Ron M Jones
MD FRCA

As an anaesthetic trainee Ron Jones went to the University of Michigan and wrote his first paper whilst there; he was first author, “Narcotic-induced chole-dochoduodenal sphincter spasm reversed by glucagon” [1]. This was followed by another on the same topic [5]. He maximised his opportunity as there was a third paper published on the topic of “Use of pentolinium in postoperative hypertension resistant to sodium nitroprusside” [6]. His experience of working there is described in the journal Anaesthesia in 1981 [12].

He returned to the UK and worked in Nottingham as a senior registrar. With Tom Healy he wrote a review on the subject of “Anaesthesia and demyelinating disease” [2]. He soon became a consultant and was determined on an academic career.

Jones became senior lecturer at Guy’s in 1982 and became the foundation professor of anaesthesia at St Mary’s Medical School in 1990, a college of Imperial College. The rearrangement of the various London establishments was complex.

In the years 1981, 1982 (a quiet year), 1983 and 1984 thirty three papers were published; a prodigious amount and indicative of his determination. This was to be the peak of his productivity.

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1 J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916
Types / Subjects of publications

**Neuromuscular (excluding case reports)**

1983: [20] The rat phrenic nerve diaphragm was a common preparation used in the Nottingham academic department. This study was with Brian Pollard. The synergism of mixtures of tubocurarine and pancuronium and tubocurarine and alcuronium were demonstrated but a mixture of alcuronium and pancuronium was not synergistic. Synergism would become a significant feature of Pollard’s work.

1983: [19] This letter pointed out an error of interpretation by Donati, Ferguson and Bevanii of a paper published by Williams, Webb and Calveyiii. An interesting start to the study of neuro-muscular blockade; at least it demonstrated their understanding of the physiology. Jones was at Guys Hospital when this was published.

1984: [30] Edrophonium reversed atracurium neuromuscular blockade more rapidly than neostigmine when 21 patients were studied. “A $T_4$ ratio of 0.5 was confirmed to be compatible with the reliable and safe reversal of atracurium - induced neuromuscular blockade”. A sustained 5s

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ii Donati F, Ferguson A, Bevan DR. Anesth Analg 983;62:3146

iii Williams NE, Webb SN, Calvey TN. Br J Anaesth 1980

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head lift was one parameter of adequate recovery. More recently 0.7 or even 0.9 have been recommended.


1985: [46] “Factors affecting train-of-four fade”. This study suggested that a fixed T4 ratio (a measure of fade) may have different consequences with different drugs; it was said that it was the absolute height of the fourth twitch that determined sustained muscle power.

This was the opening article that preceded a series of studies on fade; fade being the difference between the magnitude (height) of the first twitch of the train of four and the fourth [38, 54, 55].

1985: [38] This was about the onset of neuromuscular block with pancuronium, tubocurarine and a mixture of them. Four indices of onset were defined. “The mixture had the most rapid total onset time (100.3s), tubocurarine the slowest (135.1s) and pancuronium was intermediate (124.0s)”.

1987: [54] “Relationship between single twitch depression and train-of-four fade: influence of relaxant dose during onset and spontaneous offset of neuromuscular blockade.” This study demonstrated that during block onset there was “a variable and dose-related relationship between the ratio of height of the initial twitch, T1, and fourth twitch, T4.” During recovery the same T1 values were associated with similar degrees of fade. The T4 ratio during recovery bore a fixed relationship to the initial T1 depression. (Does this mean that only T1 needs to be monitored?)

1988: [55] “Fade profiles during spontaneous offset of neuromuscular blockade: vecuronium and gallamine compared”. They studied the onset and the spontaneous offset of neuromuscular blockade using vecuronium and gallamine. Gallamine produced significantly more fade than vecuronium but there was less fade during onset than offset.

What was the clinical significance of these results?
The remaining studies of neuromuscular blockade are of a heterogeneous mixture.

1985: [41] This review covered the new agents atracurium and vecuronium and highlighted the importance of calcium and calmodulin in neuromuscular physiology.

1986: [47] The reversal of neuromuscular blockade due to atracurium with edrophonium or neostigmine was measured. Edrophonium produced a significantly faster reversal than the small dose of neostigmine but a larger dose produced a reversal time close to edrophonium. So much research was done using edrophonium but, in the author’s experience, it was rarely if ever used clinically.

1986: [48] The onset of neuromuscular block with vecuronium was quicker with doses up to ED95 x 3; higher doses did not. The pharmacokinetics was discussed.


1989: [56] “Atracurium recovery: prediction of safe reversal times with edrophonium”. Safe reversal at this time was thought to be when the T4 ratio was greater than 0.5; this is very low by today's standardsiv. The study demonstrated the ease of reversal of atracurium as long as the procedure lasted 30 minutes. It was said that “if no monitoring equipment [was] available, at least half-an-hour should elapse after administration of atracurium ... before rapid and reliable reversal [could] be anticipated.”

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iv Kopman AF. Residual neuromuscular block and adverse respiratory events. Anaesth Analg 2008;107:1756
Nerve stimulators were rarely available and if they were they were of a hand-held type, operated manually and usually when recovery was not as anticipated.

1990: [60] “Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function”. The maximum block and time to achieve it were similar in the two groups but the duration of action of doxacurium was longer in the renal failure group (not significant considering the size of the study). Spontaneous recovery was not significantly different.

1991: [67] A case report: “Resistance to atracurium in a patient with an increase in plasma alpha 1 globulins”. It was thought that this was due to binding of the drug to the protein.


