1956, i, 527.

in vitamin B12 broke down nitrous oxide and this then resulted in an oxidation of active cobalamin to an inactive form[vii]. Methionine synthetase and methylmalonyl CoA mutase are the only two enzymes requiring Vit B12 in mammals. Deacon et al's study [119] involved the measurement of the activity of both, in rats, in the presence of nitrous oxide. They showed that nitrous oxide rapidly caused inactivation of the cytosol enzyme methionine synthetase, but the mitochondrial enzyme, methylmalonyl CoA mutase, was unaffected. This difference was unexpected.

An editorial on the subject was published at almost the same time [120]. Several points were made…one was that significant depression of bone marrow was not seen in vitro, citing their own work in 1976 and it was also pointed out that the work by Banks in 1968 (see footnote) was not recognized for its clinical significance, "a sad reflection on interdisciplinary communication".

At that time the methylfolate-trap hypothesis suggested that 5-methyltetrahydrofolate [5MTHF] becomes metabolically trapped. 5MTHF cannot be metabolised via the methionine synthase pathway or converted to its precursor methylene-tetrahydrofolate and the cause…..B12 deficiency.

The 'team' investigated the effect of nitrous oxide inactivation of vitamin B12 on rat hepatic folate and this had implications for this hypothesis [121]. Their data did not support the hypothesis. They found no 'trapping' of 'methyl' folate, and suggested that a failure of folate polyglutamate was the major defect.

Two years later they investigated "serum methionine and hepatic enzyme activity in anaesthetists exposed to nitrous oxide" [122]. The report was very reassuring at a time when scavenging of exhaled anaesthetic gases was in its infancy. Serum concentrations of methionine, leucine, isoleucine and valine were normal, as were the activities of aspartate transaminase and gamma glutamyl transpeptidase. However in the same year they described megaloblastic haemopoiesis after multiple exposures to nitrous oxide", Lancet [123]. This was diagnosed in a patient with porphyria who used Entonox (50% nitrous oxide:50% oxygen) for physiotherapy. In the same year they wrote a letter to Anesthesiology [124] explaining their experience with folinic acid as a

[vii] Banks, R. G. S., Henderson, R. J., Pratt, J. M. J. chem. Soc. 1968, section A, p. 2886.

therapeutic prophylactic agent to prevent the megaloblastic response. This had been described by O'Sullivan et al[viii] . They found it didn't work.

A study published in 1983 [125] showed that the effects of chronic exposure to nitrous oxide were dose dependent. They failed to demonstrate any effect at 450ppm, the ED 50 being 5400 ppm; they thought the American recommendations of 25 p. "unduly restrictive".

Further studies on the haemopoietic toxicity of nitrous oxide in patients [126] showed that haematological changes did take place – however the patients were ventilated with 70% N_2O for up to 24h; an abnormal time when compared with normal clinical practice. Some of these changes [megaloblastic] had reverted after a week but there were still dyserythropoietic effects.

Three years later Nunn et al published a paper that seemed to contradict their earlier letter to the Lancet, they used folinic acid to protect against nitrous oxide teratogenicity in the rat [127]. Their hypothesis was that some teratogenic effects were due to interference with folate metabolism and that folinic acid may prevent them. The rats were exposed to 70-75% nitrous oxide on day nine of their pregnancy with or without folinic acid. No significant differences in fetal survival occurred but the number of ossified sternebrae was reduced only in the nitrous oxide group not receiving folinic acid. Major skeletal abnormalities in the untreated nitrous oxide group were significantly increased to five times that of the control groups; their hypothesis was proven true.

Another study that seemed to contradict their Lancet letter (unless I am mistaken) was "Megaloblastic bone marrow changes after repeated nitrous oxide anaesthesia. Reversal with folinic acid" [128]. A patient required a second anaesthetic seven hours after a previous N_2O anaesthetic and was treated with 30mg folinic acid as a prophylactic and did not develop bone marrow abnormalities.

They studied the effect of short-term administration of nitrous oxide on plasma concentrations of methionine, tryptophan, phenylalanine and S-adenosyl methionine in man[129] [tryptophan was reduced by 30% but there were no significant changes in methionine and phenylalanine concentrations] and later, in rats where they detected interference with thymidine synthesis in bone

[viii] O'Sullivan H, Jennings F, Ward K, et al. Anesthesiology 1981;55:645-649

marrow associated with a highly significant reduction in hepatic methionine to 62% of control [130].

In 1987 Nunn wrote a review on the "Clinical aspects of the interaction between nitrous oxide and vitamin B_{12}" [131]. He addressed wound healing and infection [no effects reported], pregnancy ("…it is the view of the author that the use of nitrous oxide in pregnancy during the period of organogenesis is inadvisable in the light of present knowledge." This was in the absence of any direct evidence), exposure to trace concentrations (in contaminated operating theatre there did not seem to be problem but in the poorly ventilated dentist's surgery with high flows of gas dU suppression tests and abnormal polymorphs had been reported), nitrous oxide abuse (subacute degeneration of the cord) and the problem of the patient with subclinical B_{12} deficiency (synergy with nitrous oxide exposure makes the problem worse; note: vegetarians may also be at risk because man's only source of vitamin B_{12} is from animal products).

Teratogenicity

There had been a great interest in the teratogenicity of anaesthetic agents over the previous decade and in 1987 Nunn's team wrote on the "Fetotoxic potential of general anaesthesia in relation to pregnancy." [132]. The bottom line on this audit, in this author's view, is that there is no clinical evidence showing an adverse effect of anesthesia on the incidence of congenital abnormalities, and this view was supported by four other studies acknowledged in the paper. However, they still persisted with the statement "in our view, it seems inadvisable to administer nitrous oxide to any woman known to be in early pregnancy."

Oxygen toxicity

The next gas to come under scrutiny was oxygen used in high concentrations…it is commonly known that even breathing 21% oxygen can lead to death after about 70 years.

This work started quite early, in 1978 [133]. Hamster lung fibroblasts were grown in culture and exposed to oxygen (40 – 90%) for up to four days. The damage to the cells' chromosomes was dose related; 100% of nuclei were

affected by 95% oxygen after 72h. A similar study two years later examined the effect on pulmonary macrophages and alveolar epithelial type II cells [134].
The cells stopped dividing after 17 hours and started to die after three days. One conclusion from this study was that these cultures were good test-benches for the testing of drugs efficacy against oxygen toxicity.

It should be noted that at least hyperoxia has no effect on methionine synthetase activity in rats." [135]

In the 1970s and '80s intensive care units were becoming mainstream clinical units and patients with severe pulmonary malfunction were being cared for. Many received high concentrations of oxygen to maintain arterial oxygen levels; this however was accompanied by the risk of causing further cellular damage. In a study published in 1990 they describe the changes in lung permeability in rats exposed to 100% oxygen [80]. They discovered that changes started at 48h and that by 60h there was sufficient damage to cause pleural effusions.

The following year they found an early marker of lung injury and also described the usefulness of antioxidants in the amelioration of the lung damage [136]. The marker was oxygen uptake by a purified mitochondrial fraction in the presence of succinate and ADP; this was reduced by 20% after three hours. The antioxidants were N-acetyl cysteine, dimethyl sulphoxide and allopurinol.

There are many more papers worthy of inclusion but these above should suffice…an extraordinary output.

Let's finish with a few less physiology based publications [137-141].
1977: Egyptian antiquities at the Royal College of Surgeons of England. As might be expected this is a cataloguing of antiquities that were given to the College of Surgeons by Sir John Bland-Sutton in 1943. At the time of writing anaesthesia was still a faculty of the College – Nunn's qualifications at that time reflecting this state of affairs – MD, PhD, FFARCS (Fellow of the Faculty of the College of Surgeons).

1996: Ancient Egyptian medicine

1997: Staffs as walking aids in ancient Egypt and Palestine – illustrations of Egyptians using staffs abound but very few depict individuals in imperfect health. This was due to artistic convention of the day. However some have survived and this paper deliberates on the various postures, and in one case what appears to be an example of a shortened leg with an equinus deformity.

2000: Tropical diseases in ancient Egypt – this is a detailed treatise on a variety of diseases and the examinations of the patients as described in medical papyri.

John Nunn is an acclaimed academic and not only did he write the respiratory physiology 'bible' for anaesthesia trainees (Applied Respiratory physiology with special reference to Anaesthesia, Butterworth & Co Publishers Ltd, 1969 (ISBN-10: 0407109404, ISBN-13: 9780407109407) he also wrote a book on Ancient Egyptian Medicine, Red River Books, 2002 (ISBN-10: 0806135042 ISBN-13: 9780806135045)).

What this author was delighted to find was a third book, The Tale of Peter Rabbit by John F. Nunn, Richard B. Parkinson, and Beatrix Potter.

This is the Tale of Peter Rabbit "faithfully translated and transcribed page for page into the hieroglyphic script of an Egyptian of the Middle Kingdom". I am assuming that this is the JF Nunn that you have been reading about. What a finish.

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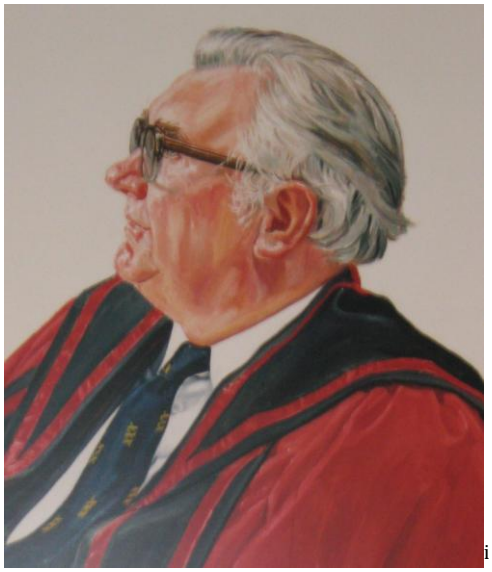 [i]

John Dundee's academic career virtually spans the whole period covered by this book, his first publication being in 1950 and the last reference in 1998. He was a lecturer in 1953 and senior lecturer in Liverpool 1957/8, where he was awarded his PhD, and moved to Belfast in 1958 as senior lecturer and founder of the academic department there.... (Queen's University). He became a professor in 1964. He was dean of the Faculty of Anaesthetists of the Royal College of Surgeons in Ireland between 1970 and1973 and retired in 1987, but continued writing[ii].

John Dundee's output was prodigious and so to cope with this massive body of work only an overview of a selection of his publications is possible. He was possibly the Henry Ford of anaesthesia in the United Kingdom at this time, although for a great period of this time Belfast was very troubled.

He ran the research like a factory and papers rolled off the production lines at about ten a year. Dundee himself was the first author on 50% of the publications and was a regular attendee at the Anaesthetic Research Society meetings. His first publication was on "Acquired sensitivity to thiopentone" in the British Medical Journal [1]. He was to publish another 36 involving thiopentone in some way [1-37].

In 1962 the 'factory' became organised and two sets of publications were begun. Papers with the phrase "Clinical studies of" [17-20, 22, 23, 25, 38-51] , (21 publications); these were about anaesthesia induction agents and varied from standard agents like thiopentone to new agents with code numbers and ethanol. The second set began with the phrase "Studies of drugs given before anaesthesia" [52-73] and involved the assessment of premedicants and antiemetics in a variety of combinations.

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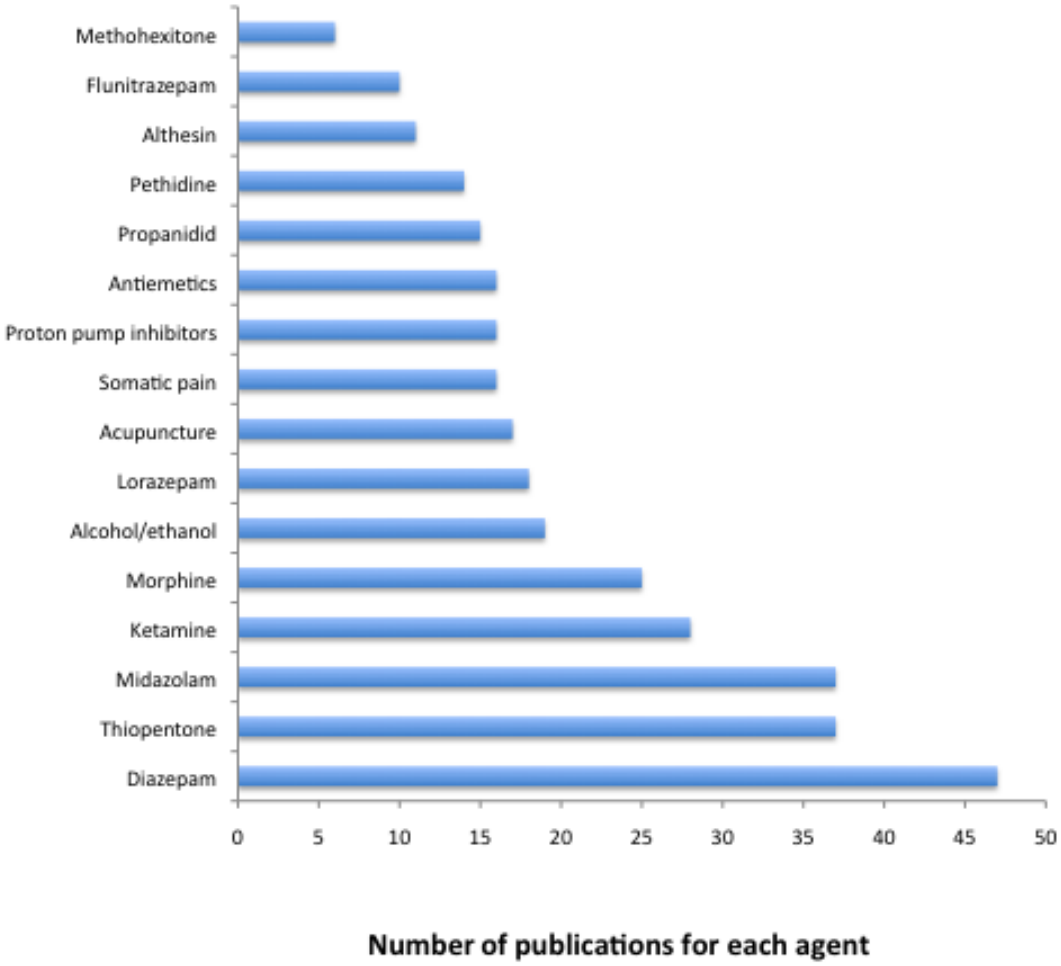
[i] Photograph courtesy of James Murray, Queen's University, Belfast.

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

Clinical studies of…

Five topics were ‘a comparison of nine barbiturates in electroconvulsive therapy’ [38], diazepam [42], ‘Ethanol’ and ‘Further investigations with ethanol’ [43, 45], the effect of premedicants and supplements on ketamine anaesthesia [48] and Althesin [25, 49].



Barbiturates in electroconvulsive therapy:

In this 1962 paper with Barron is seen the genesis of the ‘factory’ style. It is commented that for true comparisons “a fairly uniform patient population” is required and two such populations were those patients undergoing dilatation and curretage (D&C) and electroconvulsive therapy (ECT). One thousand administrations of a barbiturate were reported for ECT and, to make

comparisons easier, ECT patients do have more than one session. It is interesting to note that, in 1962, there is no mention of ethical committee consideration, or patient consent.

The side effects studied were either excitatory (muscle tremor, twitching and other involuntary movements) or respiratory (coughing, hiccough and larygospasm). There were differences but it was stated that all drugs were satisfactory for routine use in the doses used in the study.

Twenty two patients received seven of the barbiturates. Hexobarbitone and methohexitone had a high incidence of excitatory phenomena. They were able to tease out the fact that the thio barbiturates were the ones that either caused a very low incidence of problems or some respiratory upset whilst it was the 'methyl' barbiturates that caused the excitatory effects. A classification of barbiturates was proposed base on the incidence of side effects rather than on length of duration of effect.

Diazepam; Diazepam was released on the market in 1963 by Hoffmann-La Roche and in 1968 Dundee, together with Stuart Brown, wrote about the slowness of onset of the agent when given intravenously, about a minute. The variability of the patients' responsiveness was also noted. The good side was that even with doses up to 0.8mg kg-1 (a huge dose) it was not possible to guarantee the induction of anaesthesia. They commented on the absence of side effects even with large doses…the amnesia it produced was the "outstanding feature". Some patients (30%) did experience dizziness up to 24 hours after the injection and some receiving higher doses developed local venous thrombosis. At the time it was a major addition to the anaesthetist's armamentarium.

The study of ethanol as a potential induction agent for anaesthesia is a little unexpected, even though ethanol has, by 'legend', been used for centuries to relieve the pain of surgery without anaesthesia. The reading of this paper does not recommend its use. Forty patients with an atropine premedication were studied; they received up to 550 ml of 5 – 10% w/v ethanol over 5 – 8 minutes 39-55 g alcohol). Methohexitone was frequently used to complete the induction (respiratory depression only occurred when the ethanol was supplemented). There were no cardiovascular complications but emergence delirium was high!

The study was carried out on "fit female patients undergoing minor gynaecological procedures", a phrase to be heard at many ARS meetings. In this paper (1969) patient consent was sought until "For a time it was used almost routinely in one gynaecological unit and patient permission was not then sought."

Delirium on induction as well as on emergence and methohexitone was used to overcome this problem. The anaesthesia was maintained with 75% nitrous oxide with oxygen. All four patients classed as "drinkers" needed the methohexitone supplementation. All patients were cardiovascularly stable.

Some patients who required methohexitone had significantly prolonged recovery, emergence delirium occurring in about 50%, it did not seem to upset the study patient but it did upset other nearby patients. Amnesia, "surprisingly", did not occur, but emesis and headache were – was this an iatrogenic hangover?

The second paper involving further observations on ethanol as an induction agent followed in 1970. Three hundred patients were studied; some were premedicated with chlordiazepoxide, some just with atropine. Surprisingly greater doses of alcohol were required with the chlordiazepoxide premedication than without. Cardiovascular stability was noted but all the adverse sequelae of the previous study were still a problem making ethanol an unsuitable agent for routine use.

Ketamine was introduced in 1962 by Parke-Davis and quickly found a role in anaesthesia. Bovill and Clarke et al investigated the role of premedicants in the suppression of those ketamine effects that were undesirable, primarily the hypertensive response and emergence sequelae. Sixteen different combinations of drugs were studied…contrary to (my) general understanding, "Tranquillizer and hypnotic drugs and droperidol-containing mixtures were the least effective." Even 30 mg diazepam was reported as being unsatisfactory in controlling the emergence phenomenon. Opiate and hyoscine mixtures were the most efficacious. Compared to other conventional intravenous induction agents it was not as easy to use.

Finally in this brief overview of "Clinical studies of…" we come to CT1341 (Glaxo Research Laboratories). In 1971 this was "a new steroid anaesthetic". The first steroid anaesthetic was hydroxydione (1955). CT1341 had been shown

to be rapidly acting, short duration and with few side effects[iii]. This paper was a dose finding study in 300 patients; the doses given ranging from 20µl/kg to 200µl/kg. Because CT1341 was a mixture of two agents its dosage was more conveniently expressed as a volume per unit weight. The same protocol was used for assessing induction and recovery as in other papers discussed previously.

Above 30µl/kg all patients became unconscious, excitatory effects increased with dose as did hypotension. It was determined that the 50 – 60 µl/kg doses were ideal. It had a low postoperative nausea rate and unpleasant dreams were rare (6%).

Four years later CT1341 was now Althesin. Carson et al. (including Dundee) studied 150 patients and compared Althesin with thiopentone and methohexitone. Althesin was found to be a very suitable agent for outpatient anaesthesia but the recovery rate was not as fast as methohexitone.

This overview indicates the sort of work carried out on 'the factory floor" by Dundee and his team.

Studies of drugs given before…

This selection of papers starts at the same time, 1962, all published in the British Journal of Anaesthesia. The first was "A method of pre-operative assessment"[52]; a variety of studies followed involving a whole range of combinations of drugs, atropine and hyoscine (1964) for example and several morphine related papers (1965/66); benzodiazepines (1968-1977) and in 1968 there was a further evaluation of the method of study, a review of the experience with 10,000 patients.

The first paper obviously sets the scene for all the others…as the authors set out in the abstract "The need exists for a comprehensive study of the effects of drugs given before anaesthesia, including an assessment of their pre-operative effects, action on course of anaesthesia, and sequelae which may be attributed to their use. The subjects for such a study should be from the same sex and age group, from one hospital, and the operative procedure and anaesthetic technique

[iii] Campbell, D et al. (1971) Brit. J. Anaesth., 43, 14.
Child, K. J. et al (1971) Brit. J. Anaesth., 43, 2.

should be constant." The main point being made here is that for good comparisons there must be consistency in all aspects of the study and that the patients should also be as consistent as possible. Sedation, apprehension, excitement, local effects, dizziness, emetic and cardiovascular effects were all noted. The initial study was that of atropine vs. atropine and pethidine. The desired effects were given a positive score and the toxic effects a negative one, a net rating was then possible. The statistical analysis was not straightforward, it used RIDIT analysis[iv]. To quote the paper again, "In ridit analysis a specified series of patients is chosen as the control reference set ("identified distribution") and all comparisons are made Relative to the Identified Distribution—hence origin of the word RIDIT. The individual scores in the identified distribution are replaced by ridits, which bear a relationship to the incidence of each score in the total series."

The 1964 paper comparing atropine and hyoscine as premedicants is a good example of the 1962 initial benchmarking study. Ridit analysis is not specifically stated but reference to desired and toxic effects and net scores is made, and a reference to the 1962 paper. Atropine produced tachycardia without sedation and hyoscine produced sedation with a low incidence of tachycardia, it also reduced postoperative emesis.

Tacrine (tetrahydroaminacrine) is an anticholinesterase and had been promoted as a drug that a) prolonged the effect of suxamethonium and b) as an antagonist to the sedation and respiratory depressant effects of morphine[v]. The combination of tacrine and morphine was studied, as usual, in "healthy women scheduled for minor gynaecological operations" and the results were that tacrine seemed to increase dizziness and nausea, and postoperative muscle pains were worse in the tacrine/morphine group when suxamethonium was used – contrary to previous work by Gordh et al and several others[vi].

Papaveretum was a popular, commonly used opiate for premedication in the 60s and 70s, used commonly with hyoscine, scopolamine, (Omn and Scop).

[iv] Bross, I. D. J. (1958). How to use ridit analysis. Biometrics, 14, 18

[v] Stone, V., Moon, W., and Shaw, E. H. (1961). Brit. med. J., 1, 471
Simpson, B. R., Seelye, E., Oayton, J. I., and Parkhouse, J. (1962). Brit. J. Anaesth., 34, 95

[vi] Gordh, T., and Wahlin, A. (1961). Acta anaesth. scand., 5, 55

Papaveretum was/is a mixture of alkaloids of opium, about 50% morphine (see the detailed description in the paper) and codeine, narcotine and papaverine. There was a substantial body of evidence against the benefits of papaveretum over morphine and yet, as is pointed out in the introduction to the paper there seemed to be a "curious divergence between apparent logic and clinical experience". It was this that stimulated the study. There were no "startling" differences between the drugs. One difference was the low incidence of hypotension during anaesthesia with the papaveretum-hyoscine mixture – there did seem to be some "basic difference in the spectrum of pharmacological actions". The bottom line was that papaveretum was not significantly better than morphine but that it had shown that it might be worthwhile studying various mixtures of the opium alkaloids.

Benzodiazepines were coming on the market in the 1960s and gaining a place in anaesthetic practice as premedication [61, 62, 66, 71, 72]. Chlordiazepoxide was the first and it was studied in a comparison with diazepam…together with a placebo. The comparison also included data from previous studies on opiates and phenothiazines. The results indicated that, indeed, these drugs did alleviate pre-operative anxiety and that they were as good as most opiates and with fewer side effects. It was suggested that they could be used as a "pre-preanaesthetic-medication", i.e. the day before! The cost of these agents was a factor at that time…diazepam being thirteen times as expensive as morphine.

Ten years later lorazepam was put through the factory mill [72]… it was low in onset and long lasting, the i.m. injection was painful. Oral premedication resulted in reliable sedation and was thought to be a useful premedicant as long as a quick recovery was not necessary. Anterograde amnesia was significant.

Morrison, Hill and Dundee reported an evaluation of the 'method of study' in 1968 [63], by this time 10,000 patients had been enrolled. They wanted to investigate the potential sources of bias; a significant paper, it does show a concerted effort to 'get it right'. In brief the study showed that age, body weight and the use of different observers did not influence the outcome; the frequency of observers' visits to the patient, the type of operation and the duration of the operation did.

Several pieces of advice may still apply today…eliminating patients who weigh more than 89kg reduces the variance and positive skew of the distribution of patient weight. Fixed doses of drugs vs. weight related doses was also discussed, in small studies it was suggested that weight related doses should be used but that in big studies (100 patients) fixed doses were acceptable as the results were comparable to drugs given on an individual weight basis. Logistically this was much to be preferred for blinded studies. Frequency of visits by the observers was important...it was thought that the visits themselves might have a placebo effect, in fact drowsiness was enhanced by more frequent visits as was apprehension, so both arms of a study should have equality in the frequency of assessments. As the duration of anaesthesia increases so do the emetic sequelae… in many of these studies the length of anaesthesia only ranged from 2 – 12 minutes, the incidence of emesis increasing by 100% or more, so once again, each arm of a study should have procedures of equal length. To quote their closing sentence "Only by rigid adherence to detail can reproducible results be obtained"; so true in the biological sciences.

Case studies:

Dundee, like many other medical writers, found opportunistic case studies…Addison's disease and adrenocortical insufficiency [2, 74], myasthenia gravis [75], dystrophia myotonica [5], porphyria [76, 77] and tetanus [78, 79]. There were also several publications on atopy and anaesthesia [80-82] and, as was appropriate at the time, halothane [83-86] and related hepatitis [87].

The Addison's disease report is interesting on several (could possibly be considered pedantic) points. The units used in this 1951 publication include 'stones' for weight (6.35 Kg) but does include a conversion, similarly with morphia gr. 1/6 (10mg), percent for the haemoglobin value, a blood pressure 96/60 without units, and other blood component measurements, sugar and urea, in percent. The abbreviation D.O.C.A. was also used without elaboration. The most interesting of statements is "Owing to a misunderstanding 0.4 g. thiopentone was administered." This may not be the first description of a drug error but it is interesting…in the author's own experience of thiopentone use in

the 1970s this dose would appear large for a 70Kg patient, this patient weighed 57Kg. Hypotension and prolonged sedation occurred.

With regard to the myasthenia gravis publication, a small dose of gallamine was used for the diagnosis of the disease; it was compared with d-tubocurarine. Two patients found gallamine less unpleasant and this was attributed to the 'respiratory sparing' effect of gallamine.

Porphyria and thiopentone [76, 77] was a lethal cocktail as the article in Anesthesia and Analgesia shows…in one series 77% of patients with paralysis had received a barbiturate whilst only 35% of patients without paralysis had[vii].
Atopy, in combination with allergy and previous anaesthetic experience was covered in three articles [80-82] ; after interviewing 10,000 patients in the British Isles the overall incidence of atopy (eczema ,asthma and hayfever) was 8.5%, atopic patients had an incidence of allergy of 36% compared with the non-atopic population – 11%. Some unusual figures came out of the audit, the obstetric population has a higher incidence compared with non-pregnant females (does pregnancy induce atopy?) and the 'cardiothoracic' subset of male patients had a higher incidence, does this mean that males with atopy have a greater risk of cardiothoracic disease? From these 10,000 patients the frequency of type of anaesthesia was collected, 67% had had a previous anaesthetic, and 20% of these in the previous four weeks. Over half of them had been given halothane [83] . And so, finally, the old topic of halothane and hepatitis [84-87]. The first paper studied liver function tests after repeat (two or more) administrations of halothane (63 patients) and enflurane (66 patients). Halothane produced the higher incidence of enzymatic changes.

Hypothermia and acupuncture:

Two subjects on which multiple papers were written were induced hypothermia [88-92] and acupuncture [93-109].

[vii] Goldberg A. Quart. J. Med. 28:110 and 183,1959

Hypothermia

Between 1953 and 1964 there were eight papers on hypothermia, one of the first, whilst he was working in Liverpool, was on the production of hypothermia and was an animal study. They used deep anaesthesia, curarization and a 'lytic cocktail', chlorpromazine, pethidine and promethazine. Cardiac arrest occurred in three dogs at 23, 23.5 and 26.5 degrees centigrade. Three types of hypothermia all appeared effective but chlorpromazine appeared to be the active ingredient of the 'lytic cocktail'. The publication in 1955 [90] describes the management by induced hypothermia (on multiple occasions) of a patient who had a cerebral aneurysm bleed…in the sub-title of the paper are the words "a clinical study of a hopeless case" [viii]. Jumping forward to 1964 [92], there is an article on the "Pharmacology of hypothermia". This is a comprehensive document, co-authored with RS Clarke, on drugs used to induce hypothermia, reduce the untoward effects of hypothermia and how hypothermia influences the actions of other drugs, a fitting final publication on the theme.

Acupuncture

In the 1970s, perhaps even a little earlier, reports were coming out of China of the use of acupuncture for major surgery…it became a 'hot topic'. Of the many claims for its use its antiemetic effect proved a valuable area for research. Of the seventeen papers, from 1986 to 1991, Dundee was the lead author in sixteen; he was obviously very interested in the topic of the antiemetic effect of stimulation of the P6 point.

The 1986 paper [93] reported two consecutive studies including a randomised set of anaesthetics, one arm received nalbuphine and acupuncture, one dummy acupuncture with premedication and one with premedication alone. It was reported that acupuncture significantly reduced perioperative nausea and vomiting; the mechanism inexplicable. It was reported to reduce morning sickness [97] and was shown to be effective against chemotherapy induced nausea [100, 105].

[viii] A totally irrelevant comment here is that what we take for granted now in the quality of graphics was so far in the future…the graphs are hand drawn and can be seen to be so.

A 1991 study where either saline or 1% lignocaine was infiltrated at the P6 point is fascinating. There were 37 patients in each group; when saline was used 30 patients had neither nausea nor vomiting, in the lignocaine group, over the study period of six hours an average of 21 patients were free from symptoms, a p value of 0.014.

