

J. G. WHITWAM

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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

ⁱ Nunn JF. B.J.A. 1999;83:916

findings but a fourth paper on the detailed observation of 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.

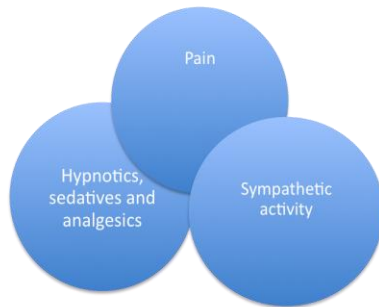
Flumazenil (a benzodiazepine antagonist) arrived on the scene and in 1988 Whitwam wrote on this novel agent in a variety of journals and became its mouthpiece in British anaesthetic circles [38-42, 46, 48-50].

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].

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.

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.

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.

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 not discussed 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 CO₂ 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. In 1993 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], chondrocalcinosis 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 figureⁱⁱ.

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

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ⁱⁱ Obituary: <http://www.guardian.co.uk/theguardian/2010/jan/05/joe-whitwam-obituary>

ⁱⁱⁱ Day-Case Anaesthesia and Sedation; Principles and Practice of Sedation with RF McLoy; Day Case Anaesthesia; Anaesthesia: v. 1: Topical Reviews with J Norman; Outpatient with SK Kallar; Quality Control in Endoscopy: Report of an International Forum held in May 1991

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