Odds and ends:

To complete this partial, annotated bibliography, there are several other, single, publications of interest… David Waldie [110], who was he? Anaesthesia related iatrogenic disease [111], mysterious deaths at Ann Arbor [112] and the death of a volunteer [113] are some. There were also overviews of many subjects but one of note is that of total intravenous anaesthesia (1978 and 1984) [114, 115], looking forward to research in the eighties [116] published in 1979 and an enigmatic title "The last of the fifty – a time of change" [117]

David Waldie was a Scotsman who qualified as a surgeon in 1831 but he was more interested in chemistry and gave up medicine around 1840. He was responsible for improving, if not perfecting, the extraction of chloroform from chloric ether; could come in useful for Trivial Pursuits.

The anaesthesia related iatrogenic disease was published in the Nova Scotia Medical Bulletin…its impact factor is unknown to the author.

"Death of a volunteer" is a letter to British Medical Journal (Clinical Research Edition) commenting on a death associated with pharmacological research, involving midazolam…the volunteer developed aplastic anaemia. Comments are made on the remuneration of researchers and their inability of to cover potential damages. Still of great importance in the light of more recent deaths in volunteers[ix]. In New Zealand clinical research is either indemnified by a the drug company, if they are sponsoring the study, or by ACC, the no blame accident covering 'insurance' (Accident Compensation Corporation).

"Research in the eighties" is a one page editorial in the British Journal of Anaesthesia, the final two sentences are "Let the clinicians document the failings of our available agents or machines and the companies will know wherein lies

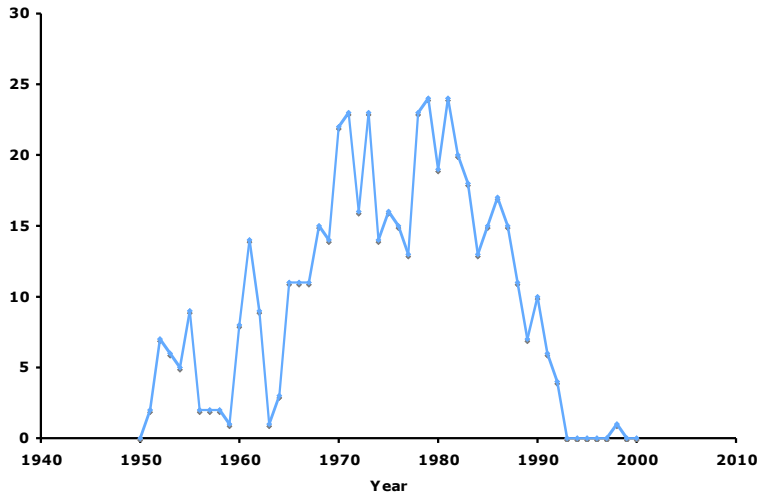
[ix] http://www.i-sis.org.uk/LDTC.php (last visited 2010)

the most profitable field for research. Proper feed-back from clinicians to research workers and industry will make research relevant to all concerned." He extols the virtues of past researchers and, in effect, states that the modern academic is less likely to make such an impact as Magill or Macintosh.

"The last of the fifty – a time of change" [117] is an oration in October 1985 at the Royal Victoria Hospital (Belfast). It is an historical overview of change in medicine, and in particular anaesthesia. It is particular to Belfast but it could be mirrored in any British city. The "last of the fifty" refers to the consultant 'Staff' of fifty (there were others) who were elected to a body that communicated with the Hospital Management Committee and University. Positions only became available on the death or retirement of members. JW Dundee was the last of the fifty to be elected as it was a time of change.

The list of references below may well be incomplete, John Dundee published articles in non-English journals, and chapters in books, for example "Monitoring for drug safety" edited by William HW Inman[x].

Dundee and his team of workers produced a large body of work that portrays the use of para-anaesthetic and anaesthetic drugs over a period when anaesthesia was undergoing, arguably, its greatest change.



Number of publications per year

[x] 2nd Edition, 1986. MTP Press ISBN-0-85200-721-3

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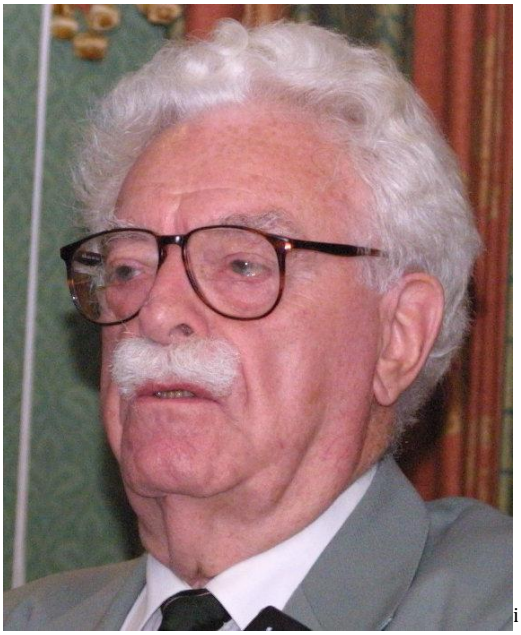
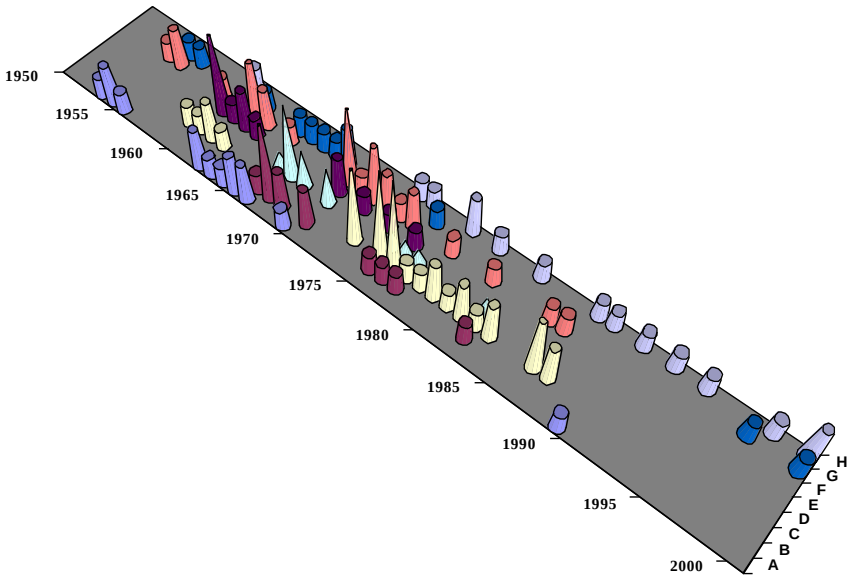
J P Payne
MB Edin, FFARCS, DA

 [i]

JP Payne, over a period of more than forty years, wrote on a variety of topics relating to anaesthesia; these fall into several main categories, hypoxia, the measurement of alcohol in blood and breath, the effect of drugs on the neuromuscular junction, physiological measurement and various papers on ethics and education.

Payne was part of a team and the following names should be recognised as eminent team members: JA Bushman, CM Conway, DW Hill, R Hughes and N Sugai.

Payne's references, [1-76] are discussed and references [77-150] refer to his papers not discussed in the text.



A	B	C	D	E	F	G	H
Oxygenation	Alcohol	NMB	Technology	Measurement	Pharmacology	Clinical	Ethics etc.

Publications from Payne's team from 1950 – 2000

[i] Photograph courtesy of Alistair McKenzie and the History of Anaesthesia Society

Hypoxia:

Payne published a paper , in 1953 in the British Journal of Anaesthesia, based on a presentation to the Scottish Society of Anaesthetists titled 'Controlled hypotension in theory and practice'[1]. He was then working in the Department of Anaesthesia at the University of Manchester. This is an interesting article comparing the clinical use of 'bleeding' for hypovolaemic hypotension with the use of ganglion blocking agents. It included case reports of bleeding patients up to two litres for the facilitation of neurosurgery. He commented on the ease with which anaesthesia was maintained at low blood pressures and postulated that at <50mmHg (?systolic) patients might remain asleep without anaesthesia. There followed a discussion on consciousness, in terms of philosophy, physiology and pharmacology; tissue metabolism was considered of importance in maintaining consciousness.

Two papers in 1954 investigate oxygen consumption in cats[2 3]. The second one showed that the reduction in VO_2 due to bleeding was greater than due to sympathetic blockade, possibly due to the vasoconstriction, and suggested that the fall in VO_2 during sympathetic blockade was secondary to the absence of the "normal complement of adrenaline".

In a joint investigation with Nunn in 1962[4] Payne reported postoperative hypoxaemia; oxyhaemoglobin saturations of 90% (PO_2 of 65mmHg). This was a landmark paper. Both Nunn and Payne were lecturers at the Postgraduate Medical School, Hammersmith. They described how it stayed low for 24 hours, and the lowest PO_2 recorded was 39 mmHg, the highest 82mmHg. They suggested that this was a strong case for the use of oxygen masks in the postoperative period. Another paper published in 1963 supports this work[5]. Oxyhaemoglobin desaturation was found in every patient and was relieved by oxygen enriched air. It was not related to a particular anaesthetic agent or surgery. The PCO_2 values were normal so it was not thought to be due to under-ventilation. Further work on hypoxaemia in the perioperative period was published in late 1964[6]. Hypoxia during surgery, as well as in the postoperative period was a surprise finding, and some patients were found to be hypoxaemic before surgery[7]. Atropine was thought to be the causative agent[8]. Intramuscular atropine was shown to reduce oxyhaemoglobin

saturation compared with control patients. This is contrary to a later paper where it was shown that only atropine administered subcutaneously seemed to cause a fall in PaO_2[9], it was not seen with the intravenous or intramuscular routes. The mode of action was thought to be mechanical, secretions or a change in surfactant. The magnitude of the fall was in PaO_2 was related to age. PaO_2 = 102.5 – 0.22 (age)

Over these early years, mid fifties and sixties, JPP seemed to have affection for chloroform; he was chloroform's last champion [10]. Several papers seemed to be fighting a rearguard action for its continued use; its arrythmogenicity being a complication of too light anaesthesia.

Alcohol[ii]

Payne, Hill and King (Research Department of Anaesthesia, Royal College of Surgeons, England) in 1966 produced a report on the distribution of alcohol in blood, breath and urine[11]. The work was carried out in anaesthetised dogs and volunteer humans (a choice of whisky, gin or rum). Great attention was paid to the validation of the measurement techniques and the following conclusions were reached. Absorption of alcohol from the stomach was slower than from the duodenum and the rate of absorption varied widely, the uptake being related to the dose and the rate of drinking.

Carotid jugular equilibrium occurred quickly but the measuring of venous blood alcohol was only of value after the peak arterial concentration had been reached. The uptake of alcohol by the tissues would lead to an underestimate of arterial alcohol before the peak.

Analysis of alcohol in the breath tended to underestimate arterial levels, possibly due to V/Q abnormalities, or possibly due to uptake of alcohol by mucus. If alcohol was in the mouth an artificially high level was recorded.

A good correlation between blood and urine only held if the peak concentration in the urine had passed and the bladder had been emptied 20 – 30 minutes earlier. The advice given was that two samples should be collected at thirty minute intervals and if the concentration in the first was greater than the second then accuracy was assured.

[ii] The breathalyser was introduced in Britain on October 9th 1967, it is partly responsible for reducing alcohol related deaths from 13000 pre-1967 to 2500 in 2006.

In 1967 the accuracy of gas chromatography method for alcohol was assessed and confirmed the work by Curry et al.[iii] that gas chromatography combined with an internal standard and an integrator could determine alcohol content accurately in five minutes. An investigation was carried out into the conversion factor of 1.33 for blood levels from urine levels[12], similar work was published in France, Spain and Germany[13-15]. Stevens et al.[iv] however showed the methodology to be invalid in the "less rigidly controlled environment of a busy police station". The range of blood: urine ratios were such that miscarriage of justice was possible. The value of alcohol in capillary samples of plasma and red cells was also discussed. The plasma's alcohol concentration was not the same as blood alcohol concentration as the red cells contain a lower concentration[16]. The blood concentration would depend on the haematocrit. It was suggested that venous blood should still be used. The mean urine: blood ratio was 1.44:1 with a range of 1.10 to 2.44.

The Ministry of Transport Road safety Act, 1967, stated that 107 mg of alcohol in 100ml urine should be treated as equivalent to 80 mg of alcohol in 100ml blood.

Further work, in 1968, on the plasma vs. blood alcohol problem confirmed the work of others and reinforced the view that plasma/breath ratios, or plasma/urine ratios should be used as these were independent of haematocrit. Numerous allied papers were published on the topic over the years and much debate about breath analysis[v].

In 1976 another measurement technique[17] proved equally problematic with wide variation in results and a clash with Wright (Clinical Research Centre, Harrow,of 'Wright's Respirometer' fame) where he said "not only are their results much worse than those obtained in recent years by a number of reputable observers, but they give a picture of the present understanding of the subject that is very out of date". [vi]

[iii] Curry AS, Walker GW, Simpson GS. Determination of ethanol in blood by gas chromatography. *Analyst* 1966;91(88):742-3.

[iv] Stevens PJ, Mason JK, Bowden CH. Comparative ethanol concentrations in blood and urine during social drinking.. Medicine, Science and the Law 1966;*6(2):96-102*

[v] B M Wright. Breath, alcohol, and the law. *Br Med J*. 1977 July 9; 2(6079): 121

[vi] B M Wright Breath, alcohol, and the law. Br Med J. 1977 May 7; 1(6070): 1216–1217.

An interesting final foray into the effects of alcohol was an investigation of alcohol related flushing of the face and neck, a possible genetic trait, that occurs in situations where the alcohol in the blood exceeds 20-35 mg/dL[18]. Alcohol and aldehyde dehydrogenase enzyme deficiency cause the blood acetaldehyde to become abnormally high. Absorption of alcohol could be retarded by a combination of H1 and H2 antagonists and thus reducing the peak concentration.

Neuromuscular blockade:

'Jimmy' Payne worked on the pharmacology of neuromuscular blockade (NMB) from 1958 through to 1987. He demonstrated in 1958 that d-tubocurare (dtc) was different to the other relaxants available at the time in being enhanced by carbon dioxide, K^+ had no effect[19]. Dtc was different from suxamethonium, decamethonium and gallamine by having a pKa value 8.1 – 9.1, as compared to 13. This phenomenon was examined further[20-22]; was it due to a change in the ionic state? Probably not; was it a specific effect on dtc – a chemical union where the hydroxyl groups were neutralised and potency increased?

In 1959 he described suxamethonium tachyphylaxis[23], a progressively diminishing effect of successive doses could then be explained by the residual competition block antagonising the depolarising effect of succeeding doses of either decamethonium or suxamethonium. He hypothesised that all NMB agents may pass through a depolarising phase which is later followed by a competitive block. In 1962 the duration of a variety of agents was tested in the presence of the serum from jaundiced patients[24], the decrease in effect was considered to be due to increased protein binding and the increased effects of the tropeine derivative by the low serum cholinesterase.

A ten year gap separates this work from his later publications; his co-workers were N.Sugai until 1976 and R.Hughes until 1986. Hughes was with Burroughs Wellcome and oversaw the introduction of atracurium.

At the Anaesthetic Research Society (ARS) in Liverpool (April 14th 1973) 'Jimmy' Payne presented one of his most obsessive subjects, that of the value of tetanic contractions vs. single twitches in the assessment of NMB[25 26]. Tetanic contraction was considered a more sensitive measurement of neuromuscular

function by Gissen and Katz (1969)[vii]. It was shown that the tetanic response disappeared more quickly than single twitches. At the ARS at the Hammersmith (London), November 1973, Payne's team reiterated the importance of using both single twitch and tetanic stimulation for the study of suxamethonium [26]. It was suggested by Sugai and Payne[27 28] that the response to tetanic and single twitch stimulation represented different aspects of response of the neuromuscular junction, that there may be enough acetylcholine (ACh) for repeated single twitches but not for sustained tetanic contractions.

Payne used the tetanic tension ratio (TTR) [29], which was the height at the end of the stimulation period divided by the height at the beginning, and single twitch technique to elucidate neuromuscular function in parallel with combinations of nondepolarising agents, depolarising agents and anticholinesterases. Using combinations of suxamethonium and edrophonium[30] he came to the conclusion that that tachyphylaxis and change in character of the NMB were parts of the same phenomenon. Amongst the drugs studied were suxamethonium, decamethonium[31], dimethyltubocurarine[32 33], tubocurarine, and gallamine[34]. One pharmacological goal was the 'clean' muscle relaxant without cardiovascular effects – dimethyltubocurarine had some of the required properties.

The interaction between halothane and NMB was also studied[35]. It was thought that the then effect was a pre-synaptic one because the enhanced block was only evident when tetanic stimuli were applied, this could be caused by impairment of Ach release.

A significant paper was published in the BJA in 1980. This was a study of the NMB properties of neostigmine[36]. It was shown that repeated doses of neostigmine caused an increase in NMB as documented by the TTR and the severe fade lasted twenty minutes. This blockade was potentiated by suxamethonium and antagonised by gallamine. The big difference between the effects of the frequency of stimulation was clear. Tetany in the presence of inhibition of acetylcholinesterase and an increase in Ach caused prolonged end-plate potentials (EPPs) to summate and cause persistent depolarisation of the

[vii] Gissen AJ, Katz RL. Twitch, tetanus and posttetanic potentiation as indices of nerve-muscle block in man. *Anesthesiology* 1969;30(5):481-7.

post synaptic membrane and the mobilised Ach reserves became exhausted leading to fade.

The single twitch method of neuromuscular assessment showed an increase in twitch height with neostigmine, this was said to be due to the increased amounts of ACh available and augmented and prolonged the EPPs but in insufficient quantities to produce NMB. Payne advocated the use of tetanic stimulation for assessment of NMB because it was more physiological. This work supported the early work done by Briscoe in 1936/7.[viii] It would appear that the 'neostigmine resistant block' was in fact a neostigmine induced NMB.

There were many papers investigating the technological aspects of electromyography (emg)[29 37-40]. As new neuromuscular blocking agents came available for study Payne's department was at the ready; fazadinium was assessed in 1976[41]. Fazadinium did not stay in clinical use very long; it was suggested that with repeat doses it might produce a profound NMB. Atracurium was evaluated between 1981 and 1986[42-47], and vecuronium in 1987[48]. Much work was done on atracurium with R Hughes, atracurium being a Wellcome product and worked in the Pharmacology Department of the Wellcome Research Laboratories in Beckenham in Kent. The work with atracurium covered most aspects of its anaesthetic usage. The mathematical mechanism for producing a rate constant for recovery was described[45].

Technology

Payne summarised anaesthetic monitoring requirements in a non-specialist journal in 1970[49], the differing requirements between intra-operative and postoperative requirements being highlighted. ECG monitoring was not routine at this time but it was advocated, citing the work of Johnstone in 1948 on the effects of anaesthetic agents on abnormal heartsix. Real-time computing in patient monitoring 1971, 1972[50 51] was now a real possibility.

[viii] Briscoe, G. (1936). Shift in optimum rate of stimulation due to prostigmine. J. Physiol. (Lond.),88,48P.
----------(1937). Optimum stimulation rates for red and white skeletal mammalian muscles, and shift in rates produced by the eserine group. J. Physiol. (Lond.), 90, 10P.

[ix] Johnstone MW. (1948) MD Thesis. Queens University, Belfast.

Payne's team had an obvious interest in measurement and technology. Payne's team was in at the beginning of the use of the telephone system to transmit data, papers in 1968, 1970, 1972, 1976[52-55] all indicate the potential use for real-time analysis away from the clinical environment; three waveforms could be sent at one time. In 1964 Levine and Jossman had published on the same topic. [x]

EEG analysis during anaesthesia was carried out in 1976[56] using a telephone link to an Elliott 903 computer, they did a fast Fourier analysis and then returned the processed information back to the anaesthetic room. This work was part of Perry's PhD thesis and followed on work by Kiersey et al.[xi]

Mass spectrometry, another technical innovation in anaesthesia research, was used in 1976[57] to measure the loss of anaesthetic vapours from breathing circuits during and after anaesthesia. This was an early investigation of the pollution of operating theatre air and hence the requirement for scavenging.

Ethics and Miscellany

Payne had an interest in humanitarian aspects of anaesthesia as well as the scientific, and often they crossed paths.

History: Professor Payne was a great supporter of chloroform, in 1955 he published an article in Medicine Illustrated [10], twenty-six years later he wrote about chloroform again – 1981[58], and in 1998[59]. It was said to be good, "Admittedly, at that time…" the newer agents weren't available "… but it would be surprising if any of these later drugs were shown to be vastly superior to chloroform." There was said to be a great demand worldwide for a safe, cheap, potent, non-explosive and easily stored agent.

He wrote on anaesthetic deaths in 1983[60], stating that anaesthesia cannot be blamed for all surgical deaths and complaining that surgeons are unwilling to study the problem. He emphasised the need for audit to be accepted – (Medicine Digest 1982. 8 p35) and dental anaesthesia in 2000 [61].

He wrote on the resuscitation of the apparently dead[62], the quality (the degree of excellence) of measurement 1970[63] and on the ethics of the use of

[x] Levine IM. Jossmann PB. Tursky B. Meister M. Deangelis V. Telephone telemetry of bioelectric information. *JAMA. 188:794-8, 1964 Jun 1.*

[xi] Kiersey DK. Faulconer A Jr. Bickford RG. Automatic electroencephalographic control of thiopental anesthesia. Anesthesiology. 15(4):356-64, 1954 Jul.

halothane 1974,1986 [64 65]. The 'Quality of Measurement' article was a report on his presentation of the Clover lecture on 18th March 1970 at the Royal College of Surgeons and was a progress report of his seventeen years as Head of Department.

Ethics and Halothane: Prof. Payne wrote several editorials and they always had a lively, brusque style. The Committee of Safety of Medicines (CSM) made comments about the safety of halothane without referral to clinical anaesthetists and this caused great concern as it was considered to be a clinical decision as alternatives to halothane may have their own risks which could be greater. Quoting Professor Parkhouse...is it the CSM's place to "enter the arena of clinical judgement?"[xii]

In 1975 he wrote on responsibility and accountability [66]. He took the Committee on Safety of Medicines to task on their controversial letter about halothane. He compared the responsibility of individuals for their actions with the apparent freedom of responsibility that committees enjoy, committee members passing the buck to the chair, the chair reciprocating in a similar manner.

In 1978 animal experimentation was the focus [67] and was stimulated by Smyth's monograph Alternatives to Animal Experiments[xiii]. He was commenting on the activists' against animal experimentation need for replacement techniques, which is laudable, but is quite different to whether it is possible. Public concern over the Thalidomide tragedy had stimulated a need for legislation requiring more testing; so the public's view on animal experimentation was in fact not unanimous.

In the same year another editorial tackled the problem of research in intensive care units[68]. He castigated medical staff for avoiding issues and praised a nurse for a paper on the topic in the same journal[xiv]. He took the Royal college of Nursing to task for providing nurses with "Girl Guide" type guidelines on ethical issues. He advocated greater communication between clinicians and

[xii] Parkhouse J. Letter: Halothane and liver damage. British Medical Journal. 3(5934):807, 1974 Sep 28.
[xiii] Smyth, D. H. (1978). Alternatives to Animal Experiments. London: The Scolar Press Ltd in Association with the Research Defence Society.
[xiv] Bishop VA. A nurse's view of ethical problems in intensive care and clinical research Br. J. Anaesth. 1978 50: 515-518

patients and/or patients' relatives, "Patient's diseases are not the personal property of the clinician".

The place of arterial cannulation in research had been hotly debated because there was great fear of real damage to the radial artery (large rigid cannulae being used) and in 1990 the ethics of arterial cannulation in research, in volunteers, was discussed[69]. An audit of the sequelae of arterial cannulation was carried out and the bottom-line was that the risk was low, that small bore cannulae were just as good as large ones and that only those experienced in the art of arterial cannulation should do them on volunteers.

Other topics were medical education 1960[70] 1980[71], the place of alternative therapies 1987 [72] and 1992, pay parity for academics, 1992[73]. There had been an agreement on pay parity but this was all offset by deterioration of work conditions and a decline in academic morale – an all time low - and that the outlook was bleak.

Thirty years on: the anniversary of the founding of the Anaesthetic Research Society, 1988[74]. In 1952 the Faculty of Anaesthesia (Royal College of Surgeons) asked for the setting up of a research department, this happened in 1957. A research meeting was proposed but not universally condoned (it might set up an elite group of anaesthetists) but John Gillies[xv] said "Get it going and they will all be there." It was an opportunity for those engaged in anaesthesia research to discuss their objectives openly and frankly with similar minded colleagues, the organisation had no permanent officers, no fees and all decisions were made at a dinner after the meeting.

Awareness [75]: Payne considered awareness to be totally avoidable and that the aftermath for a patient was severe, that it was a form of post traumatic stress disorder and that the patients should receive appropriate support and therapy.
Multiple authorship 2000[76]: This communication is really a moan about short articles that have six or seven authors names attached, he called these co-authors citation seekers and that it should be the responsibility of the reviewers and editors to curb the activity.

[xv] Post WWII Reader in Anaesthetics, Edinburgh.

Jimmy Payne's career was certainly vibrant, as was his manner at research meetings, a brusque but able team leader.

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Cyril M Conway

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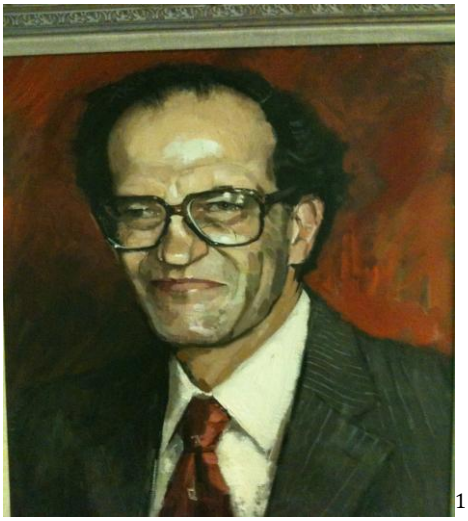 [1]

1n 1976 Cyril Conway was a member of the Magill Dept. of Anaesthetics in the Westminster Medical School. Professor Conway became head of the combined anaesthetic departments of Charing Cross and Westminster Hospitals in 1983. He died in 1986.

Many 'new researchers' start their publication list with a case report or description of some clinical problem…this was the case with Cyril Conway [1]. This was followed by an assortment of papers [2-4] until 1962 when, with Jimmy Payne, he had a publication in Nature [5]. This was about standard bicarbonate values of whole blood. In all Conway had nine publications in collaboration with Payne and most of them are associated with hypoxaemia in one guise or the other [5-13]. More details of these papers can be found in Payne's bibliography. There was one more publication on the topic of "Arterial oxygen tensions in surgical patients" with Conway as the sole author [14].

Conway's interest in pharmacology was reflected in a variety of papers [2, 4, 7, 15-20], the subject matter included the anaesthetic ethers, the cardiovascular effects of various induction agents, the effect of anaesthetic agents on myocardial contractility (see below) and, of some academic interest, the Antoine equation coefficients for inhalational anaesthetic agents [19]. This is not a paper but a letter to the British Journal of Anaesthesia about an article by Rodgers and Hill[2]. It points out errors that the authors acknowledge. As the authors state, Professor Conway diligently examined their paper in great detail. From his work on breathing circuits, detailed below, he obviously had a great eye for mathematical precision.

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[1] Photograph courtesy of Neil Soni, Imperial College London.

[2] Rodgers, R. C, and Hill, G. E. (1978). Equations for vapour pressure versus temperature derivation and use of the Antoine equation on a hand-held programmable calculator. Br.J. Anaesth., 50, 415.

Cardiorespiratory physiology

In 1970 a paper was presented, with Blackburn JP as the primary author, … this was on 'Myocardial carbon dioxide response curves' [21] and this was followed in 1971 with "The effects of anaesthetic induction agents upon myocardial contractility" [18], an abstract. There were five papers all with Blackburn as the primary author on aspects of myocardial contractility. To quote a section of their paper on 'An analogue device for measuring the pre-ejection period (PEP)' [22] "The pre-ejection period (PEP), may be derived from the three waveforms by subtracting left ventricular ejection time (LVET) from total electromechanical systole time (EMT)" and this had had to be done manually.

A paper on $PaCO_2$ and PEP [23] was published in Anesthesiology in 1972. Using $1/PEP^2$ as an inotropic index they studied the myocardial response to changes in arterial carbon dioxide tension, in dogs and humans. An initial rise in inotropy with carbon dioxide was thought to be due to sympathetic stimulation …in dogs this had been able to be blocked with beta-blockers. With high levels of carbon dioxide myocardial depression occurred. In dogs halothane shifted the response curve downwards and the final thought was that the Paco2/myocardial response curve could be used to evaluate drugs that affect the myocardium.

In the 1970s analogue computers for analysis in medicine were in their 'heyday', they very useful for pharmacokinetic and hydrostatic (cardiovascular) type modelling. Blackburn et al here describe a complex analogue system for determining the beat-by-beat PEP value. This was quite a 'tour de force'. They compared hand-calculated values to computed values and the r value was 0.976. There were obviously problems (noisy phonocardiogram and ill-defined dicrotic notches the main ones.

In their final joint publication they studied the effect of the Valsava manoeuvre on systolic time intervals under various conditions, on healthy patients, prior to surgery. Postural change, beta-blockers, ganglion blocking agents and halothane and methoxyflurane were all assessed.

With 'light' anesthesia the majority of subjects responded appropriately even after beta blockade and ganglion blockers. Adding more volatile agent to the anaesthetic abolished the response, PEP changed markedly whether the responses were blocked or not.

This concluded the work with Blackburn et al.

Measurement

Like all academic anaesthetists devices of measurement are the most important of research tools and Conway also had his share of studies of measurement devices. He evaluated "a battery of coagulation techniques" [24], the "Rapox" paramagnetic oxygen analyser [25, 26], three electronic respirometers [27] and he wrote an article on "Anaesthesia and measurement" for the Proceeding of the Royal Society of Medicine [28]. However he is probably best remembered for his mathematical analysis if the dynamics of breathing systems.

Circuits

1976 was a productive year for Conway's experimental and mathematical appraisal of breathing systems. The first publication in 1976 [29] was in fact an abstract from that Anaesthetic Research Society held in London in October 1975. He was working at this time in the Magill Department of Anaesthetics in the Westminster Medical School. He explains in the abstract how in any semi-closed rebreathing system some rebreathing will occur if the fresh gas flow is below a critical value and that the values of the oxygen-carbon dioxide mixtures in various parts of the circuit, if plotted on an oxygen/carbon dioxide graph, all lie on a single gas exchange line, see below for more details. He goes on to explain how with a single modification of the alveolar air equation alveolar concentrations of gases can be determined. He states, "The behaviour of any circuit can be deduced if the composition of vented gas can be forecast."

Two papers in the same journal were then published, and cited each other[30, 31]. The first was "A theoretical study of gaseous homeostasis in the Magill circuit" [30] and was a more detailed description of the findings of the ARS abstract. Mapleson, almost twenty years earlier, had deduced that the Alveolar CO_2 ($FaCO_2$) = CO2 production / fresh gas flow. The $FaCO_2$ was not affected by changes in ventilation. This paper is a purely mathematical treatise on the subject and it assumed that the subject was breathing spontaneously, in a steady state and that the gases breathed were oxygen and nitrogen. Through a lengthy series of equations, along the lines of the alveolar air equation, he was able to show that whether there was complete gas mixing, no gas mixing, or partial gas mixing, the mean inspired gas concentrations (oxygen and carbon dioxide) will be the same. The last paragraph of this paper is interesting in that there is a short discussion on the use of controlled ventilation using the Magill circuit

(normally wasteful on fresh gas) where he states ""Replacement of the usual simple expiratory valve of the Magill circuit by a valve which does not permit gas venting during inspiration would allow this simple analysis to be extended to include the passively ventilated subject". The author believes that this was the basis on which the Carden ventilator was constructed[3].

Following on was "An experimental study of gaseous homeostasis and the Magill circuit using low fresh gas flows". The Magill circuit was probably the most commonly used breathing system in the UK at that time. Volunteers were used to breathe a "non-narcotic" mixture of gases through a standard Magill circuit using various gas flow rates. Previous work in this field had indicated that rebreathing should not occur unless the fresh gas flow rate was at or below the 'minute alveolar ventilation'[4]. This study confirmed this finding but also showed that variations in ventilation could perturb the system, in particular, following a deep breath at low flows the exhaled carbon dioxide could reach the reservoir bag and change the dynamics of the circuit. The end-tidal gas concentrations changed very little even when this change was associated with marked changes in ventilation and inspired gas concentrations.

The next paper[32] continued the description of the concept of being able to deduce alveolar gas concentrations from the gas mixtures in the breathing system, and this paper generalized the idea to all semi-closed systems. Conway, again, was the sole author. Here he describes a 'black-box' approach to the analysis. He refers to the geometrical approach for the solution of the alveolar air equation that was suggested by Leigh and Tyrrell in 1968[5]; this geometrical approach is based on the fact that all gases (inspired, expired, and vented) must all contain "mixtures of varying proportions of fresh and alveolar gases" and these values can be plotted on an oxygen vs. carbon dioxide diagram (x-y graph) and a straight line relationship exists which can be used to advantage. The line plotted (the gas exchange line) is related but not equal to the respiratory exchange ratio; Conway himself had collaborated with Leigh in 1972 when they determined the interrelationship between FiO_2 and the gas exchange ratio in the oxygen-carbon dioxide diagram [33].

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[3] Fletcher IR et al. Anaesthesia 1983;38:1082-9. Tham EJ et al. Brit. J. Anaesth 1993;71:741-746

[4] Kain ML and Nunn JF. Anesthesiology 1968;29:964

[5] Leigh JM and Tyrrell MF. Br J Anaesth. 1968;40:430

The final paper of this series in 1976 was an experimental paper on the newly introduced Lack circuit[6]. The advantages of the Lack over the standard Magill (Mapleson A) was that the expiratory valve was proximal, rather than at the patient end, and that the reservoir bag was near the fresh gas inlet rather than on the expiratory limb as found in the Bain circuit. The manufacturer's information leaflet states that the "fresh gas flow requirements [*for a Mapleson A system is*] theoretically equal to a little more than the alveolar ventilation, i.e. 4-5 litre/min for a 70kg adult". The paper, first author PK Barnes, found that the resistance to breathing was unacceptably high and that rebreathing occurred in spontaneously breathing volunteers when the gas flow rate was equal to the minute ventilation; minute ventilation being significantly more that alveolar ventilation. They suggested a flow rate of 1.5 x minute ventilation.

In 1977 two 'circuit' related papers were published, first a theoretical and experimental study of the Mapleson D system [34] and then an analysis of the Bain system [35], a co-axial modification of the Mapleson D.

In the first paper a mathematical analysis was carried out along previous lines of thought and the coaxial version of the Mapleson D (a Bain circuit) was used when ventilating the lungs of dogs. A significant endpoint of the study was the production of a series of multiple regression equations that related carbon dioxide levels in a linear way to fresh gas flow and total ventilation. The last figure in the paper is a graphical nomogram whereby knowing the fresh gas flow and the ventilation the $PaCO_2$ can be predicted. This was followed by a volunteer study breathing a non-anaesthetic gas through a Bain circuit. It was recommended, "at least three times the minute volume appear to be necessary to prevent rebreathing". These findings were not universally accepted; some years later, following further publications, Spoerel and Bain disagreed with the recommendations in the correspondence section of the BJA and could not understand how the Bain (coaxial D, T-piece) could differ so markedly from the non-coaxial T-pieces[7], Conway replied [36] in defence of his position. In 1980 another paper on the Lack circuit was published, this time in Anaesthesia [37]. There was a great deal of controversy about the required gas flow rates and the importance of rebreathing, another worker, David Humphrey from South Africa, entered the fray in 1982 where he

[6] The Lack circuit is a co-axial breathing system that has the characteristics of the classic Mapleson A type. It was designed and developed by Dr Alistair Lack and Bill Quick of MIE. http://www.historyofmie.co.uk/viewproduct.asp?id=lack

[7] Spoerel WE and Bain JA. Br J Anaesth 1986;58:819-822

compared the Lack, the Magill and the Bain breathing systems all under the same conditions[8]. The Lack system seemed to come out best for spontaneously breathing adults.

In 1981 Conway turned his attention to circle systems – the first being on the factors that affect carbon dioxide homeostasis [38] and the second on "alveolar gas relationships with CO_2 absorption" [39]. The first used an experimental lung model with controlled ventilation without carbon dioxide absorption. In brief carbon dioxide removal was most efficient at low respiratory frequencies and was well correlated with fresh gas flow and minute ventilation if the frequency was kept constant. The mixing of fresh gas and exhaled gas was thought to be responsible for some paradoxical results when frequency was changed. The second paper a Conway classic. Again he uses the 'black-box' analogy and creates a myriad of equations to determine the dynamics of the system, again using the oxygen-carbon dioxide diagram originally described by Rahn and Fenn 1955[9]. Take a weekend and read this paper. Accurate alveolar gas concentrations cannot be predicted but the black box approach does indicate how the system should be used, high flows at the beginning of the anaesthetic (for 20 minutes) when the system is least stable, and then low flows – the long time constants of the system making any changes in alveolar gas concentrations very slow…at very low flows the gas composition should be monitored. A critical letter about his analysis (more along the lines of the futility of it) was rebuffed [40]. Conway would have been in his element with modern monitoring.

Two papers in 1984 [41, 42] , the first addressed the factors that should be considered when using closed and low flow systems (Acta Anesthesiol. Belg.) and the second on the concentration and second gas effects (where the fast uptake of one gas increases the concentration of the other and therefore enhances its uptake) in circle systems. These factors were more comprehensively explored in the subsequent years and in 1986, the year he died, a further three papers on gaseous homeostasis in circle systems were published [43-45]. The first one was the description of a model and the second a validation of the model.

[8] Humphrey D. J Roy Soc Med. 1982;75:513-524
[9] Rahn H and Fenn WO. American Physiological Society 1955

The model consisted of two parts, the subject and the breathing system. The multi-compartment subject model described by Mapleson[10] was used, the lung component modified to accommodate a variety of gases. The model of the circle system assumed complete mixing of gases and complete carbon dioxide removal. The paper needs to be read to understand all the intricacies of the calculations…the program was written in Pascal. The subject model made calculations on a heartbeat to heart beat basis and the gas concentrations in the breathing system were calculated for every respiratory cycle. There is an extensive discussion on the intricacies of the model and its problems; because of the calculations rates for the subject and the circle are different some errors are "both summated and compounded" at low fresh gas flows.

In the second paper, the model's performance in several tests, including a nitrogen washout test when 'breathing' oxygen and the estimation of the model's functional residual capacity by using helium, tested the 'functionality' of the model. The performance of these tests was good and reproduced the results of some previous studies, including the use of nitrous oxide. It was therefore deemed to be a good test bed for the prediction of the behaviour of circle systems.

The final paper was an application of the model to the dynamics of a classic anaesthetic mixture, Oxygen, nitrous oxide and halothane (or methoxyflurane). A range of flows and concentrations were used and the effects on gas concentrations by the concentration and second gas effects studied. As is known, a circle system, when compared with a non-rebreathing high flow system, will reduce the rate of uptake of anaesthetic agents and this will increase in magnitude as the fresh gas flow decreases. The whole paper is a work of great magnitude and displays the value of models in the understanding of the real world where clinical studies of this nature would have been even more difficult with many more confounding factors.

Cyril Conway died in post in 1986.

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Edgar Arthur Cooper

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"The expertise of the average person who gave anaesthetics…" before World War II "was a technical expertise which had evolved from many years of empirical practice, rather than a mastery of some field of academic knowledge" from his inaugural lecture "The Edge of the Knife" in 1968[1].

[i]

The practice of anaesthesia has changed dramatically in the last fifty years of the twentieth century.

Ed Cooper worked in the Department of Medicine at the University of Birmingham as a National Coal Board Research Fellow prior to moving to Newcastle upon Tyne. He was first assistant (1957-62), then a consultant, and became Professor of Anaesthesia in May 1967, until 1980 when he resigned from this appointment.[ii]

His inaugural lecture[1], "The Edge of the Knife", delivered on Monday 4th March 1968 covers many aspects of his work and indicates a sense of humour. "When I called on Professor Miller to kneel and kiss hands on my appointment to the Chair he assured me that he was sorry I'd got the job. He had hoped someone bright would have applied."

He followed similar interests as his predecessor (Edgar Pask) in Newcastle in that he studied the interactions between man and respiratory equipment and the measuring equipment used in the studies. Equipment-related work will be described first and then the physiological studies.

Equipment and Measurement

In the 1950s the measurement of carbon dioxide in gas mixtures was a problem (Ramwell 1957)[iii] because the molecules of the diluent gas caused an alteration in its infrared

[i] Photograph courtesy of Gary Enever, RVI, Newcastle-upon-Tyne.

[ii] Before 1963 the medical school in Newcastle was part of King's College of the University of Durham, the 1964 intake of students became graduates of the new University of Newcastle-upon-Tyne.
Photograph courtesy of Dr Gary Enever, Newcastle Upon Tyne, UK

[iii] Ramwell PW. The infrared analysis of carbon dioxide during anaesthesia. *British Journal of*

absorption spectrum, the pressure broadening effect. Previous work by Coggeshall and Saier[iv] had indicated that if the partial pressure of the diluent gas was large; although the pressure broadening effect may be large, it would be fairly constant over small changes in concentration.

In 1957 Cooper simplified the measurement of carbon dioxide in the presence of nitrous oxide by producing a single calibration curve that could be used for concentrations of nitrous oxide between 60% and 80%[2]. It was determined that when using a calibration chart for 60-80% nitrous oxide the error in the measurement of carbon dioxide was less than 7.5%. The effect of water vapour was very small <0.03%. There was much discussion on the source of errors.

Scientific methodology is of paramount importance in research, a sine qua non, and part of the methodology is error elimination. Cooper was meticulous in this aspect of his work. He discussed the errors in measuring expired gases in Anaesthesia (1959)[3]. The slip of gas past valves, the pervious nature of Douglas bags, the peculiarities of dry gas meters, distensibility of tubing, compressibility of gases and the use of complete respiratory cycles to measure volumes per unit time rather than using fixed time periods. The Lancet in 1960 carried a description of a tapered PVC bag that had been designed to measure expired gases[4]. The gas was collected over a known number of respiratory cycles and then a rod was used to roll up the bag, like rolling up a tube of toothpaste, until the bag was tense. The volume was then read off a scale, simple, but, presumably, effective.

Two further papers by Cooper in 1960 investigated the work involved in breathing through respiratory equipment[5,6], obviously of great importance to rescue services in mines, self-contained breathing apparatus of any kind, and in anaesthesia. Respiratory protective devices (gas masks, filters and closed circuit breathing apparatus) were studied by producing pressure volume diagrams from the application of a sine wave pump to the breathing system under test. Flow through such apparatus was rarely laminar and previous workers, Silverman et al[7], had suggested that "a limit on external respiratory work appears to be the best basis for stating tolerable limits of resistance". Work by Cooper, comparing man with a sine wave pump at different minute volumes, had

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Anaesthesia 1957;29(4):156-9.

[iv] Coggeshall ND, Saier EL. Pressure broadening in the infrared and optical collision diameters. *J. Chem. Phys.* 1947;15:65.

demonstrated that the correlation was such that apparatus could effectively be tested using a sine wave pump. Six breathing systems were tested and the total work increased with increasing minute volume - work done against elastic forces becoming negligible at high minute volumes, work done against friction forces becoming dominant.

$P = kn (V)^n$ - Reynolds showed that n could be determined for any system and could be used to describe roughness or tortuosity of the system. On a logarithmic plot of P vs. V the gradient is n. Through some mathematical contortions it was shown that constant flow bench tests correlated well with physiological testing using pressure volume loops. A set of standards for breathing apparatus was laid out. One stated that expiratory work had to be less than 50% of total respiratory work at high minute volumes.

Minute volume estimation[8]; this must have presented a problem at this time as the device described was produced as an alternative to the vagaries of the pneumotachograph which were considered bulky, complex, a fire risk, and were associated with zero drift. In addition the changing composition of anaesthetic gases affected their accuracy. The mechanism was ingenious, involving the measurement of a fraction of the total flow by allowing flow through a shunt in parallel with the main respiratory circuit. It had the inherent fault of manual, discontinuous, measurement of flow using a moving soap film. Needless to say the pneumotachograph has survived to the electronic age (and the use of non-explosive anaesthetic agents); this device did not. It seems extraordinarily complex and was developed through 'trial and error'.

The indirect estimation of arterial pCO_2 had been attempted by many methods to avoid the invasive procedure of arterial puncture[v]. In 1961 Cooper addressed the problem[9]. Arterialised ear-lobe capillary blood was shown to be acceptable if the patient was not in a state of 'autonomic upset' (pallor, sweating, abnormal pulse or blood pressure). Rebreathed gas - having the same tension as mixed venous blood -was shown not to have this problem, although the systematic error was large. Collecting blood from the back of the hand during unimpeded flow was also acceptable, the pCO_2 difference between hand and artery being 1.6 mm Hg, SD ± 4.2 mm Hg. End-tidal carbon dioxide, collected by an automatic sampler, underestimated arterial carbon dioxide by variable

[v] Collier CR. *Journal of Applied Physiology* 1956;9:25.
Campbell EJ, Howell JB. The rebreathing method of estimating arterial and mixed venous carbon dioxide ftension. *British Journal of Diseases of the Chest* 1960;54:137-8.
Campbell EJ, Howell JB. Simple rapid methods of estimating arterial and mixed venous pCO2. *British*

amounts, in bronchitic patients by the order of 10-15 mm Hg. However, the conclusion drawn was that the rebreathing technique was the technique of choice.

The rebreathing technique was originally suggested by Plesch[vi]. It involved the prefilling of a 'rebreathing bag' with carbon dioxide (either from a pre-mixed cylinder or by the subject rebreathing oxygen in a bag for 90s) and at the end of an inspiration the subject began breathing from the bag, in only a very short time the concentration in the bag equilibrated with the alveolar carbon dioxide and the gas concentration could then be measured.

Apart from a teaching article on the measurement of ventilation[10] twenty years passed before the next equipment related paper was published, passing from the era of valves to that of transistors and micro-chips. The ability of a chemical-sensitive field-effect transistor for on-line measurement of K^+ was investigated[11]. Intermittent blood flow through a 'butterfly needle' enabled the measurement of K^+ and it was found to be slightly lower than that measured by flame photometry, 3.8 mmol L^{-1} compared with 4.1 or 4.03 mmol L^{-1} using Corning 450 and 902 flame photometers. Blood was sampled for 8s at 32s intervals, the main problem was maintaining anticoagulation.

Physiology

"On the efficacy of intragastric oxygen" (1960)[12] was the title of a detailed study into a method of resuscitation that must rank only second to 'cupping' as a stupidity. It highlights the state of medicine in the late fifties although more logical means of resuscitation had been considered for centuries[vii]. Newborn kittens were rendered severely anoxic and were given intragastric or intra-intestinal oxygen. Survival time, rate of haemoglobin desaturation and rate of fall of oxygen tension were measured, as was the rate of loss of oxygen into the blood stream from the gut and the effect of minimal pulmonary oxygenation. Although this technique was widely used this study provided no evidence to suggest physiologically important amounts of oxygen were transferred from the gut to the circulation. Under optimal conditions less than 0.02 ml min^{-1} of oxygen was

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Medical Journal 1960;1(5171):458-62.

[vi] Plesch JZ: exptl Path Ther 1909; 6: 380

[vii] "Nearly one millennium ago, authors recommended ventilating via a bellows and a tube in the trachea. In 1767, the Dutch Humane Society published guidelines for resuscitation of victims of drowning, stating: 'keep the victim warm, give mouth-to-mouth ventilation, and perform insufflation of smoke of burning tobacco into the rectum'." Michael Ardagh. A brief history of resuscitation. The NZ Medical Journal, 2004;117, 1193

absorbed but the anoxic liver probably consumed this. The average newborn kitten required 0.3 ml of oxygen per minute for 'bare and tenuous survival'.

The Infant Resuscitation Committee at the Maternity Pavilion of the Winnipeg General Hospital, in 1956, stated that "Carbon dioxide and intragastric oxygen are not advised by the committee" for the resuscitation of neonates[viii], citing Waller, and Morris[ix]. A commentary on the inappropriateness of intragastric oxygen was published in the BMJ four years later[x]. Cooper's work was supported by a similar study by Coxon[xi]. It is an interesting commentary in that it reviews the origin of the use of intragastric oxygen; the idea originated with A Yllpő, (Acta paediat. (Uppsala), 1935, suppl. 1, 122 (referenced from BMJ commentary)) but was later described by Y Akerron and N Furstenberg[xii].
The bottom line was "This method should now be abandoned, particularly as its use may delay more effective measures."

In 1967 Cooper published two papers on physiological dead space during passive ventilation[13,14]. As the sole author, as with the majority of his papers, he by necessity must have personally carried out the work. The first paper describes the detailed methodology and incorporates much of the experience from previous studies - measurement of gas tensions, gas volumes, minimising leaks, criteria for assuming steady state and so on. The final measurement of V_D/V_T at what he terms 'constant ventilator activity' was such that "the standard deviation of individual values about the mean for each subject was 0.83% (range -1.9% to 1.8%).

The second paper presents the results from patients studied. The units used were a mixture of imperial and metric. Patients were ventilated at a 'standard' rate, the tidal volume was 80 ml per stone (12.6 ml kg^{-1}) at a frequency of 15/min. Ninety eight percent of recorded physiological dead space was >4ml kg^{-1} and with increasing tidal volume the dead space became larger. Radford et al. in 1954 had produced a nomogram that was said "to estimate proper ventilation during artificial respiration", these assumptions were said

[viii] Scmidt O, McLandress M, Cruickshank L: An evaluation of infant resuscitation. Canadian M.A.J 1956; 75: 503-6
[ix] Waller HK, Morris D: Resuscitation of the newborn with intragastric oxygen; Akerren's method. Lancet 1953; 265: 951-3
[x] Intragastric oxygen. British Medical Journal 1962: 483-4
[xi] Coxon RV: The effect of intragastric oxygen on the oxygenation of arterial and portal blood in hypoxic animals. Lancet 1960: 1315-7
[xii] Akerren Y, Furstenberg N: Gastrointestinal administration of oxygen in treatment of asphyxia in the newborn. Journal of Obstetrics & Gynaecology of the British Empire 1950; 57: 705-13

to be not valid under conditions of general anaesthesia and passive ventilation[xiii], since the volume of the dead space in ml was not numerically equal to the patient's body weight in pounds. The mean value for V_D/V_T was 52.2% (range 33.5% - 68.8%), much larger than during spontaneous, conscious breathing. This paper of Coopers confirmed work by others that the Radford nomogram was not suitable for use during anaesthesia[xiv], this included work by Nunn's team[xv] and by Thornton in Sheffield[xvi]. .

As the subjects, or patients, age increased so did the V_D/V_T ratio. By 'standardising' the results of other workers Cooper either produced a correlation with age where previously none existed or improved the correlation. Thornton's series matched Cooper's best. Combining the results from his patients (50) and the other workers' patients (70) Cooper was able to produce an equation relating physiological dead space to age with a correlation coefficient of 0.70. His 'rule of thumb' equation was:

V_D/V_T % = 33 + age / 3 SD ± 6.93%

This study must have involved a great amount of personal work and should be noted as contributing to the confirmation of the fact that changes in respiratory physiology under general anaesthesia, in particular during passive ventilation, are different to those occurring in awake subjects.

Other papers by Cooper are of a miscellaneous nature, 'Tracheostomy and controlled respiration', 1961, is a review[15], and, in essence, states that the bigger the hole and the bigger the tube the better. 'Oral neomycin and anaesthesia',1963, was one of the early descriptions of the neuromuscular blocking properties of antibiotics[16]. Other publications are listed in the references[17-22]; a few have been omitted because, although referred to in various texts, they could not be located.

The cartoon below returns us to the beginning of this report as it reflects a man of varied interests and a sense of humour; the individual graphics reflecting the variety of

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[xiii] Radford EP, Ferris BG, Kriete BC: Clinical use of nomogram to estimate proper ventilation during artificial respiration. New England Journal of Medicine 1954; 251: 877-884

[xiv] Gain EA: The adequacy of the Radford nomogram during anaesthesia. Canadian Anaesthetist's Society Journal 1963; 10: 491-500

[xv] Campbell EJ, Nunn JF, Peckett BW: A comparison of artificial ventilation and spontaneous respiration with particular reference to ventilation-bloodflow relationships. British Journal of Anaesthesia 1958; 30: 166-75

Nunn JF, Hill DW: Respiratory dead space and arterial to end-tidal carbon dioxide tension difference in anesthetized man. Journal of Applied Physiology 1960; 15: 383-9

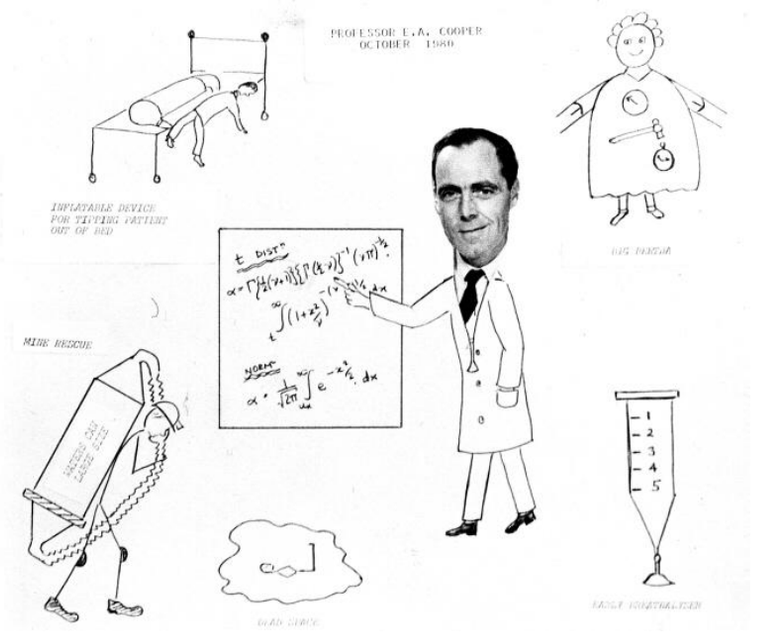
Nunn JF: Predictors for oxygen and carbon dioxide levels during anaesthesia. Anaesthesia 1962; 17: 182-94

[xvi] Thornton JA: Physiological dead space. Changes during general anaesthesia. Anaesthesia 1960; 15: 381-93

topics in his writing[1].

A final quote from the inaugural lecture:

"But wherever academic anaesthesia may lead: the skies, the seas or the solid dry land[xvii], our prime function is to protect our patients from the agony and the danger of the edge of the surgeon's knife. This we do by standing at the edge of another knife, the knife edge about which their existence see-saws and swings, for it is our job to stabilise and prevent the platform from reaching the limits of its traverse – wakefulness or death."



Cartoon courtesy of Dr Gary Enever, Department of Anaesthesia, RVI, Newcastle upon Tyne, dated at the time of his resignation from the Chair.

[xvii] This is a reference to the work of his predecessor Professor Edgar A Pask who worked during WWII on safety equipment for military personnel both at sea and in the air.

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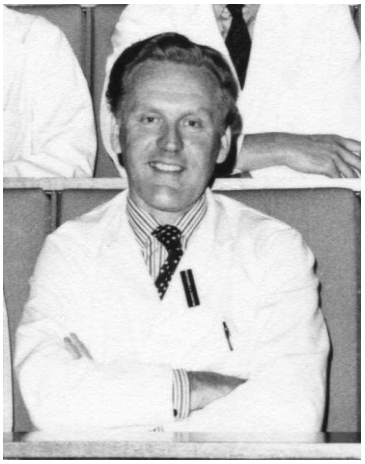
22. Cooper EA: Device for the estimation of the rate of work on passing air by sine wave flow. Journal of Scientific Instruments 1959; 36: 436-438

Andrew Thornton

MD MB BS Lond FFARCS DA



Andrew Thornton moved to Sheffield in 1963 (he had been a research fellow at Guy's Hospital) and became Professor in 1971. He left in 1983 to take the chair of anaesthesia in the Chinese University of Hong Kong.

Professor Andrew Thornton's work can be classified under four main headings - clinical reports, general scientific studies, dental sedation and adverse reactions to drugs. They range from 1958 to 1988.

Clinical reports:

The first reports from Andrew Thornton were from his time in the army and described the management of a crushed chest injury using intermittent positive pressure ventilation (IPPV) and continuous curarisation. Anaesthetists had been using curare to create a 'balanced' anaesthetic since about 1942 but its use in intensive care was, obviously, later, because the first intensive care unit was not established until 1953 during the infamous polio epidemic in Denmark. The second publication from Guys Hospital was an assessment methodology for the efficacy of bronchodilators (antispasmodics) [1, 2].

From here on the publications become more specifically associated with anaesthesia [3]. By 1963 he had moved to Sheffield, had his Fellowship of the Faculty of Anaesthetists (F.F.A) and was working in the Regional Cardiovascular Centre [4-6]. Sheffield was to be his base for most of his academic life. These papers on various problems associated with anaesthesia for cardiac surgery were associated with two papers on the estimations of blood loss during surgery [7, 8], a problem that has not been solved satisfactorily today (2009); of the methods tried the colorimetric technique was considered the most useful/convenient.

In 1963 there was a most extraordinary investigation into the aetiology of cot death [9]. This involved the study of six infant cadavers where spontaneous respiration was simulated. The cadavers were positioned supine,

laterally and prone, and a variety of different pillows were tested. The bottom-line of this study was that the position did not seem important but that the nature of the pillow was. In the views of the authors the best pillow studied consisted of a covering of loose mesh material having a large number of small holes. The pillow was filled with curled plastic pieces forming a loose slightly springy network. This seems to have been the first study to analyse this problem in a physical way; a truly innovative approach.

Two papers on the assessment of Citanest [10, 11], two on the problems associated with chronic respiratory disease and anaesthesia (a common problem in the industrial midlands) [12, 13], and then some interesting early work on postoperative epidurals with an infusion of fentanyl [14], adding knowledge to previous work in 1979 and 1980 by Behar et al[i] and Bailey et al[ii] respectively, and total intravenous anaesthesia [15] using etomidate.

Science

The investigation of basic physiological entities (like physiological dead space and analysis of respiratory gases) was still underway in the early nineteen sixties and Andrew Thornton was amongst the investigators. [16-19]. In 1960 he was collaborating with John Nunn at Guys Hospital, London.

At the same time computer technology was rising fast but its use in anaesthesia research was of the analogue variety; these computers were useful for the teaching and research into the distribution of drugs and gases [20-23]. The examples described in the BJA article of 1968 included hydrodynamic and electronic analogues that were able to mimic the complex relationships involved in carbon dioxide and oxygen stores, and in the uptake of general anaesthetic agents. With digital computers dominating the scene in the 21st century these analogue systems were the easiest to program for complex inter-related exponential functions... the hydrodynamic systems were also great visual demonstrations[22].

[i] Behar, H, Olshwang D, Magora F, Davidson, J.T. Epidural morphine in treatment of pain. Lancet 1979: 1: 527-9.
[ii] Bailey, P.W, Smith, B. E. Continuous epidural infusion of fentanyl for postoperative analgesia. Anaesthesia 1980; 35 1002-6

Intravenous sedation:

Andrew Thornton's main interest seems to have been in the field of dental sedation; in 1969 intermittent methohexitone was the investigative drug of choice. [24-28] A letter to the editor of the British Medical Journal has his team of Dixon, Hatt, Mann and Perks writing about their experience with methohexitone which is in response to, and supportive of, a paper by Robinson et al (Birmingham)[iii]. This paper by Robinson had caused an uproar which lead to the threat of libel action by Mr S.L. Drummond-Jackson[iv]. In brief it was shown that airway obstruction, hypoxaemia and hypotension were common during the use of repeated doses of methohexitone, and it was suggested that some of the deaths associated with dentistry were caused by the technique. The references listed include detailed accounts of the research methodology; it included psychological testing of the patients to assess the 'banishment of fear of dentistry', aspiration of radio-opaque dye (testing of laryngeal competence), measurement of cardiovascular and ventilatory parameters and oxygenation. '*Methohexitone and its application in dental anaesthesia'* [26] is a review article and covers all aspects of the subject.

The use of methohexitone (references 1969 -1971) tailed off and diazepam took its place [29-31], (references 1970 – 1973). Associated with these studies were reports on anxiety [32] and patient responses to dental surgery with and without sedation[33]. Letters discussed the 'dental anaesthetist of the future [34, 35]. This was followed by another 'new' agent Althesin (removed by the manufacturers in 19xx), references are dated 1976, [36, 37] this was quickly followed by flunitrazepam - 1976-1980 [38, 39]. Midazolam took over in 1982 [40-42] and is still in use today.

Adverse reactions to drugs

A different set of papers on drug interactions and allergy began in 1975 when collaboration with John Watkins began [43-49]. In 1975 it was known that there were alterations in the concentrations of components of the complement system

[iii] Wise, C., Robinson, J. S., Heath, M. J., and Tomlin, P. J., British Medical Journal, 1969, p525 and 540

[iv] Drummond-Jackson, S. L. Ed. (1967). Intravenous Anaesthesia - S.A.A.D. 3rd edn. p. 155. Swindon: Swindon Press

and white cell numbers when sampling blood from patients with an anaphylactic type of response to intravenous drugs, thiopentone, methohexitone and Althesin in particular. In letters to the British Journal of Anaesthesia and Anaesthesia a request was made for anaesthetists to send blood samples to the Sheffield research unit if a patient had experienced an anaphylactoid type of response. This was the attempt to overcome the problem of the rarity of the 'anaphylactoid' event.

A paper in 1976, "Identification and quantitation of hypersensitivity reactions to intravenous anaesthetic agents" advocated the measurement of plasma complement C3consumption and conversion in sequential blood samples taken at intervals over the 24 h following an adverse response. Irrespective of the actual mechanism involved, it was said to provide a simple and convenient method for assessing hypersensitivity reactions.

Cremophor El, a detergent, a mixture of some 50-60compounds, was used to solubilise some intravenous agents. In 1978 its role in adverse reactions to intravenous anaesthetic induction agents was suspected. It was used in Althesin and Epontol (propanidid), two popular agents at the time. Again, in a letter, it was stated that there was no established correlation between intradermal skin testing and systemic responses.

The request for blood samples from the British anaesthetic workforce worked and almost 100 samples had been received by 1979. It was once more stressed that the clinical features of the anaphylactoid response are predominantly a result of the release of histamine, without involving IgE antibodies. Skin-testing pre-judges the mechanism of the reaction whereas examination of changes in complement, the immunoglobulins, and IgE specifically is the best approach.

Andrew Thornton contributed to the safety of dental sedation by the systematic study of the effects of various agents on cognition, respiration and the cardiovascular system. This work spanned the years 1969 -1983, a considerable body of work with a team of collaborators that included RE Atkinson, NR Bennett, PR Clarke, CD Day, RA Dixon, PS Eccersley, MJ Harrison, SD Hatt, TJ Hughes, D Lamb, P Mann, VC Martin, ER Perks and S Woodhead.

The publications of most interest are these rigorous assessments of cardio respiratory changes during dental sedation but the investigation into cot death and the use of analogue computers are also of note. His co-authorship of papers published in Nature[50] and in the Journal of Applied Physiology[21] must have also been very gratifying, the first on the genetics of human serum cholinesterase and the second on the electronic analogue for the distribution of carbon dioxide in the body.

Andrew Thornton was also involved in the organisation of a supernumerary Senior House Officer training scheme in the area served by the Sheffield Regional Hospital Board, later the Trent Regional Authority, which was a significant improvement on existing training methods and he was also co-author of several books – Aids to Anaesthesia, Basic Sciences and Clinical Practice (with Tom Healy and Michael Harrison), Techniques of Anaesthesia with Management of the Patient and Intensive Care (with Cyril Levy) and Adverse Reactions to Anaesthetic Drugs.

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J. G. WHITWAM

MB ChB MRCP FFARCS

Joe Whitwam trained in anaesthesia in Leeds and at Case Western University in Cleveland, Ohio. He became senior lecturer at the Royal Postgraduate Medical School in 1969 and Reader in 1973. He succeeded Prof. JG Robson to become professor and director of anaesthesia and critical care for the combined Hammersmith, Queen Charlotte's and Charing Cross hospital group. He retired in October 1996.[i] His interests can be classified under four headings, pharmacology, physiological aspects of pain and autonomic nervous activity, clinical practice and equipment, particularly high frequency ventilation.

Hypnotic agents:

Joe Whitwam hit the ground running when he started publishing. In his first year (1962) he had two papers published, one in the British Journal of Anaesthesia and one in the British Medical Journal, an auspicious start.

Methohexitone was the subject of ten publications from 1962-1980 [1-10]. However, the popularity of methohexitone waned as other agents became available, diazepam [11-14], Althesin [15-18], Etomidate [19-21], Minaxolone [22, 23], propofol [24-30], and Midazolam [13, 14, 27, 31-47] and Flumazenil [13, 14, 27, 31-50].

The first paper [1] was a simple descriptive study of apnoea with methohexitone and thiopentone (no difference), the second [2] a clinical comparison of these two agents in the outpatient setting (more movement with methohexitone but complete recovery quicker). A paper on methohexitone in dental practice[4] was another so-so description of its use without unexpected findings but a fourth paper on the detailed observation of

[i] Nunn JF. BJA 1999;83:916

modified electroconvulsive therapy (ECT)[3] is very interesting. From what the authors say there had been no previous description of ECT using the combination of atropine, methohexitone and suxamethonium. More papers came along (1973-1980) on methohexitone, two with Anita Holdcroft involving its use for Caesarean Section.

Propofol became available for study in 1982 [24] and he continued to study its effects (comparing it with thiopentone in 1985 [25]) in various ways[24-30, 43, 45, 47]. Whitwam studied many animal models for autonomic research and this involved using hypnotic agents, including propofol [27-30]. These projects were a team effort; D Al-Khudhairi, D Ma and M.K. Chakrabarti were three co-workers. The animal work will be visited later.

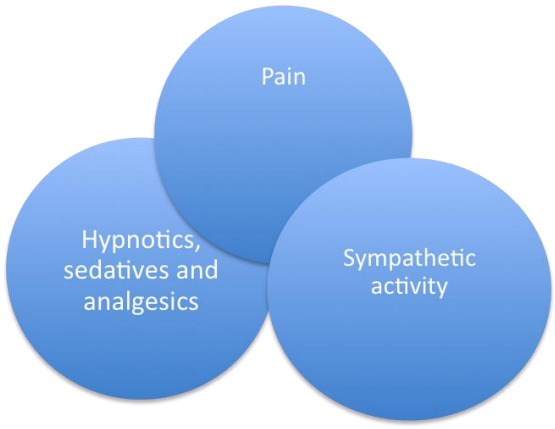
Flumazenil (a benzodiazepine antagonist) arrived on the scene and in 1988 Whitwam wrote on this novel agent in a variety of journals and became its mouthpiece in British anaesthetic circles [38-42, 46, 48-50].

His work on the clinical implications of hypnotics is an impressive body of work, too great in volume to be discussed here in detail however there was a comprehensive review written in 1978 of the then current agents [51].

Starting at the beginning...with C Kidd and IF Fussey, neurophysiologic studies were carried out on dogs [52-55]. They were, amongst other things, a study of the effects of baroreceptors on the sympathetic responses to noxious stimulation. The detailed neurophysiological reports in the specialised journals are beyond this authors understanding, in brief "A rapid increase in pressure in a vascularly isolated perfused carotid sinus has been shown to inhibit a reflex response in efferent sympathetic nerves of the dog evoked by electrical stimulation of the radial nerve" but an 'anaesthetist' orientated version was published in the British Journal of Anaesthesia in 1970 [56]. This was a presentation to the Anaesthetic Research Society in Aberdeen. Stimulation of peripheral nerves in the dog evokes a response in the sympathetic nerves…this particular study was to determine the effect of baroreceptors on this response as baroreceptor activity inhibits spontaneous sympathetic nerve activity. Physiological activation of the baroreceptors was shown to have an inhibitory effect.

Pain and sympathetic activity:

Much of Joe Whitwam's work involved a combination of pharmacology, pain, and sympathetic physiology and cannot be easily separated. The following is an attempt to summarise collected works.



In 1973 he was a joint author with Morgan and Page investigating pain thresholds following the injection of thiopentone and Althesin (CT 1341)[16], at that time a new steroid anaesthetic agent. There was no difference between them, with medium clinical doses there was a reduction in both pressure pain and thermal pain thresholds. A similarly study was done with diazepam[11]. An interesting study of pain thresholds with nitrous oxide (1976 [57]) showed that that 50% nitrous oxide was only marginally better than 33% in increasing pain thresholds over a period of ten minutes. A 45 minute administration resulted in a doubling of the pain threshold from which they concluded that there was some adaptation of the nervous system over this time.

Using various search terms 'sympathetic' resulted in the display of 35 publications [28, 30, 37, 42, 44, 53, 54, 56, 58-84]. Three specifically on 'baroreceptors' [53, 56, 58], six on 'peripheral' nerves [53, 54, 61, 85-87] and six on vagus related work [59, 83, 84, 88-90]. The remainder, with a variety of goals, investigated the effect of various agents on the autonomic system.

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Further work with Fussey and Kidd in 1973 [58] showed that "In intact preparations the latency of evoked responses in sympathetic nerves was found to *vary progressively during a cardiac cycle*; the maximum increase in latency was observed with the responses that occurred at that phase of the cardiac cycle when the baroreceptors exert maximal inhibition on spontaneous sympathetic activity." That is, beat to beat changes in baroreceptor activity, and therefore blood pressure, are a major influence on the sympathetic response to peripheral nerve stimulation.

In 1975 there was an investigation of the use of direct current to cause selective block of large peripheral nerve fibres [86]. It was shown that direct current could be used in this manner but because of nerve damage was unsuitable for clinical use. In '76 he wrote a historical 'perspective' on the nomenclature of peripheral nerve classification [87]. Whitwam's work on autonomic activity spanned the years 1967 – 2004, amongst many papers on various aspects of autonomic control processes there were investigations into the effects of anaesthetic agents and, in 1987, a novel ventilation technique…high frequency ventilation[90]. This paper with Harrop-Griffiths and Chakrabarti described its effects on afferent vagal activity. Recordings from the vagus nerves of anaesthetised dogs during conventional and high frequency ventilation were analysed. There was a decrease in

the mean spike counts per minute as respiratory frequency increased. This was thought to be intuitively correct, as pulmonary stretch receptor activity would be related to tidal volume.

Later, in 2000 and 2004 work turned to effects of drugs on vagotomised rabbits. Increases in desflurane concentration was shown to evoke a transient vagally mediated sympathetic excitation but that there was a dose related central depression of the sympathetic system, to below baseline levels at 12% [83]. The hypotension and bradycardia due to fentanyl was studied and because 'intact' rabbits had more autonomic depression than vagotomised rabbits it was concluded that the effects of fentanyl were mainly due to direct depression of sympathetic activity.

There are many other papers in this field of research to be covered in this bibliography.

Equipment studies:

One of Joe Whitwam's long-term collaborators was MK Chakrabarti, his studies are principally around the effects of various types of lung ventilation. 1983 a novel, valveless, ventilator was described where the driving force for ventilation was a jet of gas in the expiratory limb of a T-piece like system (this is a paraphrase of the description). The driving gas was not inhaled as long as the expiratory limb was greater than one tidal volume. It was valveless, would tolerate spontaneous respiration and could be used at any frequency [91-93]. The airway pressure was 30% less than with a Manley (conventional) ventilator. A second innovation (1984) involved the continuous insufflations of air or oxygen down both lumens of a Carlens tube; this washed out CO_2 and provide oxygen during complete apnoea [94, 95], an improvement on standard apnoeic oxygenation techniques. [43]

In addition to these investigations there were other studies which concentrated on the physiology and clinical use of high frequency ventilation [90, 96-112]. Many of these papers extol the virtues of valveless and high frequency ventilation for their minimal impact on the cardiorespiratory system and ease of weaning, this applied to both adult and paediatric practice. In1993 their investigations moved on to computer controlled closed

anaesthetic breathing systems. It was designed to rapidly achieve a pre-set anaesthetic concentration [113-115].

One study of note, in 1993, was one by Cook et al.; this was a description of "True patient-controlled sedation". A modified patient controlled analgesia device was modified to enable a patient to self dose with propofol or midazolam during a minor gynaecological procedure. It appeared to work well, recovery from propofol was quicker than from midazolam using critical flicker fusion tests [43]. Recovery from sedation/anaesthesia was also investigated by Scott and Whitwam using a choice reaction timer; the time it took to respond to the device was the measure of recovery…control patients decrease their reaction time with practice; post anaesthesia the reaction time increases but after 24hr there was found to be no difference between the different anaesthetic techniques [116].

A quantum change in anaesthetic practice was about to take place in the late 1980s; the advent of pulse oximetry; Taylor and Whitwam's article on "The current status of pulse oximetry. Clinical value of continuous noninvasive oxygen saturation monitoring." described the principles by which it worked and their closing comment was "Pulse oximetry may make a significant contribution to the safety of anaesthetic practice" [117]; a glorious British understatement. Another related paper followed [118] comparing the accuracy of five different models.

Aortic compression by the uterus during the final stages of pregnancy was detected using the Finapres digital arterial pressure monitor, one on both finger and toe. The compression was detected when the toe pressure was reduced in the absence of changes in the finger [119, 120]. The tilt required to relieve the compression was found to be very variable and the factors associated with the compression were a high foetal head, the occipito-posterior position and early cervical dilatation, see related paper [121].

Other equipment related publications are [110, 122-133]

Clinical

The clinical publications are wide ranging from the description of clinical signs during electroconvulsive therapy [3] in 1963, through a wide range of case reports: nitrous oxide filling a gas-filled ovarian cyst [134], management of patients for yttrium-90 [135],

Eisenmenger's syndrome [136] (which suggested that the risks had previously been overstated), vasoactive adrenal tumour [137], (a review of APUDOMAs [63]), general anaesthesia for total body irradiation[138], chondro-calcinosis in acromegaly [139] and paroxysmal nocturnal haemoglobinuria (Budd-Chiari syndrome) [140]. The last explaining the need for an anaesthetic involving drugs unlikely to cause complement activation.

Immunological processes was the subject of an editorial in 1979 [141] associated with a whole section on immunologically related topics. This was followed by several other papers: Borlessa et al. 1982 (complement changes associated with cardiopulmonary bypass) [142], Schifferli et al. (complement changes in stored blood) [143], in 1986, Boralessa again ("C-reactive protein in patients undergoing cardiac surgery.") [144], Rowe et al. 1986 (C-reactive protein concentration after renal transplantation) [145] and Pepys et al. 1994, a slightly different topic (skin prick tests for anaphylactic/anaphylactoid reactions) [146].

Even the humble cup of coffee did not go uninvestigated, in 1989 Galletly et al. published "Does caffeine withdrawal contribute to postanaesthetic morbidity?" [147]; this at a time when it was difficult to get a decent cup of coffee in the UK.

Joe Whitwam covered a wide range of topics in his department and was obviously a leader of a team of co-workers; a larger than life figure[ii].

The remaining references [148-158] are listed below; the list may not be complete and does not include textbooks[iii].

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Michael D A Vickers

MB BS FFARCS

 [i]

Mike Vickers has publications spanning the years 1963 to 2007. His interests were mainly pharmacological with many papers examining the management of postoperative pain. The determination of blood volume, the management of shock and various papers associated with the operating theatre environment (pollution and safety) were also timely. Mike Vickers was also a medical politician; involved with the Anaesthetic Association of Great Britain and Ireland and had views on manpower subjects both in the UK and Europe.

He started out a First Assistant in Newcastle upon Tyne (1963-5) then became a lecturer at the Royal Postgraduate Medical School. He was the Director of the Clinical Investigation Unit at Dudley Road Hospital, Birmingham (1968-1976) then taking the chair in Cardiff.[ii]

Pharmacological interests:

The first time Mike Vickers' name appears when searching the literature is in 1963. It is either a publication on the mismanagement of suxamethonium apnoea[1] or a comment at a meeting of the Royal Society of Medicine on methohexitone[2]; the work must have been done whilst at the Middlesex Hospital.

The comment about methohexitone was concerning its epileptogenic properties, amongst others. A comment, "the prolongation of recovery time after

[i] Portrait by David Griffiths, courtesy of Professor Judith Hall, Department of Anaesthetics, Intensive Care and Pain Medicine, Cardiff University. (the picture has been cropped).
[ii] Development of academic anaesthesia in the UK up to the end of 1998
J F Nunn. British Journal of Anaesthesia. London: Dec 1999. Vol. 83, Iss. 6; pg. 916-33

increasing the dose [*of methohexitone*] was not so marked as with thiopentone" is of interest in light of future debates about intermittent methohexitone for sedation for dentistry.

Of the four publications about cholinesterase the first was based on a case report ("misleading evidence was obtained from studies of neuromuscular conduction" and it was suggested that "if facilities for testing neuromuscular conduction are available the urge to administer an anticholinesterase drug must be restrained until post-tetanic facilitation is markedly present.") [1], the second a review [3] and the other two, in 1968, were letters concerning the setting up of a Cholinesterase Research Unit[4, 5]. The initial experiences from this unit are documented in 1970[6]. Sixteen families had been studied.

In 1970 he collaborated with Tom Healy, John Robinson and others into the sedative effects of diazepam and its suitability for dental sedation, see Healy for details on this work... patients were assessed during routine dental treatment under local anaesthesia... overall the technique proved of benefit and patients were safe to leave accompanied by an adult within one hour[7-9]. This was followed by another paper in 1972 on the subject of 'biochemical evidence of anxiety in dental [phobic] patients'[10]. They detected a rise in catecholamine production but this occurred only with the actual event rather than anticipation of it. Diazepam did not reduce the level of circulating adrenaline or the heart rate to normal. "Diazepam had little effect on the adrenaline level in the normal volunteers".

There is a large gap between this work and further work on sedation using saccadic eye movements as a measurement tool. Saccadic eye movements are rapid, simultaneous movements of both eyes in the same direction. In 1991 four papers were published, three on saccadic eye movements with cyclopropane, halothane, nitrous oxide, isoflurane and propofol [11-13] and one paper on the arterial-venous concentrations occurring during propofol infusions[14], there was a second one on this topic in 1996[15].

The null hypothesis for the saccadic-eye-movement work was that there would be no difference between equi-MAC concentrations of the various agents. Nitrous oxide was indistinguishable from air at equi-MAC concentrations that

produced mark changes with isoflurane. Previous workers, using higher concentrations, had shown effects[iii]

The work with propofol was an attempt to show whether venous sampling could be used instead of the potentially more hazardous arterial puncture. At the low concentrations studied, even with a better arterialisation technique (electric blanket around the arm), the use of venous samples were still considered of limited predictive value in an individual subject. As was stated – there was a high correlation between samples but low predictivity.

A variety of papers were written between the years 1966 and 1987 on pharmacological topics – adrenergic drugs, gamma hydroxybutyric acid, the effect of age on pethidine plasma concentrations, and the effect of various premedicants [16-22]. However, there is an interesting body of work on the management of postoperative pain [23-35].

Postoperative Pain

The first paper (1979), with Chakravarty as the lead author, compared burprenorphine and pethidine given intravenously on demand, a precursor to the ubiquitous patient controlled analgesia of today[23][iv]. The use of the Cardiff Palliator was first described in 1976[v]. Buprenorphine was shown to produce a good quality of analgesia but it had similar side effects to morphine. Individual consumption varied widely; this was put down to the variable amount of pain perceived by the patient which was thought to be "correlated with personality" and different sensitivity to the drug.

The nefopam study[24] was unable to differentiate between the analgesic effect of nefopam and morphine but nefopam was shown to have no obvious cardiorespiratory side effects; sweating with nefopam was a problem. Nalbuphine[31], meptazinol[26] and pentazocine[28] were all studied in various combinations with morphine, pethidine and buprenorphine. Nalbuphine seemed to less effective when the patients moved, meptazinol was associated with more

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[iv] Forrest, W H, Smethurst, P W R, and Kienitz, M E, Anesthesiology, 1970, 33, 363; Sechzer, P H, Anesthesia and Analgesia ... Current Researches, 1971, 50, 1 and Keeri-Szanto, M, Canadian Anaesthetists' Society Journal, 1971, 18, 581.

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nausea and vomiting but pentazocine was quite comparable to buprenorphine. None of these drugs are now in common use. Later on (1992-95) tramadol was studied [32, 33, 35], this drug is in use.

Two letters and one paper on the mechanics and concept and assessment of patient controlled analgesia were produced from this department between 1979 and 1983[25, 29, 30]; the first letter is a description of the way the need for pain relief decreases with time and that how the only person who knows how much pain relief is required is the patient. The other letter is a criticism of another comparison of analgesics[vi], between i.m. morphine, sublingual buprenorphine and self-administered pethidine – the authors felt that the nurse administered i.m. morphine dosage was unusually high and that they were acting as an "expensive, manual 'ondemand' system". These authors had shown no difference between the self-administered and staff-administered methods.

In '83 Slattery did an open comparison of staff administered vs. patient admisnistered pain relief, patients who self-administered their analgesia had less pain but received more analgesic than the staff-administered group. Confounding factors suggested that a blinded study should be performed.
Patient controlled analgesia is a mainstay of postoperative pain control and this department had a major role in its acceptance.

Blood volume:

Between 1968 and 1971 there was a flurry of papers on blood volume determination and the value of intravenous fluids for resuscitation.

The first [36] was on the use of a single tracer (radioactive iodine) and the Pitman Blood Volume computer. It was to highlight the possible methodological errors and the associated the danger that "the 'answer' on the dial may be given undue credence". The potential errors included the random nature of isotope decay, the number of counts, the distance of the measuring device and shielding from the sample, mains voltage, the timer and the quality of the supplied isotope and others, including patient factors. The discussion of the case for the use of blood volume estimation using this technique ranged around the topic of physician understanding of the results of the analysis and "whether the value of

[vi] Ellis, R., Haines, D., Shah, R., Cotton, B. R., and Smith, G. (1982). Pain relief after abdominal surgery. Br.J. Anaesth.,54, 421.

the information is commensurate with the cost of obtaining it, particularly when compared with the relative ease and low cost of central venous pressure measurement." It was agreed that certain clinical states made central venous pressure unreliable, such as shock and renal and heart failure and therefore it might have a use. This paper was followed in 1969 by a method using two tracers, red cell labelled with Cr and radio-iodinated human serum albumin[37]. This technique was shown to provide extremely accurate results for the determination of red cell and plasma volume, and supported other work carried out using this technique.

Using the dual tracer technique three papers (I, II and III) were published on the value of Macrodex (dextran with mean molecular weight of 70,000) for the replacement of blood loss/maintenance of blood volume [38-40]. In study I 22 patients undergoing major surgery with expected blood loss were recruited, half received blood replacement and half Macrodex, six dropped out which left only 16. There was no significant difference between the two groups; for significance with 16 patients the differences would have had to be great to 'show-up', and it was admitted that the anaesthetists had some bias within the management of the two groups and that there was a tendency to undertransfuse. Study II examined the changes in the peripheral haematocrit and the "whole body/large vessel" haematocrit ratio. The ratio between the two has been termed the F_{cells} ratio. The difference between the two values is due the microcirculation having more plasma and fewer cells than the whole blood volume taken as a unit. There was a fall in the F_{cells} ratio in patients whose volume was replaced with stored blood and no change in patients infused with Macrodex. This increase in peripheral haematocrit increases viscosity and may be deleterious to the circulation in the postoperative period. The third paper followed the effect of transfusion/ Macrodex infusion on the postoperative haematocrit, comparing the immediate postoperative status with the state two hours later. Blood transfusion resulted in an increase (10%) in the measured red cell volume over this two hour period and that was without any additional transfusion. This was not seen with Macrodex. It was concluded that the use of Macrodex for fluid replacement had a beneficial circulatory effect unrelated to blood volume and it was not known whether this was due to differences in

haematocrit or viscosity. This may have had a significant effect on practice within the UK.

A paper in the Postgraduate Medical Journal [41] was an overview of the use of isotope studies in the management of patients and the limitations, particularly in shock states; a minor review.

The final article [42] (very short) was on the problems associated with measurement of the fluid spaces. It was stated that moderate blood loss causes a shift of interstitial fluid into the vascular compartment and sequestration of some red cells. Interstitial pressure falls following haemorrhage and this is not reversed by transfusion of blood alone, Ringer-lactate helps. Dextrans do not reverse this fall but survival rates improve.

Safety

Theatre Explosions

Three papers published from 1070-173 deal with hazards in the operating theatre, particularly fire and explosions, a fourth in 1978 [43-46]. Between 1947 and 1954 thirty-six explosions resulted in three deaths; with the implementation of recommendations from a working party there were no explosions in theatres in the following fourteen years. It was thought that the recommendations were excessively cautious, and expensive, and so some experiments were carried out to determine whether explosive levels of ether were actually achieved in the operating theatre. This is of historical interest only as the use of explosive agents (including cyclopropane) ceased in the late 1970s. The bottom-line was that money was being spent on the grounds of alleged patient safety when it could be spent on better equipment or more staff.

The final paper was written after the advent of laparoscopic surgery and the discussion includes the scenario where hydrogen might diffuse across the bowel wall and create an explosive mixture in the gas filled peritoneal cavity. The arguments put forward negate this possibility.

Equipment

A miscellaneous collection of papers dealt with a variety of equipment related topics; dry gas meters, scavenging, anaesthetic records, face mask, ventilator

malfunction and two of interest – pulse-oximetry and colour coding of drug syringes [47-53]. The pulse-oximetry article is an editorial in the British Journal of Anaesthesia at a time when pulse-oximetry was being introduced into the UK. It outlines the mechanics of the measurement of the haemoglobin saturation and describes the limitations. At this time (1989) progress was rapid and we would not now consider giving an anaesthetic without one. Twenty years late the World Health Organisation (2009) is working towards making pulse-oximeters available for use worldwide in developing countries.

As far as colour coding is concerned, the letter in Anaesthesia represents the frustration at getting some sort of consensus for colour coding nationally (in the UK) let alone trying to get an international standard. Colour coding is now commonplace, the next step is the use of bar-codes to enhance safety to enable the recognition of the drug before it is administered.

Miscellaneous

Other interests over time included an examination (with EA Pask in Newcastle) into the safety of using and teaching the use of less than 20% oxygen in the anaesthetic mixture (there was a technique that used 100% nitrous oxide for induction of babies!), it was shown using a modified anaesthetic delivery system which 'blinded' the study that there were no real advantages... this was in 1966[54]. A letter on anaesthesia and driving was printed in the BJA and the Lancet[55, 56] and in 1983 an editorial on "The pursuit of quality in anaesthesia" in the BMJ[57]. This is an interesting insight into the early move to critical incident reporting and care of the sick doctor. It touched on the use of psychological testing for the selection of anaesthetists, on administration within departments and postoperative care.

Pollution at this time was also a favourite topic and there were many devices devised for the extraction or absorption of exhaled anaesthetics [58, 59]. He was involved in three articles on how to do research. "1 - Before you start", "2 - Writing the protocol" and "4 – Getting the work done"; no. 3 was written by WW Mapleson [60-62]. He was also active in getting clinical audit underway, highlighting citation errors and pointing out alleged bias publishing [63-65].

Medical Politics:

Mike Vickers was active in the medico-political-manpower-health

The articles on manpower started in 1968, and continued through 1981/82, to 1996 [66-71]. He was also interested in the selection process for anaesthesia [72-78], particularly psychological testing and structured interviews. As late as 1999 he was still very concerned that "We, [anaesthetists].....airly [sic] dismiss such tests as 'Women's magazine psychology', all the more arrogant since we make no attempt to counter this by becoming expert in selection by interview." He was making the point that the airline industry has a greater interest in weeding out accident prone personnel.

He was intimately involved in changes in anaesthesia at home in the UK [79-82] as well as in Europe, particularly European training and the European Academy [83-86].

The following references have not been studied [87-102]

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Gordon McDowall

MB ChB FFARCS MD

 [i]

A scientist starts with disorder and through his work attempts to comprehend the problem and produce solutions to the chaos.

To review the work of one man in academic medicine is difficult; it is akin to unravelling cottons in a needlework basket. Some cotton ends obviously belong together but others are deceptive in their origins. Academic medicine is usually the domain of teamwork and, unless one is in the team, it is difficult to identify the originator(s) of ideas. It also has to be accepted that a person who successfully organises a complex project is as worthy as his innovative co-worker.

This review of the published work of Gordon McDowall will by necessity not differentiate between the work that was, by and large, his and that in which he played a minor role. All the other workers are named in the references, some just once, some many times and without them the important work that was carried out-could not have been completed.

Gordon McDowall and his colleagues, after a shaky start, made a determined effort to investigate pathophysiological mechanisms in neurosurgical patients and hence rationalised their anaesthetic management. Teamwork is essential for his type of protracted study and the following names should be recognised as eminent team members: AM Harper, I Jacobson, I McA Ledingham, J Barker, and WB Jennett 1963 - 1969. VW Pickerodt, NJ Coroneos, NP Keaney, W Fitch, JM Turner, JR Lane and MM Ali 1968 - 1978. E Moss, Y Okuda, NM Dearden, D Powell, and T Ishikawa, 1973 – 1986. RM Gibson worked with McDowall for a period of 15 years, publications dating from 1971 – 1986.

[i] Photograph courtesy of Professor PM Hopkins, Academic Unit of Anaesthesia, Leeds General Infirmary

Dates given in this text, as in all other sections, refer to dates of publication. McDowall's papers that are discussed are references 1- 63, references 64-107 are papers not discussed in the text.

To create order out of the many papers published the work has been divided into the following categories:

I The effect of drugs on cerebral blood flow and intracranial pressure

Ia The effect of drugs or procedures on cerebral blood flow. This is rather non specific in that changes in cerebral blood flow may be brought about in several ways but it enabled the early quantification of effect.

lb The effect of drugs or procedures on intracranial pressure. Similarly this is also a simple approach to the work but the combination of **Ia** and **lb** culminated in McDowall's MD Thesis in 1967.

Ic Postdoctoral work on the effect of anaesthetic agents on cerebral blood flow and intracranial pressure.

II The effect of drugs or procedures on cerebral metabolism

III The effect of induced hypotension on cerebral blood flow

IV Head injury, its pathophysiology and management.

V Measurement of intracranial pressure

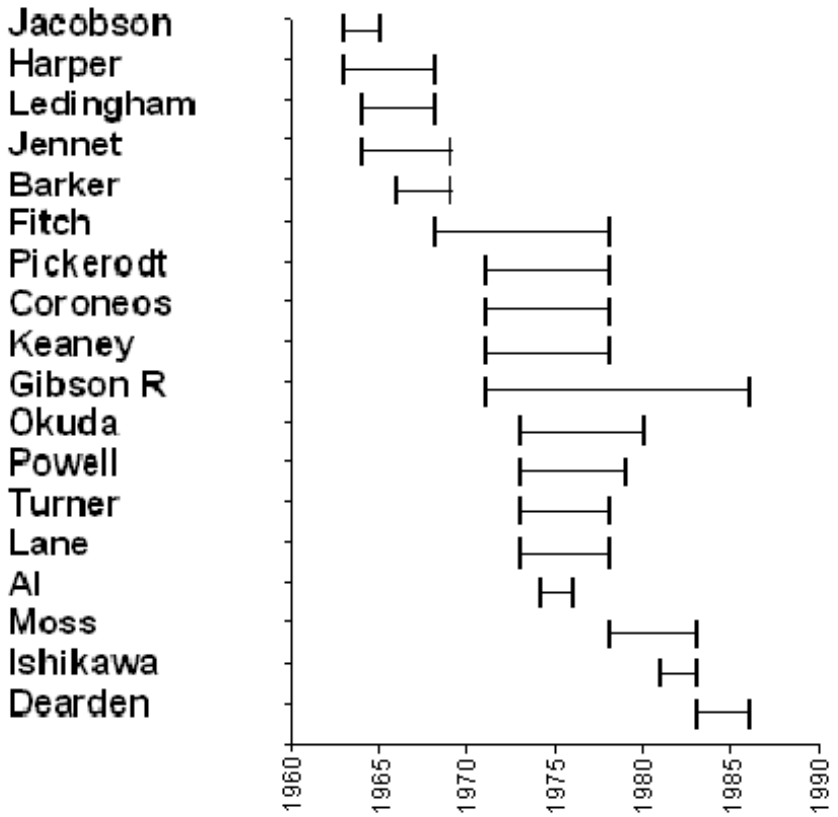

Fig. 1. Timelines for McDowall's co-workers who had more than three publications with him.

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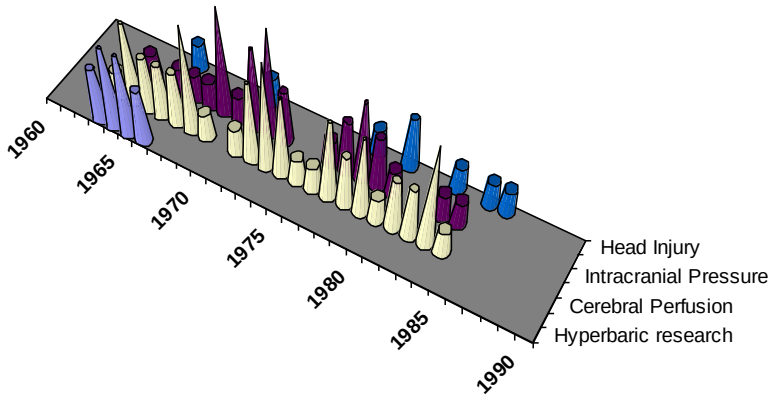

Incidence of publications from 1960 -1990

Ia The effect of drugs or procedures on cerebral blood flow

McDowall was an anaesthetist working in the University Department of Surgery at the Western Infirmary Glasgow where he was the ICI research Fellow. The earliest research paper that includes Gordon McDowall as an author was in 1963 in the British Journal of Anaesthesia [1]. Halothane 0.5% was shown to reduce cerebral blood flow by 46% and oxygen uptake by 49%. Halothane was labelled as a cerebral vasoconstrictor, to quote "In view of this evidence…we feel that it is possible that al1 potent general anaesthetic agents, intravenous and inhalational will prove to be constrictors of the cerebral vasculature…" This paper stands out as being one that caused some concern as it became established that halothane was a potent cerebral vasodilator. Reasons advanced for the results were the use of nitrous oxide in the control studies but not when halothane was used, the possibility of regional differences in blood flow at low concentrations of halothane and the low concentrations of halothane used, 0.5% or less. However, no significant change in cerebral blood flow was noted when halothane concentration was increased by 0.5% increments up to 3%.

In this same year, 1963, McDowall had three further papers published in prestigious journals - the Lancet [2, 3] and Nature [4]. The first Lancet paper described an internal carotid endarterectomy under two atmospheres of pressure. The increased partial pressure of oxygen was insufficient to enable the procedure to proceed without using an intraluminal bypass. His third publication followed immediately being the next paper in the same Lancet, an auspicious start. This paper demonstrated that cerebral blood flow decreased significantly at one and two atmospheres of oxygen and thus nullified the improvement in blood oxygen carriage at these pressures. This study confirmed previous work by Harper, Kety and Schmidt, and Lambertson.[ii] The decreased blood flow did not return to normal on return to air at one atmosphere.

[ii] Harper AM, Glass HI, Glover MM. Measurement of blood flow in the cerebral cortex of dogs by the clearance of krypton - 85. Scott Med J 23(1):98 1961;6:12.
Kety SB, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. Journal of Clinical Investigation 1948;27:484-492.
Lambertsen CJ, Kough RH, Cooper DV, Emmel GL, Loeschicke HH, Schmidt CF. Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. J Appl Physiol 39(5):714-7 1953;5:471-486.

The principal co-author in this work, and in future work, was AM Harper, Wellcome Senior Research Fellow in Clinical Science. He had multiple publications on measurement of cerebral blood flow. Krypton 85 was injected into a carotid artery and the flow in the cerebral cortex deduced from its clearance — this was the method of Lassen and Ingvar, 1961. [iii]

The article in Nature demonstrated the lack of influence of large changes in venous pressure on cerebral blood flow.

A paper in 1964 [5] presented the results of a further study into cerebral blood f1ow and oxygen uptake at one and two atmospheres pressure. The results seem to repeat the results presented earlier [2]. However, one area in the discussion that merits noting is that it was suggested that hypoxic brain may not respond to oxygen at high pressure by vasoconstriction. This wi11 be studied further in section II.

Another study published in 1964 [6] compared the effects of halothane and trichloroethylene on cerebral blood flow and confirmed the absence of effect of the latter, oxygen uptake fell by 20%. The results were presented at the International Symposium on Regional Cerebral Blood Flow in March 1965.

The fluctuations of cerebral blood flow with and without nitrous oxide were also demonstrated and it was postulated that there were two opposing forces determining cerebral blood flow, the vasoconstrictor effect of cerebral metabolic depression and a direct vasodilator effect [7].

With the knowledge that chloroform was a potent cerebral vessel dilator and increased cerebral blood flow the first study in which McDowall had participated was repeated [8]; two patients scheduled to undergo carotid endarterectomy were anaesthetised using 0.5%-1.0% chloroform in 100% oxygen in a hyperbaric chamber. Only one patient had an endarterectomy, the jugular venous pO_2 was 72 mm Hg at 1 atmosphere pressure, 125 mm Hg at 2 atmospheres and following the endarterectomy it rose to 240 mm Hg. These were higher values than had previously been recorded and it avoided the use of

[iii] Lassen NA, Ingvar DH. The blood flow of the cerebral cortex determined by radioactive krypton. Experientia (Basel) 1961;17:42 - 43.

an intraluminal shunt. One patient became mildly jaundiced after the chloroform anaesthetic.

At the Second European Congress of Anaesthesiology in Copenhagen (1966) data was presented on cerebral blood flow and halothane that was more in line with other workers [9] Wollman et al. and McHenry et al.[iv] With 0.5% halothane the cerebral blood flow in dogs rose by 16% over the first twenty minutes and then fell towards control values, with 2% halothane the increase in flow was 24% and it was sustained. Four percent halothane caused a lowering of blood pressure and cerebral blood flow fell. There was a progressive decrease in oxygen uptake with increasing halothane concentration which was thought to be due to depression of oxidative mechanisms.

Returning to the effects of oxygen on the cerebral vasculature a presentation in International Anesthesiology Clinics [10] demonstrated the effects of oxygen on cerebral vessel tone from hypoxic to hyperoxic levels. Cerebral blood flow was shown to increase at about 50 mm Hg PaO_2 (30-40 mm Hg PvO_2) and had doubled at 40 mm Hg PaO_2. At hyperoxic levels cerebral blood flow had been shown to steadily decrease, being 75% of control at three atmospheres.[v] This contradicts work presented by McDowall to the 3rd International Congress on Hyperbaric Oxygenation [11] where it was shown that cerebral blood flow did not change at three atmospheres of pressure if the carbon dioxide level was maintained (hyperbaric oxygen leads to hyperventilation and a lowered $PaCO_2$ in the spontaneously breathing patient). This presentation showed the great reserve of cerebrovascular dilatation enabling 60% of the circulatory oxygen to be available at 30% saturation.

It was also noted that during hypovolaemia (50mmHg systolic blood pressure) where the cerebral blood flow was down by 40%, hyperoxia did not

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[iv] Wollman H, Alexander SC, Cohen PJ, Chase PE, Melman E, Behar G. Cerebral circulation of man during halothane anesthesia: effects of hypocarbia and of d-tubocurarine. Anesthesiology 59(6):526-31 1964;25:180 - 184.
McHenry LC, Slocum C, Bivens HE, Mayes HA, Hayes GJ. Hyperventilation in awake and anesthetized man. Effects
on cerebral blood flow and metabolism. Archives of Neurology 1965: 270-277.

[v] Lambertsen CJ, Kough RH, Cooper DV, Emmel GL, Loeschicke HH, Schmidt CF. Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. J Appl Physiol 39(5):714-7 1953;5:471-486.

reduce flow further and oxygen uptake, which was depressed, returned to normal. This work was also thought to demonstrate that metabolic rate was not determined by $PaCO_2$.

Continuing the work with halothane in 1967[12], it was demonstrated that cerebral blood flow still increased with increasing concentration even if the blood pressure was low, but above 90 mm Hg systolic. During hypotension it was not possible to demonstrate vasodilatation as the hypotension itself caused vasodilatation. Cerebral blood flow was therefore increased at a time when oxygen need was decreased, and therefore halothane was said to increase cerebral tissue $P0_2$ and decrease tissue PCO_2.

lb The effects of drugs or procedures on intracranial pressures

In 1965 McDowall presented a paper at the Annual Meeting of the Association of Anaesthetists of Great Britain and Ireland in Edinburgh, "Cerebrospinal fluid pressure measurements during anaesthesia". This was subsequently published in Anaesthesia in 1966 [13].[vi]

The work presented by McDowall at the Anaesthetic Association meeting involved CSFp measurement during anaesthesia for surgery on patients with

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[vi] Previous work by Stephen et al, Small et al. and Bozza et al. considered the changes in intracranial pressure following the use of volatile agents to be insignificant - possibly because the changes occurring were obscured by other factors in their investigative methodology. Marx et al., and Galindo and Baldwin , (1962 and 1963 respectively) had demonstrated increases in cerebrospinal fluid pressure (CSFp) with halothane. Marx et al. thought there was a relationship between a rise in venous pressure and CSFp and Galindo and Baldwin had difficulty differentiating between the effects of hypotension and the effects of halothane. However Hunter, in his book on Neurosurgical Anaesthesia, showed quite clearly his demonstration that in the clinical situation with controlled ventilation intracranial pressure could rise with halothane. According to his writing he was obviously confused by the conflicting research - a reference was made to McDowall's paper showing the increased cerebrovascular resistance with halothane.

Stephen CR, Woodhall B, Golden JB, Martin R, Nowill WK. The influence of anesthetic drugs and techniques on intracranial tension. Anesthesiology 59(6):526-31 1954;15:365-377.

Small HS, Weitzner SW, Nahas GG. Cerebrospinal fluid pressure during hypercapnia and hypoxia in dogs. Am J Physiol 234(1):H74-9 1960;198:704-708.

Bozza ML, Maspes PE, Rossanda M. The control of brain volume and tension during intracranial operations. Br J Anaesth 58(5):494-7 1961;33:132-146.

Marx GF, Andrews IC, Orkin LR. Cerebrospinal fluid pressure during halothane anesthesia. Canadian Anaesthetist Society Journal 1962;9:239-245.

Galindo A, Baldwin M. Intracranial pressure and internal carotid blood flow during halothane anesthesia in the dog. Anesthesiology 59(6):526-31 1963;24:318-326.

Hunter AR. Neurosurgical Anaesthesia: Blackwell, Oxford University Press, 1964.

prolapsed discs, it was assumed that they had normal CSF pathways. Following induction of anaesthesia lumbar puncture was performed with the patient in the lateral position - in the first 12 patients the CSFp was measured using a fine bore saline filled manometer and in the remaining 12 patients the pressure was transduced and recorded. It is pertinent to be reminded that in the early 1960s electronic measurement was not as ubiquitous as it is today.

Control measurements were made with N_2O / O_2 / IPPV and then the volatile agent was added and the changes followed for ten minutes. Halothane 0.5% caused the CSFp to rise by a mean of 68.2 mm H_2O from a mean control value of 117.1 mm H_2O. The increase in pressure occurred in less than three minutes and peaked between 3 and 16 minutes. Venous pressure rose by a mean of 6 mm H_2O. The discussion indicates that the authors did not consider the rise in CSFp related consistently to the initial CSFp or $PaCO_2$. Ryder et al.,[vii] 1952, had shown that increases in CBF had less effect on CSFp when that pressure was initially 1ow which was the case after hyperventilation, and this therefore explained the reduced effect of halothane on CSFp following hyperventilation.

In the same paper the results from some animal work was included in which recordings of cerebrovenous pressures were made - they demonstrated that the venous pressure was always less than the CSFp; they considered this at strong evidence against the hypothesis that it was the increase in cerebrovenous pressure that raised the CSFp. This work appears to be the definitive paper confirming once and for all that halothane (and trichloroethylene) did cause an increase in CSFp, and presumably intracranial pressure. It was considered that the increased cerebral blood flow was the most likely cause of the increased intracranial bulk.

A previously noted paper [9] referred to the small changes “of doubtful clinical importance” in CSFp in patients with normal CSF pathways, the $PaCO_2$ was kept constant and thus the rise in CSFp was thought to be due to cerebrovasodilatation.

It was reported in the Journal of Neurosurgery [14] that two patients with papilloedema were anaesthetised using thiopentone, suxamethonium, N_2O,

[vii] Ryder HW, Espey F, Kimbell FD, et al. Influence of changes in cerebral blood flow on the cerebrospinal fluid pressure. Archives of Neurology and Psychiatry 1952;68:165-169.

oxygen and d-tubocurare; burr holes were made and a brain cannula inserted, intraventricular CSFp measurements were made using a transducer and halothane administered. The first patient (0.5% halothane) had a rise of ICP from 180/160 mm H_2O to a peak of 520/460 mm H_2O, the second (1%) had a rise of *ICP* from 155/130 to 800/620 mm H_2O. This second patient was also hyperventilated ($PaCO_2$ 19 mm Hg) and then halothane added - on this occasion the ICP rose to 350/300 mm H_2O. These two patients demonstrated the marked difference between those patients with normal physiology and those with intracranial pathology, it also demonstrated, in an anecdotal way, the value of hyperventilation.

In 1967 the University of Edinburgh accepted Gordon McDowall's MD Thesis, "The influence of volatile anaesthetic drugs on the blood flow and oxygen uptake of the cerebral cortex and on cerebrospinal fluid pressure".

Ic. Post doctoral work on the effect of anaesthetic agents on cerebral blood flow and intracranial pressure.

In 1969 [15] the ICP of thirty-four patients with intracranial space occupying lesions was studied. Halothane, trichloroethylene and methoxyflurane were used together with nitrous oxide, oxygen, opiate and relaxant. The patients were ventilated to normocapnia and were then given the volatile agent ten minutes after base line measurements had been made. Once again there was no clear correlation between the initial ICP and the pressure response to the volatile agent. Cerebral perfusion pressure fell in every patient; 1% halothane - 40 mm Hg, 0.9% trichloroethylene - 23 mm Hg. 1.5% methoxyflurane - 56 mm Hg. The mechanism mooted was that of cerebrovascular dilatation with an increase in sagittal sinus pressure, the rise in intracranial pressure being secondary to CBF and hence cerebral blood volume.

A further paper in 1969 [16] described the effect of methoxyflurane 1.5% on CSFp in patients with normal and abnormal CSF pathways. A rise in pressure occurred in both groups but in the latter the rise was of a much greater magnitude. However, methoxyflurane 0.5% in the presence of a normal CSF pathway was shown to lower the CSFp in half the patients studied. This was in

keeping with work carried out on dogs in 1965, [7]. Autoregulation of CSFp was described;

CBF ↑ ICP ↑ CPP ↓ CBF ↓ ICP ↓ CPP ↑ CBF ↑ ICP ↑

The comment was made that a decreased $PaCO_2$ may protect against the adverse effects of volatile agents but not in every patient.

McDowall studied neuroleptanalgesic mixtures in 1969 also [17], noting that droperidol and phenoperidine had a biphasic effect on CSFp whereas droperidol end fentanyl caused a fall in CSFp in both normal and abnormal CSF pathways and the decrease was significant. It was suggested that fentanyl had a different effect on cerebral metabolism.

In 1971 work with dogs [18] indicated that halothane increased the supratentorial pressure more than the infratentorial pressure and thus increased the likelihood of brain impaction with pupillary changes.

In 1972 Althesin was studied [19] in relation to CBF and ICP in baboons. Artificial intracranial space occupying lesions were created by thin walled latex balloons. Althesin 50 μl kg^{-1} was shown to decrease CBF and ICP very quickly (90s -120s) by 20% and 25% respectively. Cerebrovascular resistance rose to a maximum (133%) after one minute. Work continued in 1973 [20] and 1978 [21]. In the first paper 50 μl kg^{-1} of Althesin was shown to reduce CSFp by more than 60% with recovery in 10 minutes - mean arterial pressure only falling 10 – 20% and heart rate was unchanged; blood pressure could not account for the CBF changes because the patients were in the autoregulatory range. There was good correlation between the initial CSFp and the fall in CSFp. The second paper was a randomised comparison of Althesin and thiopentone with regard to ICP during induction of anaesthesia and tracheal intubation. Mean ICP decreased following induction and increased slightly after intubation. Five minutes after induction the patients who received Althesin had a statistically lower ICP than those that had received thiopentone. The mean change in ICP with intubation was an increase of 2.8 mm Hg from control, or 4.6 mm Hg from immediate pre-laryngoscopy values.

A paper was published in 1978 in an attempt to sort out contradictory reports [17][viii] on the value of fentanyl in neurosurgical anaesthesia [22]. In ten patients with $PaCO_2$ of < 4 kPa, and in the absence of hypotension, it was concluded that fentanyl 0.2 mg was a good neurosurgical agent. Mean arterial pressure fell to less than 60 mm Hg in two patients, CPP was less than 60 mm Hg in four patients and less than 4O mm Hg in one patient. Intracranial pressures increased or decreased slightly.

In 1979 Etomidate 0.2 mg kg^{-1} [23] was shown to be satisfactory in neurosurgical patients with space occupying lesion. The decrease in ICP was maximal at two minutes. In 1983 enflurane 2% was shown, overall, to produce very little effect on ICP [24], however there was marked variability. Four out of ten patients had to have the agent discontinued because the CPP was less than 5O mm Hg. It was considered to have less of an effect on ICP and CBF than halothane but arterial pressure had to be closely monitored.

An editorial in the European Journal of Clinical Investigation in 1982 [25] McDowall defined more accurately the meaning of the word 'autoregulation' and argued against its use when discussing the action of drugs. For example - halothane caused a fall in blood pressure but CBF was maintained, this superficially could be seen as autoregulation but in fact drugs that directly dilate the cerebral vessels paralyse their responsiveness and the increase in blood flow was a passive response to changing cardiovascular parameters. Barbiturates and hypocapnia which cause vasoconstriction maintain autoregulation.

Direct vasodilators →	CBF ↑ → ICP ↑ → CPP ↓
Opiates / hypnotics →	Metabolism ↓ → CBF ↓→ ICP ↓ → CPP ↔

[viii] Lassen NA, Ingvar DH. The blood flow of the cerebral cortex determined by radioactive krypton. Experientia (Basel) 1961;17:42 - 43.
114. Wollman H, Alexander SC, Cohen PJ, Chase PE, Melman E, Behar G. Cerebral circulation of man during halothane anesthesia: effects of hypocarbia and of d-tubocurarine. Anesthesiology 59(6):526-31 1964;25:180 - 184.

II The effect of drugs or procedures on cerebral metabolism and hence on cerebral blood flow and intracranial pressure.

It is reasonable to speculate that the rate of metabolism of an organ will determine, through some unspecified mechanism, the blood flow through the organ above a certain basal level. Metabolism is associated with oxygen uptake, carbon dioxide production and cellular function. McDowall and his co-workers studied cerebral metabolism using oxygen uptake as their indicator of metabolic change. To recapitulate; hyperbaric oxygen at 1 and 2 atmospheres pressure resulted in a decrease in oxygen uptake of 16% and 38% respectively [2, 5]. However in 1965, in the Proceedings of the 2nd International Congress on Hyperbaric Oxygenation [26], it was reported that the oxygen uptake which was reduced by hypovolaemic hypotension, was returned to normal at two atmospheres pressure of oxygen. Halothane 0.5% was shown to reduce oxygen uptake by 49% [4]; trichloroethylene reduced it by 20% and halothane by 16% [6]; methoxyflurane by 13% and chloroform by an insignificant 10% [7].

In 1966 [9] the oxygen uptake with halothane 0.5% was reported to fall 14% and 33% with 2% halothane. This paper, with regard to cerebral blood flow, was the one more in keeping with the work of others.

A more detailed investigation into the cerebral metabolism/cerebral blood flow mechanism was reported in 1967 [27]. It was professed that cerebral vasomotor tone may be determined by brain extracellular (ecf) pH, this idea being supported by the so called 'luxury perfusion', the pH of ischaemic brain being low and the blood flow increased. Cerebral blood flow was measured in dogs and the ecf pH was measured using a flat surfaced glass electrode as described by Severinghaus[ix] . Control values were recorded at normocapnia, following hyperventilation (CBF ↓, pH↑) and following the infusion of lactic acid; the pH returned to normal but the cerebral blood flow stayed low. In a second experiment after the recording of the control values at normocapnia carbon dioxide was administered (CBF ↑, pH ↓), this 'hypercapnia' was then reversed (CBF and pH returned to normal) and then lactic acid was infused (pH ↓, CBF

[ix] Severinghaus JW. Regulation of pH on the cerebral cortex. J Physiol (Lond) 232(1):30P-31P 1965;181:35P.

stayed the same). From these two experiments it was concluded that acute changes in ecf pH do not influence cerebral blood flow and that the potent effect of CO_2 was not due to a pH change. It was suggested that the intracellular pH of the arteriolar wall determined cerebral blood flow.

Similar work was reported at the III International Symposium on Cerebral Blood Flow and Cerebro-Spinal Fluid (Lund - Copenhagen) in May 1968 [28, 29]. This work was performed on baboons and confirmed the failure of pH to control cerebral blood flow providing the carbon dioxide level was maintained constant. At the same meeting a paper was presented on luxury perfusion [30]. Luxury perfusion was a term coined by Lassen in 1966,[x] it had other names including 'relative cerebral venous hyperoxia'. Aortic cross-clamping was used to create cerebral ischaemia and cerebral blood flow and CSFp were measured. After hyperventilation it was found that there was dissociation between cerebral blood flow and CSF pH. It would appear from much of this work that it was difficult to disentangle the time courses of pH changes in the various body compartments and the changes in cerebral blood flow.
Some time elapsed before there was another onslaught on the effects of cerebral metabolism on cerebral blood flow and intracranial pressure. The six papers to be discussed spanned the years 1972 - 1979 and revolved around the marked effect of Althesin on cerebral function.

The onset of metabolic depression was detected by monitoring the electroencephalogram (EEG), sometimes the result was electrical silence. In the first of these studies [31] Althesin 50 μl kg^{-1} was given to baboons, the cerebral changes occurred rapidly being maximal at 90s. Cerebral blood flow fell 40%, oxygen uptake approximately 46% and CSFp approximately 29%. Carbon dioxide and arterial pressure were maintained within normal limits for autoregulation. In some of the animals electrical silence occurred, the onset being almost instantaneous and the cerebral blood flow reduction occurred so quickly that the "metabolism - flow" control mechanism was deemed to have a very short time constant.

[x] Lassen NA. The luxury perfusion syndrome and the possible relation to acute metabolic acidosis localised within the brain. Lancet 1:369 1966:1113-1115.

Two presentations in 1973 [32, 33], one to the Physiological Society and one to the Anaesthetic Research Society, pushed this work along further but both contained the same information. Althesin was 'laced' with Technetium 99 and its arrival in the brain could be detected. Drug bolus arrival, changes in EEG, CBF and CVR were all recorded and thus the sequence of events determined. It was calculated that the maximum fall in carbon dioxide tension in the time between arrival of the Althesin and the change in vascular tone (11.8s - 7.6s) was less than 0.5 mm Hg. Carbon dioxide was therefore considered unlikely to be the metabolism - flow link.

At an Anaesthetic Research Society meeting in 1975 [34] the following argument was put forward -if changes in cerebral blood flow lagged behind a reduction in metabolism then the oxygen content of venous blood should rise, or, if metabolism and flow decreased together cerebral venous oxygen content should remain the same. It was discovered that cerebral venous oxygen content fell. Did this support the hypothesis that Smith et al.[xi] put forward that anaesthetic drugs reset the steady state level of the CBF / metabolism link?

Pursuing the link between metabolism and flow in 1978 [35] further studies into the circulatory response to cerebral metabolic depression were carried out; in these studies cervical sympathectomy and alpha adrenergic block were used to exclude the involvement of the sympathetic nervous system. The direct injection of Althesin into the carotid arteries demonstrated that the reduction in metabolism was a secondary effect, presumably from the brain stem.

The final paper in this series [36] demonstrated that brain extracellular fluid hydrogen ion changes occurred at least 6s after changes in cerebrovascular resistance and this was at least l0s after depression of the EEG. This confirmed the previous work described above. It would appear that cerebrovascular changes were not initiated by extracellular pH but it was thought that it may be maintained by it. It was suggested that some fast responding mechanism existed, either neurogenic or perhaps a change in $[K^+]$. Astrup had proposed that the

[xi] Smith AL. Dependence of cerebral venous oxygen tension on anaesthetic depth. Anesthesiology 59(6):526-31 1973;39:291-298.

increase in extracellular K^+ during seizures may be the link with the associated increase in cerebral blood flow.[xii]

III The effect of induced hypotension on cerebral blood flow, cerebral metabolism and intracranial pressure.

This work spanned the years 1972 -1983 and involved the study of the effects of hypotension caused by (a) deep halothane anaesthesia (b) sodium nitroprusside (NTP), (c) trimetaphan (TMP) and (d) hypovolaemia

a) Halothane:

The effects of hypotension due to halothane will be presented first [37-40]. Reducing the mean arterial blood pressure in baboons to 33 mm Hg for two hours resulted in reactive hyperaemia even though evidence was presented to show that hypoxia did not occur. The cerebral metabolic rate ($CMRO_2$) fell by 30%. It was obvious that autoregulation had been lost [37]. It was suggested that loss of autoregulation may have been due to very subtle ischaemic changes. Electrical silence and burst suppression had been noted in all animals that lost autoregulation; these changes were not seen if the blood pressure was above 40 mm Hg or the CBF greater than 35 ml/min. Because of the loss of autoregulation it was suggested that postoperative hypertension should be avoided after deep halothane anaesthesia.

At an ARS meeting in 1974 [39] it was shown that with a normal mean arterial pressure and cerebral perfusion pressure there was a linear response between CBF and $PaCO_2$ (25 - 70 mm Hg). It was a 4% change per mm Hg CO_2. During hypotension with a cerebral perfusion pressure of 32 mm Hg there was no such relationship. This work was set out in more detail in 1976 [40] where autoregulation was tested with noradrenaline and an 'autoregulation index' described. It appeared that responsiveness to carbon dioxide disappeared below a (?) mean arterial pressure of 60 mm Hg and autoregulation below 40 mm Hg. It followed from this that cerebral blood flow would not be impaired further by

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[xii] Astrup J, Heuser, Lassen NA, Nilsson K, B.K. S. Evidence against H+ and K+ as main factors for the control of cerebral blood flow; a micro-electrode study. Cerebral Vascular Smooth Muscle and its Control. Ciba Foundation Symposium. Amsterdam: Elsevier, 1978:313.

hyperventilation if the blood pressure was low. It was suggested here that if halothane induced hypotension had been used then postoperative IPPV should be used to prevent a rising blood pressure due to a rising $PaCO_2$ in the presence of lack of autoregulation, a reiteration of the advice in 1974.

(b) Sodium nitroprusside:

The use of NTP for the production of hypotension was reported in 1973 [41] at an ARS meeting. A hypotension of <40 mm Hg MAP of two hours duration resulted in a small fall in CBF; $CMRO_2$ was unchanged and autoregulation was abolished - this recovered gradually over several hours. Four of the animals died as a result of the irreversible cardiovascular collapse - this was reported and investigated [42, 43] and would now be accepted as due to NTP toxicity. The maintenance of cerebral blood flow with hypotension was a major difference when compared to the effects of halothane.

(c) Trimetaphan:

TMP was also being used for inducing hypotension and in 1977 and a comparison was carried out between it and NTP [44]. There was found to be no change in intracranial pressure with TMP but a statistically significant rise with NTP on induction of hypotension. When the blood pressure had fallen below 70% of control the intracranial pressure returned to control levels and then fell as blood pressure fell. The use of hypocapnia minimised the rise in intracranial pressure with NTP. It was suggested that the change in intracranial pressure was due to cerebral vasodilatation and that it should only be used if a significant degree of hypotension was to be produced and then only after the dura was opened.

(d) Hypovolaemia:

In the same year recordings of oxygen tension on the brain surface were made during hypotension [45]. Haemorrhagic hypotension resulted in an incidence of $P0_2$ of <10 mm Hg of 23%, 7.2% and 12.4% with TMP and 0.9% with NTP. NTP

was showing itself to be a mixed blessing - early rises in intracranial pressure but maintained cerebral oxygenation during profound hypotension.

Studies in 1979, 1981 and 1983 [46-48] elaborated on this work. In brief, changes in cerebral blood flow, hypoxia, and EEG changes were worse with TMP than with NTP. In the 1983 study in K^+ flux was measured. An increase in extracellular [K^+] was considered to be the result of cell membrane damage due to anaerobic metabolism with lactate production - K^+ flows out and Ca^{++} flows in. The normal [K^+] is about 3 mM l^{-1}. With membrane damage there appeared to be three phases of [K^+] rise - a slow progressive rise to 13-15 mM l^{-1}, a rapid rise from 16-40 mM l^{-1} and then a slow rise to peak at 60-75 mM 1^{-1}. Calcium ion influx occurred at about the time when [K^+] was 15 mM l^{-1}. NTP, once again, was shown to preserve membrane integrity longer at lower levels of cerebral perfusion.

The last study in this section created more confusion than confirmation of previous work [49]. The effect of the hypotensive agents on the blood brain barrier was tested using Evans blue. Hypotension was induced and then the Evans blue was injected. With an intact blood brain barrier the dye should not penetrate the cerebral tissue. It was discovered that there was far greater penetration with NTP than with TMP. Could this be due to ischaemic damage? The dye appeared in the boundary areas of blood supply even though previous work had shown that cerebral blood flow was better with NTP. Had vasodilatation with NTP opened up capillary tight junctions and, together with the raised blood pressure at the termination of the infusion (and lack of autoregulation), caused the dye to pass the breached barrier? Another suggestion was that the cerebral perfusion pressure probably increased most at the boundary areas on cessation of the hypotensive infusion and another was that NTP accelerated pinocytotic activity. Certainly the pool had been muddied.

IV Head injury — pathophysiology and management

McDowall's work in this field can be subdivided into three sections, the effect of raised intracranial pressure on the systemic vascular system, factors that effect intracranial pressure and the intensive care of head injuries.

Work on the systemic vascular responses to raised intracranial pressure was first presented at an ARS meeting in 1970 [50]. With inflation of an intracranial balloon in dogs blood pressure rose and heart rate fell. Cardiac output was unchanged but the arrhythmia index rose and remained high. A set of papers published by the Journal of Neurology Neurosurgery and Psychiatry [51-53] looked at the cardiovascular responses in detail. The animal model used, dogs and baboons, was similar to that described above and the work was divided into three phases.

Phase 1 was a study of the early changes due to the increasing size of an intracranial space occupying lesion -as intracranial pressure increased mean arterial pressure fell, heart rate fell and cerebral perfusion pressure fell. The transtentorial pressure gradient increased and so did the arrhythmia index. The arrhythmia index seemed to be the most reliable predictive factor for the onset of the systemic vascular response.

Phase 2 was the study of the changes that occurred following continued inflation of the intracranial balloon to the point where there was total decompensation and death of the animal. Intracranial pressure increased more quickly and both mean arterial pressure and heart rate increased dramatically. The increase in blood pressure did not improve cerebral blood flow or cerebral perfusion pressure. The transtentorial gradient increased further but the arrhythmia index fell. The systemic hypertensive response was shown to be the result of an increase in systemic vascular resistance (± 42%), heart rate changes lagged behind blood pressure changes. The factors causing the onset of the systemic hypertensive response were debated, at the transition point between phases I and 2 the supratentorial perfusion pressure was about 28 mm Hg and thus poor perfusion was considered a possibility, distortion (axial rotation) of the brain stem was also considered. The systemic hypertensive response started as the mean supratentorial pressure approached the diastolic arterial pressure thus allowing only intermittent blood flow. The terminal event was associated with vasodilatation, tachycardia, falling blood pressure and supratentorial perfusion

(loss of autoregulation) and an increasing cardiac output.

Phase 3 was a detailed 1ook at the effect of incremental inflation of the intracranial balloon.

It was shown that a transient vasopressor response could be evoked even at low intracranial pressures. Once again the view that acute brain stem distortion caused the increase in systemic vascular resistance was propounded; local brain compression was also mooted as a cause.

Three publications warned of the dangers of using volatile agents [54], Entonox (N_2O / O_2 50%) [55] and opiates [56] in the head injured patient. The first and last were letters but the Entonox study was carried out with intracranial pressure monitoring and included the effects of physiotherapy. Gibson et al. [57] in '75 had shown the adverse effects of physiotherapy on intracranial pressure and McDowall's study was terminated prematurely because of the gross changes recorded.

The final three papers in this section deal in some detail with the intensive management of head injuries. In 1983 the outcome of management of 76 patients was reported [58]. Two thirds of the patients had a Glasgow Coma Score (GCS) of less than or equal to five. The management regimen was controlled hyperventilation, steroids, dehydrating agents, hypnotics and intracranial pressure measurement. The aim was to keep the intracranial pressure less than 25 -30 mmHg and to avoid rises in intracranial pressure during noxious stimulation. At six months 46% had died, 4% were vegetative survivors and 43% were recovered or moderately disabled. The bad omens were a low GCS, pupil abnormalities, respiratory dysrhythmia and an intracranial pressure greater than 30 mmHg. The presence of 'A' waves was associated with 61% mortality and if artificial ventilation was required for longer than seven days then 60% were in the group of severely disabled survivors. It was noted that there was some rise in intracranial pressure on recovery and this was thought to be due to abnormal vasomotor activity.

The 1985 study [59] compared the effects of Althesin and etomidate infusions on intracranial pressure in the head injured patient. This was a double blind randomised study. Intracranial pressure fell faster with Althesin than with

etomidate; both caused arterial pressure to fall (about l0%) but cerebral perfusion pressure was well maintained. Althesin caused some liver enzyme derangement and etomidate caused adrenocortical suppression.

The final paper [60] was published posthumously and was a double blind, placebo controlled study (54 patients) of the use of steroids in the management of head injuries. The outcome at six months was reported. Both groups were shown to have the same severity of injury on admission and there was no difference between the two groups at the time of final assessment. There was an increased mortality in the patient group receiving steroid and it was suggested that they did not have a role in the management of head injuries.

V Measurement of intracranial pressure

A paper presented to the ARS in 1971 described a device for measuring extradural pressure [61]. It comprised a metal disk with perforations that led to a catheter. Pressures measured with this device correlated very well with CSFp. In 1973 the complete work using the extradural 'capsule' was published [62], for comparison a balloon measuring system was also used and related to intraventricular CSFp. The metal capsule was 9mm diameter and 2mm thick. The balloon measurements were unreliable but the metal capsule was very good; the correlation with intraventricular pressure improved with time as the bone flap sealed.

Modifications led to the development of the Leeds device, a pressure monitoring system that screwed into the skull. This had been used for ten years prior to the next publication in 1984 [63]. It was first used extradurally and then for the six years prior to publication the dura had been incised and thus subarachnoid pressure had been measured. Mendelow et al.[xiii] had reported that the device under-read pressures particularly if the intracranial pressure was high and thus an assessment was made of the device by the Leeds team and an infusion test devised to confirm the integrity of the system. Readings were found to be accurate 33 out of 69 measurements, of the remaining 36 measurements correction of the fault was possible and accurate measurements then made. If the

[xiii] Mendelow AD, Rowan JO, Murray L, Kerr AE. A clinical comparison of subdural screw pressure measurements with ventricular pressure. J Neurosurg 64(1):81-8 1983;58:45-50.

intracranial pressure was less than 20 mmHg then the device was found to under read.

References [64-109] are for publications with McDowall as an author that are not discussed above; they are either papers on topics not in the mainstream of McDowall's research, reviews or teaching articles. A few of these papers have not been seen by the author.

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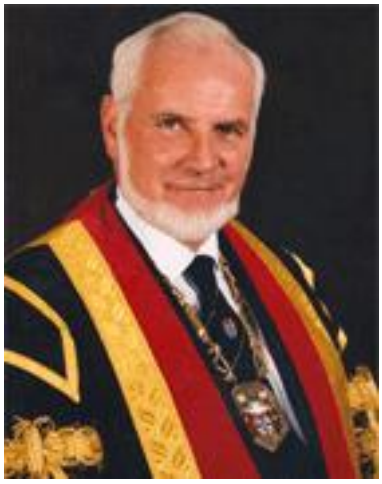
[ii]

From 1964 – 1966 Cedric Prys-Roberts was a research fellow in Leeds; he moved to Oxford as clinical reader (1967 to 1976.) In that year he became Professor of Anaesthesia in Bristol[i].

Cedric Prys-Roberts is probably most well known for his work around the topic of hypertension and anaesthesia. He also investigated aspects of cardiovascular physiology and the effects of ventilation, beta-blocking agents and volatile anaesthetic agents on them.

1967 was a big year for CP-R as he had twelve publications as joint author with R Greenbaum, and G R Kelman et al. His first two publications however were in 1966[1, 2].

The first publication, a letter to Anesthesiology, was with Greenbaum, Kelman and Nunn and was about a paradoxical decline in arterial oxygenation during hyperventilation; this had been brought to their attention by Markello[iii] and Laver and Slater[iv] in previous correspondence in the journal Anesthesiology. The comments are summarized in a table where it is shown, with data from their own department in Leeds, that PA_{O2} increases the (A-a) gradient as does the a/v difference and an increase in pH. A reference is made to a paper 'in press' (Haemodynamic influences of graded hypercapnia in anaesthetised man, BJA); there is no paper with this title but there are several papers in 1967 dealing with cardiovascular influences on gas exchange.

The 1966 paper, where CP-R was the primary author, was a comparison between in-vivo and in-vitro changes in acid-base status when either the anaesthetised patient or a blood sample was exposed to high and low levels of carbon dioxide. As expected there were differences; when plotted on a pH vs.

[i] J F Nunn. British Journal of Anaesthesia. London: Dec 1999. Vol. 83; pg. 916
[ii] http://www.rcoa.ac.uk/index.asp?PageID=1460
[iii] Anesthesiology 27;334:1966
[iv] Anesthesiology 27;335:1966

[HCO_3^{-1}] mEq/litre graph the whole blood in-vivo slope was less steep than the whole blood in-vitro. However, the plasma-in-vitro plot was even less steep. The explanation for this, citing the work of many others, was that intra-cellular buffering mechanisms (very high compared with other body fluids) come into play; so tonometric measurements do not reflect holistic physiological changes.

Hypertension

Let's first deal with CP-R and hypertension. There are seven publications titled 'Studies of anaesthesia in relation to hypertension, I-VII' covering a period of 15 years, 1971 – 1986.

The first (1971), 'Cardiovascular responses of treated and untreated patients' [3], covered the whole sequence of anaesthesia from induction to recovery in normotensive, untreated hypertensive and treated hypertensive patients. The anaesthetic used was standard at the time, nitrous oxide and halothane in oxygen. Twenty-five percent of the hypertensive patients had significant decreases in blood pressure that led to ischaemic changes on the ECG. Other hypertensive patients whose blood pressure was well controlled behaved in a similar manner to the normotensive patients. The bottom line was that "untreated high arterial pressure constitutes a serious risk to patients undergoing anaesthesia and surgery, and therefore anti-hypertensive therapy should not be withdrawn prior to anaesthesia without a compelling reason."

Paper two (1971) in the series concentrated on the haemodynamic consequences of induction and endotracheal intubation in the hypertensive patient [4].

In this study five different agents were used to induce anaesthesia and the effects on the ECG and cardiovascular parameters were observed. Neuroleptanalgesia (phenoperidine and droperidol) caused the least hypotension (propanidid and diazepam were worst) but the protection against hypertension, tachycardia and dysrhythmias was only marginally better than the other agents (methohexitone, thiopentone). It was recommended that prophylactic beta-blockade should be used to protect the patient against hypertensive crises during laryngoscopy and intubation. An interesting aspect of this paper is the use of cusum analysis and a

Manhattan graph to indicate where significant episodes of dysrhythmia occurred.

No.3: (1971) Pulmonary gas exchange during spontaneous ventilation [5]. Patients were allowed to breathe spontaneously during nitrous oxide and halothane anaesthesia. Minute and alveolar ventilation were depressed more than was expected compared to the changes in oxygen uptake and carbon dioxide production. This resulted in a moderate hypercapnia. This effect was short lived after cessation of the anaesthetic. Although the dead space was reduced because of intubation the VD/VT was increased, the tidal volume being halved. There was no evidence of progressive pulmonary dysfunction. The bottom line of this paper was that during anaesthesia, in hypertensive elderly patients, changes in cardiovascular function were far more serious than changes in pulmonary function.

No. 4 (1972): The effects of artificial ventilation on the circulation and pulmonary gas exchanges [6].
The cardiovascular responses during artificial ventilation using a nitrous oxide, muscle relaxant technique (± halothane) were studied; during (severe) hypocapnia ($PaCO_2$ of 23 mmHg) without halothane the mean arterial blood pressure fell about 30% - 40% from preoperative values, with halothane (1%) between 40% and 50%, the untreated 'hypertensives' being the more hypotensive. This was principally due to decreases in cardiac output as the systemic vascular resistance increased in all patients. Electrocardiographic evidence of myocardial ischaemia was seen in half of the treated patients and in all the untreated patients. There was oxygen desaturation of mixed venous blood but pulmonary venous admixture did not change significantly.

No.5. (1973) Adrenergic beta-receptor blockade [7].
The significant part of this paper is the oral administration of practolol for 48h before anaesthesia in a group of treated hypertensive patients; this was in addition to their normal medication. The patients maintained a higher arterial pressure intra-operatively; the cardiac output was higher and systemic vascular

resistance lower. The response to laryngoscopy and intubation was attenuated and ischaemic changes and dysrhythmias significantly reduced, from 38% to 4%.

No. 6. (1984) Cardiovascular responses to extradural blockade of treated and untreated hypertensive patients[8].
Mean arterial blood pressure changes were greater in the untreated hypertensive group of patients… for comparison the untreated hypertensive patient having a lumbar epidural had a 42% drop and the treated hypertensive patients 22%...combinations of falls in systemic vascular resistance and cardiac output. Three of the five untreated patients required intervention to maintain perfusion.

No. 7. (1986) Adrenergic responses to laryngoscopy [9].
Noradrenaline and adrenaline were measured during induction of anaesthesia and during laryngoscopy in normotensive and hypertensive patients. After induction of anaesthesia noradrenaline levels decreased; however, laryngoscopy was associated with a moderate rise in the normotensive patients but a marked increase in the hypertensive group with also an increase in adrenaline levels.

As indicated previously these studies took place over fifteen years with a variety of authors; of note are Meloche, Greene, Foex, Dagnino and Harvey. These papers are the 'skeleton' on which all the other papers about hypertension and anaesthesia hang; in chronological order they are [10-22].

A 2004 article by Howell, Sear and Foex[v] (a meta-analysis) analysed 30 studies and demonstrated an odds ratio for the association between hypertensive disease and perioperative cardiac outcomes of 1.35 (1.17–1.56). This, although statistically significant, was considered not clinically significant, as there is "little evidence for an association between admission arterial pressures of less than 180 mmHg systolic or 110 mmHg diastolic and perioperative complications." They also commented that where patients have higher blood pressures, deferring surgery might not change the perioperative risk. They also commented on the fact that many preoperative blood pressure

[v] Hypertension, hypertensive heart disease and perioperative cardiac risk. British Journal of Anaesthesia. 2004;92(4):570-583 (a review)

readings are ‘stressed’ readings and do not reflect the ‘true’ preoperative arterial pressure.

Other cardiovascular studies

Tetanus

During 1968/69 four publications on tetanus appeared [23-26]. The first, in the Lancet, with Kerr, Corbett, Crampton Smith and Spalding, was a retrospective study of 82 patients with tetanus; it was argued that the high death rate was possibly due to fluctuating overactivity of the sympathetic nervous system and not just due to the hyperexcitability of motor neurones. They noted the marked range of blood pressure and heart rate variability and also the 24h catecholamine values (from nine patients); these varied from 70 -1100 mcg/day, the normal value being 450mcg/day. Carbon dioxide production was also raised. A comprehensive discussion of the thoughts of other workers in the field is presented; the final sentence presenting their view that all the signs are probably due to overactivity of the sympathetic nervous system.

The second paper was a prospective study of 21 patients admitted to the Oxford Respiration Unit between 1966 and 1968. These patients were studied in detail. The observation was that tetanus involves an overall increase in sympathetic activity with marked exacerbations when stimulated. Once again high catecholamine levels were measured…”the more severe the sympathetic overactivity the more likely is death to occur unless specific therapy is employed”.

The remaining two papers at this time were on the treatment of the sympathetic overactivity, one in the Proceedings of the Royal Society of Medicine and one in the Lancet. In the latter article the management of four patients was described…chlorpromazine was found to be ineffectual, general anaesthesia (nitrous oxide, halothane and trichloroethylene, separately) were helpful but had to be discontinued because of toxicity. However, a combination of propranolol and bethanidine (blocks adrenergic transmission at postganglionic nerve endings) proved satisfactory. All patients survived.

The final paper on the topic of tetanus was in 1980 and was titled ‘Diagnosis of tetanus’.

Haemodynamic studies in the dog (haemorrhage, beta-blockade and anaesthesia)

Ignoring the first canine paper [27] on the effects of higher oxides of nitrogen (1967) we will move on to the effects of beta-blockade, anaesthesia and hypovolaemia. Most of this dog work was done over a four-year period 1973-77. The first [28] was an abstract in the Proceedings of the Anaesthetic Research Society at the Royal Postgraduate Medical School, Hammersmith Hospital. It addressed the anxiety of anaesthetists that patients on beta-blocking drugs might have impaired physiological responses to blood loss. Under halothane or N_2O anaesthesia dogs, that had had a myocardial infarction, were bled to up 25% of their blood volume; firstly without beta-blockade and then after beta-blockade with practolol. It was shown that the blood loss was as well tolerated in the treated state as in the untreated state, however, this was not so with propranolol. It was shown that each set of animals had an equivalent degree of beta-blockade. This was published in full in 1976 [29].

There were two papers in 1974 [30] with Foex, (beta-blockade and pCO_2 levels) and with Roberts and Foex [31](interactions of beta-blockade, halothane and hypoxaemia). In the first it was shown that hypo-, or hypercapnia, during halothane anaesthesia caused a fall in heart rate, cardiac output, and myocardial contractility with an associated increase in systemic vascular resistance, and this was greater with N_2O. This confirmed findings in a human study in 1968 [[32] and it was advised to control pCO_2 levels when studying the effects of beta-blockers. The second publication, another ARS abstract, was converted to a full paper in 1976 [33]. The bottom line was that "no adverse haemodynamic effect of the combination of propranolol, halothane and hypoxia was demonstrated".

The 1975 paper [34] in the BJA is a more searching exploration of the effects of PCO_2 levels on myocardial contractility, and does not involve beta-blockers. They were particularly interested in determining "the mechanism whereby cardiac output and stroke volume decreased during hypocapnic hyperventilation". It was discovered that myocardial contractility and ventricular filling changes little but that the left ventricle fails to maintain its output against an increased systemic load. During hypercapnoea the increase in

stroke volume and cardiac output seen must have been due to a reduction in systemic vascular resistance. A reference to the previous 1974 paper suggests that these were the same dogs as used in the beta-blocker study.

In 1976 there were three publications; a study of beta-adrenergic stimulation in anaemic animals [35] – the heart responding well – at least a two fold increase in dP/dt; Horan presented an abstract on enflurane/beta-blockade/blood loss to the ARS [36] and the full paper on beta-blockade/blood loss/myocardial infarction as mentioned previously[29].

Following these studies was a set of three papers [33, 37, 38] all including the phrase "Haemodynamic interactions/responses….".

The first; "Haemodynamic interactions of high-dose propranolol pretreatment and anaesthesia in the dog. II: The effects of acute arterial hypoxaemia at increasing depths of halothane anaesthesia." I have been unable to find Haemodynamic interactions...I. "Cardiac performance was enhanced in both groups during acute hypoxia. No adverse haemodynamic effect of the combination of propranolol, halothane and hypoxia was demonstrated."

The second; "Haemodynamic responses to enflurane anaesthesia and hypovolaemia in the dog, and their modification by propranolol." It would appear from their results that enflurane resulted in greater adverse cardiovascular changes when compared with halothane…blood pressure, cardiac output, myocardial contractility all fell and were more marked with beta-blockade. Blood loss was tolerated poorly.

And the third, "Haemodynamic responses to isoflurane anaesthesia and hypovolaemia in the dog, and their modification by propranolol." Their bottom-line statement was that "The haemodynamic response to hypovolaemia during isoflurane anaesthesia was not modified by propranolol".

To complete this animal work there are two publications that used goats, the first [39] studied the pulmonary and myocardial effects of Althesin and the second [40] assessed pulmonary arterial impedance during a halothane /N_2O/O_2 anaesthetic at different level of CO_2. Impedance did not seem to change, however

pulmonary vascular resistance increased with hypercapnoea and right ventricular work increased, it decreased with hypocapnoea.

The last comment on cardiac output in dogs was in 1999 [41], "Metabolic regulation of cardiac output during inhalation anaesthesia in dogs" which was a comment on a paper by Scheeren, Schwarte and Arndt, Acta Anaesthesiol Scand 1999; 43: 421–430.

Another large section of CP-R's work was around the subject of drug infusions.

Infusions:

Prys-Roberts had worked with Althesin (with Foex and Sear) from 1972 [39, 42] but in 1979 they started collaborating on Althesin infusions.

The first two described here were written in collaboration with Sear [43, 44] and concerned various rates of infusion of Althesin, together with nitrous oxide. . . some patients breathing spontaneously some being artificially ventilated. There was a dose dependent decrease in arterial blood pressure due to a reduction in systemic vascular resistance but heart rate and cardiac output was increased. The accompanying paper showed that there was "an approximately linear relationship between the plasma concentration of alphaxalone and the rate of infusion of Althesin".

In 1980 CP-R wrote an article in Acta Anaesthesiologica Belgica on "Practical and pharmacological implications of continuous intravenous anesthesia" [45] where it was suggested that there was a need for an index comparable to MAC for inhalational agents, we, in 2011, are still waiting for such an index.

In 1981 another couple of pairs with Sear [46, 47] compared Althesin infusions with that of minaxolone…the latter having a slower recovery time; it was suggested that this was due to its water-solubility and a larger volume of distribution. Minaxolone did not last.

1983 was a very busy year with eight publications [48-55], three of these studying Althesin; one showed that Althesin diminished the baroreflex sensitivity which allowed lower arterial pressures without tachycardia, another defined the equipotent doses needed to suppress the initial response to the

surgical incision when used in premedicated patients with nitrous oxide and the third discussed hypersensitivity reaction to the agent. There was one more study of Althesin in 1984 [56] on how age influenced the infusion rate – the 'old' age group requiring less; Althesin was withdrawn in the same year.

Also in 1983 were two papers on the use of opiate infusions [48, 50] (fentanyl and alfentanil), as one might expect there was depression of the carbon dioxide response curve, the recovery from alfentanil being quicker than that from fentanyl. "The infusion after operation provided adequate analgesia at a cost of depression of carbon dioxide responsiveness to 50% of its value before operation, but only moderate effects on minute volume and PaCO2." A further two papers on Alfentanil with nitrous oxide [57, 58] were published in 1984 and 1987 respectively.

The one study in 1983 where the named hypnotic has stood the test of time was [52] "Haemodynamic effects of infusions of diisopropyl phenol (ICI 35 868) during nitrous oxide anaesthesia in man." The blood pressure fell, as did cardiac output; the systemic vascular resistance increased during surgery (was this due to Inadequate analgesia?) but decreased without surgery. Over the next twenty years there were another 21 papers involving propofol [59-79], some involving alfentanil.

Of particular interest are the following:

1. A manual infusion scheme [65] ……. 1988
2. Computer controlled infusion [68]…… 1989
3. Interaction between fentanyl and propofol using a computer-controlled infusion of propofol [69] …… 1990
4. The effects on the EEG [75, 76, 79] … 1994 - 2004

The manual infusion scheme [65] was created by modifying a computer algorithm that was designed to achieve a particular blood concentration of propofol. A loading dose was followed by a series of infusions of reducing dosage. They reported increased cardiovascular stability and that "The quality of induction and maintenance of anaesthesia was satisfactory in every patient".

The computer controlled infusion [68] was set to achieve and maintain a blood concentration of propofol 3 μg ml^{-1} as rapidly as possible. The concentrations in

the blood were close to the set target but were up to 20% higher in those patients being artificially ventilated.

Interaction between fentanyl and propofol using a computer-controlled infusion of propofol [69]? There didn't seem to be one…except for the fact that those who had fentanyl had more satisfactory anaesthetic conditions.

The effects on the EEG [75, 76, 79]:
In the first paper in 1994, with Forrest and Tooley, he studied the changes in the Median Power Frequency (MPF) during propofol infusions over a range of conscious states. They derived MPF values for the suppression of response to verbal commands, the eyelash reflex and venepuncture. They also measured propofol concentrations. "The dose required for 50% suppression of MPF was 7.1 (6.2-8.0) mg kg^{-1} h^{-1}".

The second paper, with Tooley and Greenslade, reported the effects of propofol alone on the first 100 ms of the auditory evoked response (AER). The complex processing allowed them to derive the relationships between the blood concentrations of propofol, features of the AER and response to eyelash stimulus and venepuncture. The mid-latency Nb provided a confident prediction of the likelihood of eyelash response; a sensitivity of 100% and a specificity of 96% and an overall correctness of 98%. The Na wave was the most successful when determining the response to venepuncture.

The final paper, Tooley being the common denominator, reported an investigation into the effects of an alfentanil/propofol infusion and electrode placement on mid-latency auditory evoked response (MLAER). Data were collected from two electrode sites and the results compared with the previous study where propofol was used alone. As one might intuitively expect the infusion rate of propofol required was significantly lower than using propofol alone. Nb latency was again the best MLAER discriminator of unconsciousness. The vertex-inion electrode site gave the best protection against artefact.

Before leaving this section on infusions we should consider the following papers [80-82]; in the first paper (1987) they used the self-tuning controller of Clarke

and Gawthrop[vi], which was used with a syringe pump delivering phenylephrine (a vasoconstrictor). The patients were undergoing lower abdominal surgery during epidural analgesia, which tends to drop the blood pressure. It proved very effective and was also used to produce controlled hypotension using sodium nitroprusside infusions.

The next one in 1989 used the same controller but it controlled the administration of isoflurane, the vaporizer being controlled by an electric servomotor and clutch controlled by a BBC computer (it probably had only 128K RAM). The outcome (induced hypotension) in all study groups was "rapid, accurate, stable and reproducible" and equalled manual performance.

The final paper in this group compared the performance of the self-tuning algorithm when controlling isoflurane or nitroprusside. They were compared with another group of patients where hypotension was manually controlled using nitroprusside. They were unable to show any major differences.

There are many studies involving sophisticated techniques for the assessment of cardiorespiratory function and they are listed below, amongst other individual papers on a variety of subjects. To round off this bibliography is one article on monitoring for adequacy of anaesthesia; it displays his analytical thinking.

Anaesthesia – a practical or impractical construct?

In this editorial in the British Journal of Anaesthesia, in 1987 [83], he attempted to clarify 'our' understanding of anaesthesia and questioned the validity of 'depth-of-anaesthesia' monitors; assuming that surgery is a noxious stimulus inducing a range of reflex responses.

The section below is a paraphrase of the main points.

1. Pain is the conscious perception of a noxious stimulus and so the state of anaesthesia can be defined as that in which, as a result of drug-induced unconsciousness, the patient neither perceives nor recalls noxious stimulation.
2. Anaesthesia is an all-or-none phenomenon - there cannot be degrees of

[vi] Clarke DW, Gawthrop PJ. Implementation and application of microprocessor-based self-tuners. Automatica 1981; 17: 233-244.

anaesthesia, nor for that matter can there be variable depths of anaesthesia. The terms hypnosis and amnesia confuse the issue.

3. Analgesia is normally defined as diminished or abolished perception of pain in an otherwise conscious patient. There is little evidence at present to link the "anaesthetic" state induced by large doses of opioids to receptor-mediated activity[vii].
4. Muscle relaxation…it is illogical to include muscle relaxation induced by neuromuscular blocking drugs as a component of the state of anaesthesia. Muscle relaxation is to satisfy the requirements of the anaesthetist for laryngoscopy and the surgeon for surgical access.
5. Noxious stimulation evokes a number of somatic and autonomic reflexes; they are particularly prominent when evoked by stimulation of abdominal or thoracic viscera. The continuation of noxious stimulation into the postoperative period also evokes a metabolic and endocrine response.
6. Suppression of both perception and recall of pain can be achieved with blood concentrations of either i.v. or inhalation anaesthetics which are too low to suppress the motor responses.
7. Suppression of the motor withdrawal reflex has been used as the basis of the main quantitative index of anaesthetic potency, the minimum alveolar concentration (MAC). It is therefore implicit, that the blood concentration of anaesthetic required to suppress the somatic motor response is higher than that required to induced unconsciousness, and by implication, perception of pain.
8. Greater concentrations of anaesthetics are required to suppress breathing responses to somatic noxious stimulation, than to suppress motor responses or to produce unconsciousness.
9. Sudomotor responses (sweating) are readily suppressed by low concentrations of volatile or i.v. anaesthetic supplements.
10. Haemodynamic responses occur even when anaesthetic concentrations are high enough to prevent sensory, motor and breathing responses.

[vii] Dodson, B. A., and Miller, K. W. (1985). Evidence for a dual mechanism in the anesthetic action of an opioid peptide. Anesthesiology, 62, 615.

Roizen, Horrigan and Frazer (1981) [viii] introduced the concept of MAC-BAR as a correlate of MAC, being the alveolar concentration of an anaesthetic that would suppress haemodynamic and adrenergic responses in 50 % of patients. They found that the ratio of MAC-BAR to MAC was 1.45 for halothane and 1.60 for enflurane.

11. Hormonal responses are difficult to suppress by volatile anaesthetics, but can be partially suppressed by high doses of opioids and by regional blockade but only partially suppressed by beta-adrenoceptor blockade.
12. If one accepts the ranked order of responses to noxious stimulation then it is logical to consider anaesthesia as that state which ensures the suppression of the somatic and visceral sensory components, and thus the perception of pain.
13. Analgesia, muscle relaxation, and suppression of autonomic activity, are not components of anaesthesia. Rather they should be considered as desirable supplements to the state of anaesthesia as a means to enable surgery to be performed.
14. Any reliable indicator that the level of anaesthesia is adequate to ensure lack of awareness is highly desirable.
15. Methods have been described to achieve this, oesophageal motility, the EEG and its derived parameters and brain stem auditory evoked responses. These clearly demonstrate a dose-effect relationship for many anaesthetic agents, but do not answer that fundamental question: is it feasible to find some measure which will ensure that the patient will be unaware of, and will not recall, events and sensations during surgery?

An interesting editorial in it's analysis of the difference between what the *state of anaesthesia* is and what is called 'anaesthesia', which includes the 'supplements' that make the *practice-of-anaesthesia'* a practical construct.

[viii] Roizen, M. F., Horrigan, R. W., and Frazer, B. M. (1981). Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision—MAC BAR. Anesthesiology, 54, 390.

This is a large body of work and CP-R worked with many well-known anaesthetist-scientists, to name a few (in no particular order), Greenbaum. Kellman, Nunn, Foex, Sear, Hutton, Adams, and Edmonds-Seal…forgive me if I've missed you off.

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Alastair Spence

C.B.E., M.D., F.R.C.A.

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In 1965/6 Alastair Spence was a Research Fellow in Leeds, becoming Head of Department at the Western Infirmary in Glasgow in 1969. In 1975 he became a Reader and was Professor between 1978 and 1984. He moved to Edinburgh as Head of Department and as Professor in April 1984. He was President of the Royal College of Anaesthetists (1991-94) and retired in July 1998[ii].

Twenty percent of Alastair Spence's published output was on the topic of theatre pollution and its effects on staff, and the adverse effects on patients of inhalational agents. Another large section was on the subject of postoperative hypoxaemia, both the physiology and clinical ramifications and management. The remaining miscellaneous publications included matters pertaining to the College, to teaching/training and to aspects of worldwide anaesthetic practice

His first publication, 1967, was in the journal Anaesthesia, observations on intragastric pressure [1] with Moir and Finlay. In non-pregnant patients the intragastric pressure was 5-11 mmHg during anaesthesia, in term pregnant patients it was 5-13mmHg; these observations were confirmed by La Cour (1970) and Hartsilver et al (1999).[iii] In the same year an Anaesthetic Research Society abstract was published in the British Journal of Anaesthesia and was titled "The influence on renal function of chloroform and halothane anaesthesia in man" [2] with Linton and Patel. The author was surprised to read that chloroform was still being used, presumably, regularly in 1967. Sixty patients were randomly allocated to chloroform or a halothane anaesthetic. It was shown that, using a urea excretion test, that chloroform patients had greater renal dysfunction.

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[i] http://www.rcoa.ac.uk/index.asp?PageID=1460

[ii] Nunn JF. BJA 1999;83:916

[iii] La Cour D. Acta Anesthesiol Scand. 1970;14:5-15 and Hartsilver EL et al BJA 1999;82:752-4

Postoperative hypoxaemia

Lung function in the postoperative period became an early subject. In 1968 Spence, together with G Smith (later to become professor of anaesthesia at Leicester), with Harris wrote on "the influence of continuous extradural analgesia on lung function in the postoperative period"[3]. This was followed in 1970 by a comparison of morphine with extradural nerve block on postoperative lung function [4], and similar papers in 1971 [5], 1973 [6] and 1975 [7]. This latter paper compared patients receiving either continuous extradural analgesia or narcotic analgesia following upper abdominal surgery; there were no statistically insignificant improvements in PaO2 in the extradural group. A conclusion they drew from this was that abdominal muscle spasm was not an important factor in postoperative arterial hypoxaemia, a hypothesis that they had put forward in 1972 [8].

A paper in 1973 reported the "apparent" improvement in lung function when using Entonox [9]…the use of the word "apparent" is interesting, almost as if they did not believe their results. Entonox was used for post herniorraphy pain and was associated with an increase in functional residual capacity, the morphine group showed a decrease.

In 1977 the difference in lung function between those patients whose lungs were ventilated with oxygen and nitrogen were compared with those ventilated with oxygen and nitrous oxide… no difference was found [10].

Postoperative hypoxaemia and its relation to age was also studied and reported in a letter to Anesthesiology [11]; the PaO_2 when breathing air could be calculated using the regression equation … 81- (0.285 x age).

The subject of the mechanism of postoperative hypoxaemia was the subject of several 'overview' type publications [8, 12].

Over the next three years there was an intense effort with Smith, Dewar, Alexander, Davis and others on the physiology of postoperative oxygenation.

In 1970 another ARS presentation, "the effect of air at 1 and 2 atmospheres absolute" on respiratory mechanics, 'normal' volunteers were studied as well as a group of patients with chronic bronchitis. With increasing pressure the flow resistance increased but in the 'normal' volunteers compliance and lung volumes did not. Some of the bronchitic patients, three, out of twelve had large increases

in expiratory resistance and expiratory reserve volume. The possible use of the hyperbaric air was broached as it might achieve more uniform emptying of alveolar units [13].

Airway closure (the closing of lower airways during exhalation at low lung volumes) was studied as a possible cause of postoperative hypoxaemia [14-17]. It is the author's view that Alexander, the principal author in all papers, drove these studies. Lung function studies after elective surgery showed that functional residual capacity was reduced and was worse in those patients having upper abdominal surgery. This was related to an increase in alveolar/arterial pO_2 difference and to the amount of closure of small airways. The concept of airway closure during part of the respiratory cycle helped to explain the changes in ventilation/perfusion and intra-pulmonary shunting. These papers involved a considerable amount of work.

Apart from these clinical studies there was a series of more basic physiological research projects. In 1970 there were two publications on the topic of a nitrogen rebreathing method for the estimation of PvO_2, both with Ellis (of malignant hyperpyrexia fame – Leeds)[18, 19]. This was a mathematical and experimental evaluation of the technique as PvO_2 is a useful index of either whole body tissue oxygenation or as a component of the Fick equation for determining cardiac output. The final result involves many assumptions and, after equilibration of the bag gas with lung gas, the implication is that the gas has come into equilibrium with mixed venous gas. It would appear to be a technique with many possible confounding facets.

The effects of hyperoxia were also studied [20, 21]. Breathing 100% oxygen at 2 Ata for 5 hours caused an increase in airways resistance of 30%, thoracic gas volume increased by a quarter and specific airways conductance by 41%. Those volunteers breathing an air equivalent at 2Ata had no significant change. Excess oxygen is not good.

General clinical studies:

As in all clinical academic departments there is the usual collection of drug comparison studies and case reports, Spence and his co-workers were no different. Tubocurarine and pancuronium [22], metoclopramide [23],

pentazocine [24], glycopyrrolate [25], etomidate [26], alfentanil[27] and ketorolac[28]. The alfentanil study, a double blinded study, is interesting in that the intra-operatively the patients had smaller minute volumes, lower respiratory rates and obtunded increases in heart rate (not surprising) but that they required more analgesia postoperatively because, it was postulated, they did not take up so much volatile agent...this was considered an improvement in the anesthetic technique.

Other studies include the effect on wound healing of nitrous oxide (in rats) [29]; no effect. Does thiopentone affect the speed of onset on previously injected non-depolarising agents [30]? Not really! There were also four studies on the new agent – propofol [31-34], the first a dose finding study compared with Althesin, the second a study of the new formulation designed to avoid Cremophor-related reactions, the third and fourth a comparison with Althesin and methohexitone respectively.

Occupational hazards:

Pollution of the operating theatre atmosphere and its affects on staff was the subject of another major block of work. It started in 1972/3 [35, 36] and continued through to 1991 [37-44].

Knill-Jones was involved in many of these publications… the first study was a comparison between married women anaesthetists with non-anaesthetist married women doctors. It was reported that spontaneous abortion was significantly greater in those associated with anaesthesia, there were more congenital abnormalities and the involuntary infertility rate was higher.

An article in the Annals of the Royal College of Surgeons of England Spence describes the nature and determinants of air pollution in the operating theatre and referring to a study by Pfaffli et al.[iv] he stated that the average levels of halothane and nitrous oxide contamination were 15ppm and 170ppm respectively. A study by Vaiseman[v] had reported spontaneous abortion by 18 out of 35 pregnancies in nursing staff.

[iv] Pfaffli P, Nikki P and Ahlman K. BJA 1972;44:230
[v] Vaisman AI. Eksperimental'naya Khirugiya i Anesteziologiya 1967;3:44

In this article he is careful to point out that there was no direct evidence to indicate that the polluted theatre atmosphere was the cause of these obstetric mishaps but suggested that there was some urgency to remove contaminant gases.

In 1975 a survey of almost 8000 male doctors in the UK was reported [39], this showed that paternal exposure to anaesthetic contaminants did not affect the abortion rate, congenital abnormality rate or involuntary infertility. However maternal exposure was associated with an increase of 1.6 – 2.7 times the risk of non-exposed pregnancies.

A combined analysis of USA and UK surveys [40] reaffirmed the increased risks and also showed an increased frequency of hepatic disease amongst anaesthetists. In a review in 1978 these findings were reiterated and there was also a call for the audit of causes of death in relation to the type of work undertaken as there were some anxieties about the possibility of leukaemia and lymphoma [41].

In 1987 we move onto environmental pollution by inhalational anaesthetic agents [45]. However the title is deceptive as the 'environment' is still the operating theatre environment, but it is a very important milestone in that it reviews all the recent epidemiological analyses regarding the effects of theatre pollution and comes to the conclusion that the risks may have been overstated. Retrospective postal surveys may well have produced biased results. Important publications were those from Scandinavia, two from Sweden and one from Finland with 'hard facts'[vi].

Other adverse effects of anaesthesia:

The adverse effects of anaesthesia on patients was also studied, Gillies et al. in 1979[46], the bottom line of this report of 'anaesthetic deaths' to the procurators-fiscal (equivalent to coroner) was that many of the postmortem examinations were unnecessary and that more attention should be applied to those unexpected deaths.

[vi] Ericson A and Kallen B. Anesth. Analg. 1979;58:302 and 1985;64:981
Hemminki K, Kyyronrn P and Lindbohm ML. J. Epidemiol. Community Health 1985;39:141

Halothane and nitrous oxide continued to be battered in the late 80s and early 90s, halothane [47, 48] and nitrous oxide [49]. In the latter study formiminoglutamic acid excretion was used as a measure of folate metabolism…fifteen control subjects excreted normal amounts for six days, of fifty patients who received nitrous oxide 40% had increased excretion for the first two days…ten anaesthetists had normal excretion rates.

And finally, a cross-sectional study of complications in 16,995 patients receiving an inhalational anaesthetic [50]. The overall incidence of complications was about 14%; complications were more common in the obese and the elderly. There was a correlation with isoflurane but it was thought that this might have been due to its recent introduction and the learning curve that this involves.

Other

Over an academic career of 30 years there are going to be a number of chance, opportunistic, publications and some that are of a non-clinical nature. Alastair Spence was involved in the College of Anaesthetists and teaching, and the wider world of anaesthesia.

The following references include College / teaching type publications [51-64]. Of these the following have been selected for comment.

The paper by Mowbray [58] was an interesting example of a cascade form of teaching; ten medical students were taught basic cardiopulmonary resuscitation and then they in turn went out and taught 40 secondary school pupils…all formally assessed… a very novel idea especially in the light of the present view that early intervention, resuscitation, by the public is good in the non-hospital environment.

The comparison of candidates who passed or failed the final (Part Three) examination for the F.F.A.R.C.S. (Eng.) in 1988 by David et al. was an attempt to isolate the factors that influenced pass or failure [61]. Successful candidate thought they had better departmental support, better systematic preparation and their workload was not particularly different to those who failed (47% vs. 55%). Unsuccessful candidates were more likely to have some personal upset during preparation for the exam.

And a final foray into education with a comment on the use of simulators for management of risk [65].

Some authors have a sustained interest in the history of anaesthesia; others seem to reflect on it at the end of their careers. Three publications by Alastair Spence in 1996/7 [66-68] are about ether and chloroform, the latter turning full circle to 1967 [2] where chloroform was part of a study into the renal effects of chloroform.

"The clinical evidence for delayed chloroform poisoning" [67] is a detailed analysis of the clinical data associated with case reports of adverse events (delayed chloroform poisoning, DCP) from 1847 to 1970. It is a detailed review with 69 references. In the discussion it is made clear that many of the reports do not describe hepatic failure and in those that do the link with chloroform is tenuous. At the time when chloroform was in common use hypoxia and hypercarbia were common and, together with other factors such as semi starvation and alcohol and barbiturate use, liver damage was more likely. Thorpe and Spence concluded that, in agreement with others, that chloroform had had "a rough deal" and that by at the end of the 20th century chloroform did not fulfill the criteria to be a hepatotoxin[vii]. It compared very favourably with halothane.

Miscellaneous:

Interspersed amongst the papers on the themes described above were a miscellaneous group of articles...not all these have been seen by the author [69-84].

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Chris Hull became 'first assistant' in the Department of Anaesthesia in the University of Newcastle-upon -Tyne in 1967 and was promoted to a personal senior lectureship in 1970[i]. He became Professor of Anaesthesia in Newcastle-upon-Tyne in 1981 following the retirement of EA Cooper.

Hull was an 'equipment man' but also had a strong interest in pharmacokinetics.

Equipment

The first publication describes the development of a blood pressure recorder [1]. The development is described in great detail; it was made up of a two compartment brachial cuff with appropriate transducers to detect pressure changes, an air pump to inflate the cuffs and a method to deflate the cuffs in a linear manner. Artefact rejection was a major part of the device and it came with a pen recorder. It was able to produce a trend printout. The electronic control system was complex and, as was fitting at the time, was flameproof – explosive anaesthetics still being in use at this time. Under the subheading "Future Development" it was apparent that a pre-production prototype was under construction with upper and lower limit alarms, manufactured by Newmark Instruments Ltd. It only measured the systolic pressure but it was obviously the precursor of the famous Criticon Dinamap.

In the following year another equipment related publication, this time as a result of a presentation to the Anaesthetic Research Society at the 1969 Bristol Meeting. "The impedance cardiograph: development and applications." [2] He describes the shortcomings of existing instruments and explains how these faults

[i] Development of academic anaesthesia in the UK up to the end of 1998
J F Nunn. British Journal of Anaesthesia. London: Dec 1999. Vol. 83, Iss. 6; pg. 916, 17 pgs

could be overcome. One of the main problems was the summation of the cardiac signal and the respiratory signal…using the technique of 'computer of average transients' and the ECG signal as a trigger for this analysis. Using a PDP-8/L computer he was able to do the 'averaging' using only a few complexes and the resulting output changed rapidly with changes in stroke volume. These two papers together show a great technical know-how.

In 1971 another presentation to the ARS, "Development of an artefact-immune wave pulse counter"[3]. As the author states it describes the aim rather than the outcome, of which he makes qualitative comments. The detection of the QRS spike on the ECG was considered better than the peripheral pulse. He outlined all the problems associated with existing devices and then proceeded to produce a much improved, reliable version. There were no quantitative results with this presentation. I do not know Chris Hull's background but this work to-date suggests a very good knowledge of electronics. He was still unhappy with its performance and in 1973 presented a new improved version [4] to the ARS which was hosted by the University of Liverpool but held at Imperial Chemical Industries, Pharmaceutical Division in Macclesfield. The system now was "… immune to diathermy, electrode artefacts, movement artefacts, and mains pickup. Pacemaker potentials [were] also rejected, so that the true capture rate during pacing [could] be accurately assessed". This was a significant development.

In 1973 [5] a data logging system was described for the conversion of the data streams from physiological monitors in the labour ward to a magnetic tape. Data were collected at 10s intervals, processed through a 'specially constructed interface' and included both clinical measurements and information from infusion pumps; it was said that a C60 cassette tape could hold more than 20hours of recording. This is very advanced for its time.

The Anaesthetic Research Society (ARS) featured prominently in Hull's publications and in 1975 was hosted in his hometown of Newcastle upon Tyne. Both pharmacokinetics and computers were now very much in vogue and the use of the analogue computer promised to be very helpful in analyzing the resulting data of studies. According to Hull the previous attempts at computer

analysis were "complex and had limited application"[ii]. His version, with the help of McLeod [6], gave solutions to the pharmacokinetic data and allowed them to simulate other situations with, for example, changes in renal function, predictions of duration of drug action were therefore possible. This presentation was followed by a full paper in 1976 [7]. In this paper the technique used was demonstrated using serial plasma concentrations of fentanyl and pancuronium.

The last three publications in this group of 'equipment' related articles are about a 'demand analgesia apparatus' [8-10], 1979, 80 and 1981. The first was another ARS presentation, the second a letter and the third a full paper. The device spoke to patients ("in any language") and the dosage was limited by a reduction in the respiratory rate, it also had additional fail-safe mechanisms. Using fentanyl there was no evidence of cumulation during a ten patient study. Secher[iii] first advanced the idea of an analgesic demand system in 1971. The 'Cardiff Palliator' was described in 1976[iv] and this paper of Hull's preceded Kenny's by five years[v]. Every six minutes the device instructs the patient to press the button twice if in pain; if the patient presses the button the device then reassures the patient that the drug is being administered. A peristaltic pump drove the drug administration. A mercury-in-rubber pneumograph transducer monitored the respiratory rate and if the interval between respirations exceeded eight seconds the cycling of the device was inhibited. The control algorithm was complex. In the discussion it was said that a microprocessor-based system was being developed by Janssen Scientific Instruments.

Electrical Hazards

Electrical hazards have been a topic of editorials and comment from the early days of anesthesia and Hull published four[11-14]. The first in 1973 was in the Annals of the Royal College of Surgeons of England and it was a special edition dealing with all aspects of hazards in the operating theatre… Hull's contribution was about electrical hazards. He explained the problem associated with

[ii] Fleischli, G., and Cohen, E. N. (1966). Anesthesiology, 27, 64.
[iii] Sechzer, P. H. (1971). Anesth. Analg. (Cleve.), 50, 1.
[iv] Evans, J. M., McCarthy, J. P., Rosen, M., and Hogg, M. I. J. (1976). Lancet, 1, 17.
[v] Gillies, G.W., G.N. Kenny, and C.S. McArdle, Journal of Medical Engineering & Technology, 1986. 10(2): p. 55-7.

'transcardiac' current, 50mA upwards can cause ventricular fibrillation but, unless the heart is damaged, a current of 5 A when switched off may still be followed by sinus rhythm. The contact between the source of the current and the body tissues is of importance; dry skin is very protective, wet hands are not. He mentions the merits of good maintenance of cables and the American system of isolating transformers. This is followed by a section on microshock.

Microshocks are possible when intravascular leads are present (pacemakers) or electrolyte filled catheters. The current will be so low as to be not sensed by the patient or physician, the resulting VF unexpected. Isolated circuits are mandatory, battery driven devices ideal as long as they are not earthed.

Five years later he writes a detailed account of electrocution hazards in the operating theatre and goes into great detail…it is a worthwhile read for those interested in the subject even 30yrs later. It is the only paper where the author has seen 'Murphy's law' quoted. The 1979 Anaesthesia editorial quotes T.L.Martin from "Malice in Blunderland"[vi], "Nothing can be made foolproof, because fools are so ingenious". This is an editorial following the death of a 20yr old by electrocution in an operating theatre, in modern parlance 'all the holes in the Swiss cheese lined up' and death was the result. He laid out the problem (paraphrased) of the costs of maintenance of, or replacing of, old equipment and the appropriate communication required between maintenance staff and the theatre managers/users.

Modeling

The development of electrical analogue computers as referred to above[7] facilitated the study of drugs in a way that minimized or avoided human or animal experimentation. In 1978, with Van Beem, he addressed the problem of the model not accounting for the observed effects of muscle relaxants[15]. To the simple two-compartment model for pancuronium they added a receptor compartment and then the model behaviour came to resemble the observed effects in animal experiments. The model, with parameters consistent with renal failure, showed a biphasic response, small doses of pancuronium demonstrated

[vi] Malice in Blunderland, McGraw-Hill, New York, 1973

marginal resistance with normal recovery, whereas large doses resulted in delayed recovery in a dose-dependent manner.

Another paper in 1980 used the model to compare fazadinium and pancuronium and was used to compare potencies[16]. A 'general solution' to the three-compartment model was published in the appendix. [vii].

At this point we will continue with the muscle relaxant studies but opiates were also scrutinized [17, 18].

In the BJA of February 1983 his editorial addressed the pharmacokinetic problems associated with atracurium[19]. It was in this issue that the first account of the pharmacokinetics of atracurium was published[viii]. Hull outlines the differences between the clearance of atracurium (by the Hofmann reaction) and the clearance of previous muscle relaxants by a combination of liver and kidney function. However despite conceptual differences, and a possible array of different models, he explains how the conventional two-compartment model would be equally valid for atracurium.

"How far can we go with compartmental models?" [20] was the subject of an editorial in Anesthesiology in 1990. The discussion in the editorial was centred on two papers in the same issue that were trying to evaluate the effect of age on pharmacokinetics[ix]. Both papers were introducing a way of looking at data that he thought might be confusing. He advocates the use of simple rather than complex models – the greater the complexity the more uncertain being the value of some of the variables used. He discusses the use of an "effect" compartment and how this minimizes the measured differences between drug concentration and effect. He wants clarification over the various terms relating to parametric and nonparametric models. The problem he is addressing is really complex; (the fact that thiopentone is partitioned into lung tissue in the early distributive phase) and he points out the limitations of both studies but both studies suggest arrived at similar conclusions – distribution of thiopentone from

[vii] The author wishes to thank Chris Hull for the use of his pharmacokinetic algorithms in his own research.

[viii] Ward, S., Neill, E. A. M., Weatherley, B. C., and Corall, I. M. (1983). Br.J.Anaesth., 55,113.

[ix] Avram MJ, Krejcie TC and Henthorn TK. Anesthesiology 72;403-411,1990 and Stanski DR and Maitre PO Anesthesiology 72;412-421,1990.

the central compartment to the periphery is slowed with age and that body weight is poor at predicting the pharmacokinetics. He then goes on to describe how the problem might be resolved.

His final (team) paper on the pharmacokinetics of muscle relaxants was in 1996 [21]. They studied cisatracurium in an attempt to elucidate the differences between the young and the elderly. The clinical difference of interest was the slower onset in the elderly. Other differences were marginal.

His other pharmacokinetic publications are [17, 18, 22-27].

Miscellany

In 1969 Hull was part of a team at the Royal Victoria Infirmary in Newcastle investigating methods of preserving liver function in cadavers[28, 29]…they worked on pigs and the 1969 presentation to the Surgical Research society indicated real success. A variety of regimens were used but the one that seemed to succeed was that used in Group 3. In this group "the liver was cooled and stored for a similar period [*20-25minutes*] by perfusion with a preservative solution containing high concentrations of potassium, magnesium, and bicarbonate, together with Dextran, glucose, and insulin." It was shown that ischaemic changes were minimal and subsequent function excellent. Although the first liver transplant had taken place in 1963 it remained an 'experimental' technique until the eighties because the survival rate was at that time very poor[x]. In 1979 they investigated extracorporeal hepatic support using the pig liver [29]. Calves were connected to a pig liver on two occasions and these perfusions were tolerated for 6-7 hours. Some calves with induced liver failure also had repeated perfusions and survival was prolonged, one made a complete recovery. The immunological response was relatively benign. This work demonstrates the complexity of the work being carried out at the RVI in Newcastle and potentially of great clinical significance.

The topic of pain management occurs in several papers – a 1983 clinical trial of alfentanil for short surgical procedures [30] compared with fentanyl. Alfentanil had more post induction apnoeas and more postoperative nausea and

[x] http://en.wikipedia.org/wiki/Liver_transplantation

vomiting when associated with ergometrine. Three years later alfentanil for gall bladder surgery [31] and the following year a case report of alfentanil for a caesarean section complicated by aortic stenosis [32].

An interesting study of extradural diamorphine vs. the same drug intramuscularly showed no significant difference in pain relief…however, analgesia was more prolonged when the diamorphine was given by the extradural route [33], this was in 1983.

Lignocaine and propofol associated pain was addressed in 1985 [34], and the whole topic of control of pain in the perioperative period in 1988 [35].
Three publications in the 1990s are of a non-clinical nature. In 1994 is an article, which is well worth reading, on the responsibilities of being an expert witness [36]. It covers many practical aspects of the methodology that should be followed and how to produce the report. Not least amongst the many gems is the advice that the report should not depend on whether one is an expert for the defence or the prosecution, and to determine, within the limits of the evidence available "the most probable sequence of events" and causation. Anybody who is asked to take on the role of an expert witness should read the article carefully.

"Awareness is due to negligence during general anaesthesia for caesarean section" [37], a very strongly worded proposition which was opposed by J Thorburn of the Western Infirmary Glasgow. These were in fact arguments around the subject of the use of volatile anaesthetic agents during caesarean section and the opposing risks of awareness (too little) and uterine haemorrhage (too much). In most debates the proposition is strongly worded, as here, and it does not take into account the variability of response between patients (as is pointed out by Thorburn). The modern concepts of open disclosure of adverse events *without blame* have not quite permeated this debate. Thorburn's comment about there being "clear evidence of stress response" in many instances of awareness is not reassuring… a stress response may occur during surgery without awareness and is therefore has low diagnostic strength.

The final publication, on anaesthetic risk [38], was a record of a talk given to the Medico-Legal Society on the 8th January 1998, it was given at the Royal Society of Medicine; he was replacing Professor Aitkenhead (Nottingham) who was unavailable. He explains to a mixed audience that adverse events during

anaesthesia can range from 'misadventure' – where nobody could have predicted the event, through slips and lapses to bad decision making due to ignorance. He also explained that equipment could be designed in such a way that due to the ergonomics errors are likely to happen, he called them 'latent errors'. He described the early deaths from anaesthesia in the 1800s and the early attempts to determine the causes of sudden death, and moved on to more recent studies including the CEPOD[xi] studies, AIMs studies[xii] and the use of closed claim records. Showing the safety of new monitors is difficult, the classic is the pulse-oximeter – Hull reports that Moller in 1993[xiii] studied 20000 patients, there was a 19 fold increase in the detection of hypoxaemic episodes and half the number of ischaemic changes, but he was unable to show any difference in mortality. It was obviously a complex topic – and at that time, from reading his final comments it looked as though, at that time, there was the threat of withdrawal of legal aid for medical negligence claims. This was an interesting talk at the end of his career.

Hull had a range of interests…from 'mechanical' electronic devices, to the complexities of pharmacokinetics and dynamics, from clinical problems to medico-legal argument. He was the sole author for 50% of his publications, a significant body of work.

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[xi] http://www.ncepod.org.uk/studies.htm

[xii] Runciman WB. The Australian Patient Safety Foundation. Anaesth Intensive Care 1988;16(1):114-6

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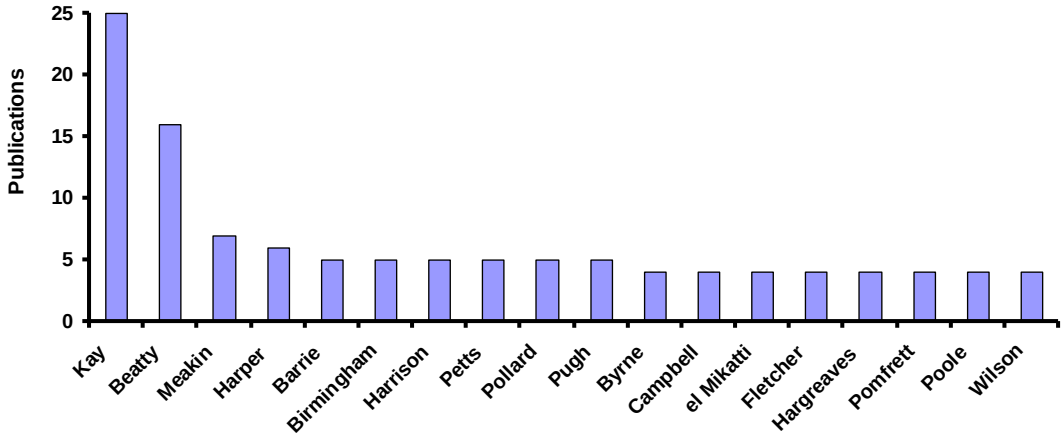
Tom EJ Healy

MD, LLM, MSc, FRCA

 [ii]

Tom Healy qualified in medicine in 1963. He worked at the Clinical Investigation Unit in Birmingham with Dr Mike Vickers and in 1975 moved to Nottingham to become Reader in Anaesthesia[i].

Academic anaesthesia at that time was a sub-section of the Department of Surgery. In 1981 he moved to Manchester as Professor. Brian Kay joined the team in 1983 as Reader, Brian Pollard in 1985 (Senior Lecturer), Chris Pomfrett (Lecturer - neurophysiologist) in 1990, and George Meakin (Senior Lecturer in paediatric anaesthesia) in 1993. Tom Healy retired in 1997.



He had more than 100 co-workers but the majority had less than five publications as joint author with him.

Tom's work can be classified by its nature under five headings; sedation, neuromuscular junction pharmacology/physiology, assessment of equipment and general pharmacology/physiology. In addition there is a miscellaneous group of publications including a few books.

[i] Nottingham Medical School was opened in 1970.
[ii] Photograph courtesy of Brian Pollard, Manchester.

Sedation:

Tom Healy's first publication was in *Anaesthesia* in 1969[1]; 'Intravenous diazepam for cardiac catheterisation', he described a diazepam technique which provided tranquil conditions without disturbing any of the vital signs. The retention of good muscle tone in the upper airway, the negligible depressant effect on ventilation and normal $PaCO_2$ values supported the conclusion that it was better than thiopentone. At that time he was a senior registrar in the Department of Clinical Investigation and Research at Dudley Road Hospital, Birmingham.

Following this publication intravenous diazepam was studied as used in the dental chair for mentally impaired patients and apprehensive children. Its effect on laryngeal competence and respiratory rhythm was also reported. Once again no clinically significant changes occurred in the cardiovascular, respiratory, or metabolic status of the patients. However in some patients there was a period of incompetence of the larynx[2]. In the same issue of the BMJ, with a multidisciplinary approach, patients were assessed during routine dental treatment under local anaesthesia. Some had been referred because of failure to complete dental treatment because of anxiety. There were two 'unsatisfactory' states but overall the technique proved of benefit and patients were safe to leave accompanied by an adult within one hour. As expected, three cases of superficial venous thrombosis occurred, a perennial problem with diazepam in its original formulation, when injected into small peripheral veins[3]. A further study was carried out for the treatment of aggressive and athetoid patients; it was thought that it would provide a useful alternative to general anaesthesia for the mentally handicapped patient. Previously 68% of the dental extractions were performed under general anaesthesia; using diazepam acceptable operating conditions were present for 84 of the 101 patients studied, with insignificant cardiovascular or respiratory changes[4], see similar publications in the British Dental Journal[5, 6].

Everything seemed 'rosy' for intravenous diazepam but some doubts were around about adverse effects. A study of laryngeal competence followed[7]; 10ml of Lipiodol was place on the back of patients' tongues after intravenous

diazepam and they were asked to swallow. Eight out of 19 patients had Lipiodol in their lungs, as seen on chest X-ray. The laryngeal closure reflex was considered to be impaired for 5-10 minutes after the intravenous injection.

Another anxiety was around the effect of benzodiazepines on ventilatory patterns, two publications (proceedings) in the British Journal of Clinical Pharmacology[8] and British Journal of Pharmacology[9] were followed by a full article in Anaesthesia in 1979[10]. The bottom-line was that despite the similarity in structure between diazepam and lorazepam the incidence of periodic breathing was much higher following lorazepam. Was this due to a direct effect on respiratory control mechanisms or due to a change in blood flow to the respiratory centre? Although interesting it did not have major implications – interestingly the lorazepam patients stayed awake whilst the diazepam patients slept.

It was another fourteen years before another foray into rhythmicity. This time it was respiratory sinus arrhythmia as an index of depth of anaesthesia or sedation, in collaboration with Chris Pomfrett and others [11-13].

Respiratory sinus arrhythmia (RSA) is the variation in heart rate that occurs during breathing. The degree of RSA was determined during propofol anaesthesia in real-time and correlated with the median frequency of the EEG. Changes in propofol

Infusion changes the degree of RSA in all patients and so it was suggested that RSA, could provide a convenient and objective index of depth of anaesthesia. The change in RSA was very fast and it was also suggested that it could be used to control intravenous anaesthetic infusions.

Measurements were also obtained in ICU patients and, again, RSA was considered to be an objective measurement of sedation.

The final paper compared the RSA at two different levels of MAC for isoflurane, 0.65 and 1.2. It was suggested that not only could RSA be used to stage the level of anaesthesia but that because of its responsive to surgical stimulation it also highlighted the needs of the patient when responding to noxious stimuli.

Neuromuscular Pharmacology:

Apart from a couple of case reports[14, 15] the vast bulk of his, and his colleagues', work falls into the category of the study of drugs that may be used during anaesthesia that interact with the neuromuscular blocking drugs of the day. This includes the assessment of interactions between muscle relaxants. This body of work stretches from drugs that are no longer used (tubocurare) through drugs that have come and gone (fazadinium, alcuronium) to the latest (2008) agent rocuronium.

The first paper in 1971 describes the effect of suxamethonium on intra-uterine pressure during Caesarean section [16] (no effect whatsoever) and in 1972 a comparison of the effect of induction of anaesthesia by thiopentone or Althesin on the duration of action of suxamethonium [17] , no difference was reported but the methodology was criticised because they used a "visual method" to estimate the neuromuscular block.[iii]

These early clinical papers were then replaced with a series of studies using an in vitro preparation to study the interactions between a variety of drugs and the neuromuscular blocking agents, this phase of research lasted a decade.

In vitro work:

1978 - Aminoglycosides and neuromuscular transmission in the rat isolated phrenic nerve-diaphragm preparation[18]: compared to streptomycin, neomycin and gentamicin which all produced a dose-dependent blockade; tobramycin had no effect at therapeutic concentrations. The effects aminoglycosides on transmission in sympathetic ganglia were also studied[19], they produce a dose-related sympathetic blockade but at concentrations greater than normal effective concentrations.

1980 - The effect of ascorbic acid on the interaction of adrenaline and neostigmine on neuromuscular transmission in a phrenic nerve-diaphragm preparation[20]. This is a technical paper on the laboratory practice of using

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ascorbic acid as a stabiliser of adrenaline solutions. Ascorbic acid did not affect the preparation to phrenic nerve stimulation but it significantly reduced the response of the preparation to neostigmine and the augmentation of this response by adrenaline. The results emphasize the need to consider the effects of preservatives in drug solutions when quantitative comparisons are made.

1981 - Disopyramide[21, 22], effective in the management of atrial and ventricular arrhythmias, was shown to have an effect on neuromuscular transmission and although alone it was unlikely to lead to cause overt neuromuscular blockade, it was thought that the simultaneous use of disopyramide and other drugs with anticholinergic (antinicotinic) properties might decrease neuromuscular transmission, significantly, particular at the end of anaesthesia where a partial neuromuscular block may still exist (disopyramide was also shown to produce a dose-related ganglionic blockade in a guinea-pig preparation).

One of the attributes of tubocurare that was used to advantage to produce hypotensive anaesthesia was its ganglion blocking effect but there was a drive for 'cleaner' agents. In 1982 the EC50 ganglion blocking/ neuromuscular blocking potency ratios of atracurium and tubocurarine were determined, the equipotent molar ratio was 48 for atracurium and 9.4 for tubocurarine; atracurium was therefore the 'cleaner' agent[23]. The final lab-bench study (1986) demonstrated that interactions between atracurium and vecuronium were of simple summation[24].

Clinical research resumed in 1979.

It was started by comparing fazadinium and d-tubocurarine[25]. There were little differences but the first dose of d-tubocurarine was markedly slower than fazadinium to achieve a 50% and 100% effect.

Another five-years passed; in 1984 two devices that measured the evoked compound muscle action potentials (EMG) produced by a train of four stimulation pattern were compared [26], there was no statistical difference.

The recovery rate from a neuromuscular block with alcuronium using edrophonium was studied showing that[27]it was more rapid than neostigmine, without re-curarization.

In 1985 a randomized study was performed to examine the induction characteristics and the possible interactions between propofol or thiopentone and three neuromuscular blocking agents, suxamethonium, atracurium and vecuronium. Apart from a greater fall in arterial blood pressure after propofol, $p< 0.05$, there was no significant difference [28]. Also in 1985 the neuromuscular blocking action of atracurium and vecuronium acting separately and in combination were compared[29]. Dose response curves were drawn and found to be nonparallel ($p < 0.05$). Atracurium was calculated to be 5.25 less potent than vecuronium (ED50). Equipotent doses of atracurium and vecuronium, determined from these dose response plots had an effect that was found to be greater than would be expected by addition of their separate actions. There is a notable difference here; see the in vitro study above where the interactions were thought to be simple summation.

Many further combinations were studied over the next five years; in 1986 the time intervals measured from the administrations of either atracurium or vecuronium to maximum or 95% neuromuscular blockade (T_{max}) were compared [30]. There was no significant difference when equipotent doses were compared. The electromyographic and mechanical responses of the adductor pollicis were compared during the onset of neuromuscular blockade by atracurium or alcuronium and during antagonism by neostigmine [31]. In 1987 the effects of atracurium and vecuronium, on the latency and the duration of the negative deflection of the evoked compound action potential of the adductor pollicis[32] and the interaction of adrenaline with neostigmine and tubocurarine were investigated[33], as was the economy of using vecuronium as a 'top-up' agent to pancuronium, to facilitate a cleaner/faster recovery[34]. Once a top-up was deemed necessary at least forty minutes had to elapse before the improved offset time was assured. A similar paper using atracurium or vecuronium to prolong the action of tubocurarine was also published[35]…it was not anticipated that both curare and pancuronium would disappear from routine anaesthetic practice. In the very early 1990s pipecuronium became available and so investigations on this new agent began. A dose response relationship was then constructed from which ED_{90} and ED_{95} values were measured and again small increments of atracurium or vecuronium (or pipecuronium) were administered

[36]. Once again the duration of the block following atracurium or vecuronium became progressively less with subsequent increments until steady state was reached. To the best of my knowledge pipecuronium is no longer used!

In a paper that stands alone, in1989, the remarkable variation in the dose-response properties of suxamethonium were highlighted, a dose of 0.3 mg/kg produced a range of blockade from 4%–90% and body surface area was shown to be more significantly related to blockade than lean body mass[37].

In 1995 the research took a slightly different approach, it was decided to identify adequate recovery from sub-paralysing doses of pipecuronium in conscious volunteers [38]. All volunteers experienced ptosis, diplopia, and difficulty in swallowing and experienced a pleasant, relaxing, sedative sensation. Except for one patient all could sustain head lift for 5 s at a TOF ratio of 0.5 and higher. All the measured respiratory variables returned to control values at a TOF ratio of 0.9. The conclusion drawn was that head lift was not a more sensitive index of recovery of neuromuscular block than a normal twitch height as was previously published[iv]. This work supported the work of several other groups[v].

To finish off this gallop through a platoon of muscle relaxants, some now definitely dead, was the study of a new agent, in 1995, rocuronium – a survivor. Intubation conditions, at 60s post-injection, using a small dose of rocuronium (0.45 mg kg^{-1}) was compared with equipotent doses of atracurium and vecuronium for ease of intubation[39]. Excellent or good conditions were more common with rocuronium and a year later rocuronium was compared with atracurium and vecuronium again, this time for use in dental day-case surgery [40]. The percentage of good or excellent intubating conditions at 60 seconds was 80% for rocuronium but only 12.5% each for atracurium and vecuronium. Another advantage was that the duration of action of rocuronium was shorter than either atracurium or vecuronium.

[iv] Miller RD. Antagonism of neuromuscular blockade. Anesthesiology 1976; 44: 318-329.
[v] Mahajan RP, Laverty J.British Journal of Anaesthesia 1992; 69: 318-319.
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Pharmacology (mixed):

There are almost forty papers on various aspects of pharmacology and anaesthesia related drugs, three will be addressed.

Chronic exposure to anaesthetic agents was a major interest in the late 1970s and the effect on rats was investigated [41, 42]. Halothane and the liver was also a hot topic at the time[43] and later the more subtle effects on mood and cognition[44], however this was in a an actively scavenged theatre.

Pregnant rats were exposed to trichlorethylene in a concentration of 100 ppm; this concentration had been reported in operating theatres[vi]. The results were an associated reduced foetal weight and an increase in the number of foetuses resorbed. The 1982 paper found no evidence of teratogenesis, but a delay in foetal maturation. There was also an increase in bipartite or absent skeletal ossification centres.

By 1988 operating theatre conditions had changed, passive or active scavenging of exhaled anaesthetic gases was common. Anaesthetists were studied in a cross-over design so that each anaesthetist worked one day in a reference facility (for example, intensive care) and another day in a scavenged operating theatre. The time-weighted exposure averaged nitrous oxide 58 ppm and halothane 1.4 ppm. The conclusion reached was that the exposure to anaesthetic agents in actively scavenged operating theatres had no detrimental effect on mood or cognitive function, a welcome negative outcome.

Ketamine was a popular intravenous anaesthetic agent and was well known for its sympathetic activity. Its effects on rat smooth muscle[45], transmission in sympathetic ganglia[46] and on cardiac and smooth muscle were all studied[47]. The rat and guinea pig models, for many interactions of an autonomic nature, were well known and utilised in the Department in Nottingham.

The effect on sympathetic ganglion transmission was dose-dependent depression in the response to preganglionic stimulation and the anti-cholinergic activity of ketamine was confirmed using the frog isolated rectus abdominis. The

[vi] Corbett TH. Anesth. Analg. Curr. Res. 1973;52, 614-617.

effects on cardiac and smooth muscle to exogenous norepinephrine were reported and low concentrations of ketamine significantly potentiated these effects. High concentrations depressed the response to sympathetic nerve stimulation. Spontaneously beating right atria were slowed by ketamine. In the presence of reuptake blockade of norepinephrine by pancuronium, ketamine caused no further potentiation of the response of the vas to nerve stimulation; a complex picture.

Many comparative studies of analgesics were undertaken [48-60], meptazinol, alfentanil, nalbuphine, controlled-release morphine, sufentanil, diclofenac and nefopam. Other pharmacologically orientated publications are listed[61-72] ranging from the antibacterial properties of local analgesic agents to a comparison of anti-emetic drugs used alone or in combination, from canine gastrointestinal motility to the effect of oral doxapram on morphine-induced changes in the ventilatory response to carbon dioxide; a wide and varied collection.

Equipment

The work of breathing through anaesthetic breathing equipment and the fresh gas flow requirements for an 'enclosed afferent reservoir breathing system' were two topics that occupied a dozen papers.

First of all there was an assessment of a Blease ventilator[73] and then the Carden[74], then the work of breathing through breathing systems[75] and adult endotracheal tubes[76, 77] (and later paediatric tubes[78]); the main purpose here was to suggest that that work was a better measurement for the comparison of endotracheal tubes of different sizes than resistance to flow. The assessment of an enclosed afferent reservoir (EAR) breathing system developed by Ohmeda came next in 1991[79]. Further works along this line of enquiry (fresh gas flow / rebreathing / paediatrics / spontaneous respiration) are to be found in papers from 1992/3 [80-85] and another paper on the Carden ventilator[86] in 1994.

Over the years there were a variety of other subjects of enquiry, blood warming[87, 88], fluid administration sets[89], jet ventilation down a

bronchoscope[90], the arterial tourniquet[91] and intracranial pressure measurement[92].

One particular aspect that interested Tom over a period of time (1984-90) was patient posture and comfort [93-95]. The latter study comprised a mathematical model for appropriate support pressure and a study to assess the role of an inflatable lumbar support. The use the support reduced the incidence of back pain by 50%. Previous back pain or arthritis, and procedures lasting more than 40 minutes, were associated with severity and an increased incidence.

Miscellaneous

In addition to the above papers were review articles[91, 96, 97], books[98-100] and commentaries[101-104].

In the latter group 'The Mancunian Way' describes the earliest records of the administration of ether in Manchester. As usual for the early days of anaesthesia there was competition to record who was first, Charles Strange, a dentist and chemist, and George Bowring, a surgeon, were the contestants.

In a letter on clinical freedom Tom expresses some forthright views on clinical freedom. To quote

> "Clinical arrogance protected or justified by a conviction in the mystic rights of clinical freedom, lies at the basis of many serious omissions or errors in patient care. Clinical freedom is the opportunity, guarded by our profession, to practise using the precautions that are correct and appropriate to the knowledge of the era in which we live. Clinical freedom may reasonably be compared with civic freedom and requires the same responsibility and the right to live and work within defined rules, rules defined not by the individual but by responsible authority."

He was commenting specifically on the current vogue for 'poor' airway management during laparoscopy and 'absentee' anaesthetists (novices left to manage the patient).

> "Each one of us certainly knows whom we would trust, or not, to anaesthetise our own mother or spouse. It is this choice which is the most formidable peer review. Clinical freedom for our profession proceeds from responsible behaviour by each and every individual so that it remains not only correct to defend it but ensures that it is worth defending, as the freedom to do what is right, to differentiate between the good and the bad and the freedom to choose within the limits that the body of our profession prescribe for us."

On the eve of the new millennium Tom completed his time as editor in chief of the European Journal of Anaesthesiology and in his final editorial comments he again addressed the nature of Freedom, quoting Pope John Paul III's Address to the United Nations General Assembly.

Apart from research activities Tom is the ultimate committee person, he is able to keep talking until all others give up and give way! He was responsible for the organisation of teaching attachments and rotations in and around Nottingham and for the development of the research department there. It was unfortunate, for Nottingham that he had to go to Manchester to be given a chair.

Tom has many stories; particularly of his academic travels…one might be wary of travelling with him! At a low point, near the end of his time in Nottingham, he thought he was never going to be offered a chair, and then he was. He was really happy, overjoyed. A few days later he was down again…he had been offered a second chair! He now had to decide which one!

I was really blessed with Tom as my mentor.

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Gavin NC Kenny

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 [i]

Gavin Kenny trained in Glasgow; became a Lecturer in Glasgow (1977), and Senior Lecturer in Glasgow (1982) and he was Head of Anaesthesia at HCI International Medical Centre, Clydebank, Glasgow from '93-'96. Subsequently he became Professor and Head of the University of Glasgow Department of Anaesthesia. To paraphrase information from the Society for Intravenous Anaesthesia's website one of his most significant achievements was the development, in collaboration with Dr Martin White, of systems for Target-Controlled Infusion of Propofol, Alfentanil, Remifentanil and other Intravenous Drugs. [ii]

Gavin Kenny was awarded an MD for his thesis on "The Application of Microcomputers to Anaesthesia and Intensive Care". The personal computer had just come of age, the Apple II having been launched in 1977, the BBC microcomputer in 1981. Kenny was there to take up the challenge of computers in association with anaesthesia from the very beginning.

His work can be easily divided into those including the word "calculator"[1] or "computer " [1-22]; closed loop [17-19, 23-39] target controlled infusions [21, 22, 24, 26, 27, 29-76] and in addition those involving auditory evoked potentials, BIS or the EEG [32, 34, 38, 39, 53, 56, 60, 73, 75, 77-85].

To begin…the first paper published was on a completely different subject… "The anion permeability of frog skeletal muscle in fluoride solutions." This must have been part of his intercalated BSc (honours) degree in physiology that he gained in 1970… "The notion that F^- itself cannot pass through the

[i] Photograph courtesy of Dr Douglas Russell - Past President, the Society for Intravenous Anaesthesia

[ii] http://www.rpdpublications.eu/SIVAUK/GavinKenny.htm

membrane is, of course, compatible with its greater 'hydrated radius' (roughly 1-4 times that of Cl^{-1}); further, it may in turn explain why so normally toxic an ion is tolerated so well by the muscles."

We will move on; it was another nine years before the next publication: "Programmable calculator: a program for use in the intensive care unit."[1]. Using the Texas TI59 calculator he was able to determine physiological parameters that might be helpful in the ICU setting; oxygen availability, deadspace and shunt fraction, and the FiO_2 required to produce a desired PaO_2. There were two more computer-based papers that year and one in 1980. They were on the topic of computer-assisted learning… the computer either controlled slides or a videocassette [2, 4], their efficacy and acceptability by students and anaesthetists was assessed [3, 86]. This was a popular topic at the time but does not seem to have maintained an overt presence in anaesthesia training. This was followed up two years later where a larger assessment (of 202 anaesthetists) was made of its use as a form of self-assessment for continuing professional development, its acceptability to the users was high – 91-100% in the four trial groups studied[6].

1984: anaesthetic records were now the topic for development… using an Apple II a record system could be set up using a light pen for data entry[8, 87] and even the downloading of data from a non-invasive blood pressure device for analysis or printing later (" …a complete anaesthetic record")[9] and a coloured trend graph could be displayed. We have to be careful not to scoff! These were days when 128K of RAM was really good.

In 1985 we now come to the beginning of the use of microcomputers for serious clinical applications[10]

There was great interest in automated (robotic) control of anaesthesia and closed-loop control of drug infusion was an important sector in this field. However it was necessary to learn how to communicate with the effector devices. The first publication was titled; "The aim was to provide a simple method of conducting the required communication between the computer and the [IMed infusion] pump using a high-level language. " The computer and the pump had to talk to each other. This was published in the Journal of Medical Engineering & Technology and so was unlikely to pass the radar of most

anaesthetists. This was followed by another paper in the same journal in the following year… "A standard microcomputer linked to a volume-controlled infusion pump for patient-controlled analgesia research."[11] It was designed as a patient controlled analgesia (PCA) device and was capable of storing, plotting and analysing data. A similar project was completed with a Braun pump [12]. In 1987 feedback to the patient using a PCA (an indication of the device being activated) was given by a voice synthesizer[88]. It was recorded that, of those patients who expressed a preference, the majority preferred the voice rather than a buzzer.

Closed loop control was still someway off.

1986, an Apple II computer was used to monitor patients with an epidural and the depending on the manual input of data about the administration of a dose of local anaesthetic or vasoconstrictor, it would change the frequency of blood pressure measurements [13].

The following year a true closed loop system was tried[23]. Reid and Kenny compared the closed-loop control of arterial pressure after cardiopulmonary bypass with manual control by a nurse. The drug used was nitroprusside (SNP) and the control was shown to be better using the computerised method. In 1982 Mitchell had described the need for such a system because of the amount of time a nurse spends adjusting the infusion rates.[iii]

This was followed in 1988 - 9 by five further studies on postoperative cardiac patients [17-19, 24, 25]. The first study involved the simultaneous infusion of an opiate and a vasodilator; the computer-controlled closed loop system was set to maintain a target arterial pressure, which was maintained longer in the group receiving alfentanil (cf. morphine).

The first paper in 1989 [17] is a technical description of their system which involves safety features and artefact rejection software. “A novel feature of this system is the clinical staff's use of a "mouse" to enter data and control the program, which makes keyboard skills unnecessary.” It was evidently in routine use in the cardiac intensive care unit. The ‘mouse’ was relatively unknown until taken on by Apple for use with the Macintosh. The early version was released in

[iii] Mitchell RR. Crit Care Med. 1982 Dec; 10(12):831-4.

1983 with the Apple Lisa. The next [18], went one step further; the computer, an ATARI 1040ST controlled two IMED 929 infusion pumps. One contained GTN and the other sodium nitroprusside. Half of the patients' vasodilator requirements were satisfied with GTN alone and the others required supplemental SNP. This publication was duplicated in the journal *Anaesthesia* [19]. The third paper [25] compares manual control of vasodilator infusions with computer assisted and closed loop control…the conclusion was that closed loop control was better than manual control but that the control achieved by nurses using a clear graphical display of their performance was not significantly different to the closed loop control.

In a way not dissimilar to the use of PCA devices to determine the morphine-sparing effect of non-opiate analgesics Kenny used the closed loop control system to evaluate the hypo/hypertensive effects of a supplementary agent, enoximone [26]. It was found that there were no significant differences in the amount of sodium nitroprusside required to maintain control and therefore that enoximone was not associated with a clinically significant effect on systolic pressure.

From the post-cardiac surgery control of blood pressure they moved onto the control of blood pressure during induced hypotensive anaesthesia [27] and during neurosurgery [29]. It was also used in conjunction with sedative agents (propofol and midazolam) [28]. "Future applications for TCI [target controlled infusion] systems" was the subject of a paper in 1998 [31]; this outlined the future of infusion pumps with algorithms for the delivery of analgesic and sedative agents, the 'Diprifusor ™' was the named product.

A significant shift now occurred, 1999; the subject of the publication was the closed-loop control of propofol anaesthesia using audio-evoked potentials [32].

They (Kenny and Mantzaridis) used the auditory evoked potential index (AEPindex) as a measure of depth of anaesthesia. The evoked potentials were processed in real time and used in a proportional integral controller to induce and maintain general anaesthesia. The technical details are complex and are well described. The propofol infusion was only part of the anaesthetic; the complete anaesthetic included an intravenous infusion of alfentanil and inhaled nitrous

oxide. The patients were all spontaneously breathing patients but at least 20% required assisted ventilation. There was no incidence of intra-operative awareness, cardiovascular stability satisfactory and movement minimal.
The authors claimed this to be the first report describing closed-loop control of anaesthesia in spontaneously breathing patients. It was also thought that it validated the value of the AEPindex as a measure of depth of anaesthesia (for propofol).

The next series of papers in this field were published in 2002 [33-36]. One, with Absalom as the primary author, used the BIS (Bispectral Index – another measure of anaesthetic depth) together with a proportional-integral-differential control algorithm. The analgesic part of the anaesthetic was an epidural, the patients having hip or knee surgery. The sedation was started manually with a TCI and passed to automatic control when settled. "The median performance error and the median absolute performance error were 2.2 and 8.0%, respectively." The technique provided adequate anaesthesia in 9 out of 10 patients and amongst other suggestions for improvement was the use of effect site-concentration instead of the current blood concentration target-controlled infusion system.

Another BIS paper (Leslie as primary author) studied sedation for colonoscopy. Patients were reported to be drowsy yet rousable, no patient became apnoeic. "Patient and surgeon satisfaction were high."

Another, with Bothtner as primary author, is a landmark study in the attempt to understand how to manage combinations of drugs (opiates and hypnotics). The models for these combinations are alinear and they approached the problem using a Bayesian based algorithm. On top of a target-controlled propofol infusion remifentanil (a very short acting opiate) was infused in a way to achieve three fixed target concentrations. The concentrations of propofol were controlled according to the closed-loop system feedback of the auditory evoked potential index. To paraphrase one of their statements…the model building with Bayesian networks represent true features of the represented data sample and promise to be versatile tools for building valid, nonlinear, predictive instruments to further gain insight into the complex interaction of anaesthetics.

The final one for that year was a letter to Anaesthesia regarding the use of total intravenous anaesthesia using propofol and remifentanil for liver resections…they used the AEPindex. They stated that it resulted in less blood loss, rapid recovery and no need doe ICU care postoperatively, the median blood loss being 615ml.

The most recent studies in this series [37-39] continue the trend and we are moving out of the 1950-2000 timeframe. However, the last paper investigates "The contribution of remifentanil to middle latency auditory evoked potentials during induction of propofol anesthesia." There is ongoing debate about whether opioids effect AEPindex or BIS; they showed that remifentanil alone did not seem to effect the auditory evoked response but it did decrease the amount of propofol effect site concentration required for unconsciousness as measured using this closed-loop control methodology.

In 2011 it is disappointing that closed-loop control of anaesthesia is still in the realm of academia.

Empirical pharmacokinetic studies

Behind these clinical applications of computer controlled infusions was a large body of work of empirical importance; studies on pharmacokinetics, data entry/collection, and evaluation of the impact or acceptability of the systems used.

Below are a few examples…

The difference, in a computerised propofol infusion system, for patients breathing spontaneously or receiving intermittent positive pressure ventilation [21]; the relationship between blood concentration and predicted concentration were statistically similar.

An index analogous to MAC (Minimum Alveolar Concentration of inhaled anaesthetic agents) has been wanted for intravenous anaesthesia. In 2000 the concentration of propofol required to prevent response to a surgical incision was determined [66]. The ‘standard’ MAC definition is the concentration of the agent that prevents movement to a standard surgical stimulus in 50% of patients. This was done with propofol although it is not an analgesic…. “the calculated blood concentration at which 50% of patients responded … was 6.8 micrograms ml-1

for patients who breathed oxygen-enriched air and 4.9 micrograms ml-1 for those who breathed nitrous oxide 67% in oxygen."

The statement that all patients are not the same when it comes to drug requirements is a gross understatement and that is why anaesthesia has been seen as the art of titration, give a dose and see what happens and then respond accordingly. In 2008 there was an attempt to derive the covariates for age and gender so that an improvement in the infusion algorithms for propofol could be improved [76]. The 'pharmacokinetic accuracy' was determined by the percentage prediction error, bias and precision, as were wobble and divergence; nonlinear mixed-effects modelling (NONMEM) was used. The results were complex but they "achieved a relatively simple and practical covariate model". Simulation using this model improved the performance of the TCI system, especially in elderly female patients.

Computers and education

For a decade 1979-1989 there was a flurry of papers on the use of computers in teaching [2-4, 6, 14, 86, 89, 90].

These papers are possibly the most dated as information technology has changed so much since the last paper in 1989 [90]. "Information technology in postgraduate medical education." It was stated; "information technology in postgraduate medical education has developed rapidly over the last 5 years"… the internet revolution didn't even start until 1993/4. They described the setting up a of a computer-based information system in postgraduate centres in the West of Scotland with a viewdata service, library facilities, computer-assisted learning, word processing, and statistics and an electronic mail system provides rapid communication between users. This was very much state of the art stuff.

Miscellaneous 'other' clinical publications

There are number of publications with Kenny's name attached of the normal clinical variety [42, 51, 91-112].

Let's just look at a few.

Akthar et al [42] studied one hundred patients, opioids were not used. One set of patients received 60% nitrous oxide in oxygen, the other 100% oxygen, all received a propofol infusion. There was no statistical difference in the nausea and vomiting rates. It would have been better if the 100% oxygen group had had an oxygen/nitrogen mixture.

Turfrey et al [51] compared the postoperative outcomes of patients having coronary artery surgery, one group had a thoracic epidural, all patients had a general anaesthetic (propofol/alfentanil). Those patients in the epidural group had about half the incidence of new arrhythmias (18% vs. 32%) and a trend towards a lower incidence of respiratory complications. Extubation times were much shorter.

McLintock et al [98] studied the power of intra-operative positive suggestions on postoperative pain. A tape was played during gynaecological surgery, one was blank, one had positive suggestions, and pain management after the abdominal hysterectomy was provide by a PCA device. Their results were that although the pain scores were similar in both groups the positive intra-operative suggestions reduced morphine requirements.

Gajraj et al [112] examined the antibacterial effect of lidicaine (lignocaine) when added to propofol (for the amelioration of pain during intravenous injection); the more lidicaine, the fewer the number of bacterial colonies. However not all organisms were susceptible.

Kenny has produced, or been involved with the production, of a huge amount of research that has been translated into practical clinical techniques. Propofol and analgesic infusions are now routine in the practice of modern anaesthesia and he and his co-workers have much to be proud of.

GNCK, a keen sailor, named his boat Æther (not totally appropriate for an intravenous anaesthesia advocate) and is a Past Commodore of the Serpent Yacht Club[iv]

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British Academic Anaesthetists

1950-2000

Anaesthesia in 1950 was basic, ether and chloroform still in use. Monitoring was, apart from the senses of sight, hearing, smell and touch, minimal. Over the next half century huge, unimaginable, changes took place and many anaesthetists in various countries led the way.

This book tries to highlight some of the British academic anaesthetists who did research during this time. Fifteen individuals, who worked with many others, to unravel the intricacies of physiology and machinery have been selected.

Subsequent volumes will highlight the work of others; those who worked with them must not be forgotten and there are many of them.

Michael Harrison, a graduate of Newcastle-upon-Tyne, started a career in anaesthesia in 1971 in Nottingham. Over sixteen years as an anaesthetist in the UK he attended many Anaesthesia Research Society meetings and was privileged to see and hear many of the academics referred to.

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