1994: [78] “Safety and potency of ANQ 9040 in male volunteers”. This was a collaboration with Donati whose interpretation of previous work was criticised ten years earlier. ANQ 9040 was an experimental non-depolarizing neuromuscular relaxant. It was thought to have a quick onset time similar to suxamethonium. The estimated ED95 of ANQ was 1.3 mg/kg. No important adverse occurred but there was an increase in plasma histamine associated with a decrease in mean arterial pressure and a significant increase in heart rate. The onset time to neuro-muscular block was 51.3s. The histamine release suggested that it would not be clinically useful.

Let’s go now to the studies of cardiovascular content.

**Cardiovascular** (excluding case reports)

“Rate pressure product” [3] 1980 (a letter): The RPP was one of the earlier indices used in anaesthetic clinical practice – the goal was to avoid the systolic blood pressure x heart rate exceeding a certain value – for the patient with ischaemic heart disease it could be as low as 12000. So a
blood pressure of 120mmHg x heart rate of 100 bpm would be borderline.

“Cardiovascular responses and changes in plasma cation levels associated with infusion of hyperosmolar urea solutions” [11] 1981 (1981 was a very busy year). A hyperosmolar urea solution used to decrease brain volume caused hypotension and decreasing levels of ionized calcium. This was studied using dogs. There were significant reductions in arterial pressure, systemic vascular resistance, hematocrit, and levels of plasma sodium and ionized calcium. Cardiac output, right atrial pressure, arterial pO₂ and pCO₂ and plasma potassium all increased. These were considered important effects.

“Anaesthesia in first-degree atrioventricular block” [15]; letter. This was a strong criticism of the anaesthetic used for a patient with first-degree atrioventricular block – and, this was in 1983 – Jones still thought it necessary to advocate the routine use of electrocardiography during anaesthesia.

“Renin-angiotensin activation is not primarily responsible for the changes in mean arterial pressure during sternotomy in patients undergoing cardiac surgery” [23] 1984. The bottom-line was that giving an angiotensin converting enzyme inhibitor did not change the cardiovascular response to sternotomy.

“Nifedipine and cardiopulmonary bypass. Post-bypass management after continuation or withdrawal of therapy” [24] 1984. One group of patients had nifedipine withdrawn prior to cardiac surgery, another continued therapy, and there was a control group. Vasodilator intervention was required more in the ‘withdrawn’ group. This reduced the need for inotropic support but systemic vascular resistance was increased. It was recommended that nifedipine should be continued.


“Calcium antagonists” [28] 1984; an editorial.
“Cardiac rate and rhythm during anaesthesia for dental extraction. A comparison of halothane, enflurane and isoflurane” [39] 1985. Halothane had the highest rate of arrhythmia. Heart rates were highest in those patients given isoflurane, lowest with halothane.

**Inhalational agents**

1984: “Clinical comparison of inhalation anaesthetic agents” [16]. This is a lengthy review-type article.

1985: “Anaesthetic carrier gases. Their effect on middle-ear pressure peri-operatively” [45]. The middle ear pressure was measured with a self-calibrating device fitted into the external auditory meatus. The anaesthetic carrier gas was oxygen, oxygen-enriched air or nitrous oxide. Only nitrous oxide caused pressure change and it was recommended that oxygen-enriched air was the carrier of choice.

1990: “Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers” [64]. An early study of desflurane; inhalation of the anaesthetic was accomplished without coughing, breath-holding or salivation. Respiratory and cardiovascular parameters were recorded and it was noted that after 90 minutes of anaesthetic exposure there was a rapid and clear-headed recovery.

1990: “Kinetics and potency of desflurance (I-653) in volunteers” [63]. It was predicted that desflurane should cause rapid induction and recovery from anaesthesia. The MAC was estimated at 5%. In the study it was shown that after 10-minutes the alveolar to inspired concentration was 0.82. Ten minutes after cessation of desflurane the alveolar concentration fell 89%. Recovery was such that response to commands occurred about 2.7 minutes after cessation. MAC-aware was 2.42% and MAC 4.58%.

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\(^{v}\) The reference year in the Medline database was incorrect.
1990: “Biotransformation and hepato-renal function in volunteers after exposure to desflurane (I-653)” [65]. Volunteers were exposed to (on average) inspired concentration of 3.6% for (on average) 89 minutes. A huge array of tests were carried out but there “were no significant changes in any measured haematological or biochemical variable”.

1990: “Desflurane and sevoflurane: inhalation anaesthetics for this decade?” [61]; a review.

1991: “Induction and recovery characteristics of desflurane in day case patients: a comparison with propofol” [68]. Sixty patients were allocated to receive either desflurane or propofol. Loss of consciousness with desflurane induction occurred in approximately two minutes. Psychomotor scores were worse in patients given propofol which suggested that desflurane would be suitable for day case anaesthesia.

1991: “A prospective study of liver function in infants and children exposed to daily isoflurane for several weeks” [66]. Daily radiotherapy was the reason for the daily anaesthesia. There were no measurable changes in the liver function tests.


1992: “A national database on hepatitis after exposure to inhaled halothane” [69]; a letter. The idea of having a database, which Kenna and Jones would create, of patients suffering from ‘halothane hepatitis’ was to enable a study of the genetic make-up of those susceptible.

1992: “Recovery characteristics using isoflurane or propofol for maintenance of anaesthesia: a double-blind controlled trial” [70]. One hundred and fourteen patients were studied; anaesthesia being induced with propofol. Atracurium was given and nitrous oxide in oxygen. Some patients received isoflurane and alfentanil (bolus + infusion). Other patients received propofol with alfentanil as an infusion. There was a control group of subjects who did not have an anaesthetic. “There were no significant differences in awakening or orientation times” or psychomotor
testing during recovery. There were significant differences with the control group. The techniques used were all acceptable.

1995: “Is there a need for a new inhalational anaesthetic agent?” [82]; this is a discussion on the development and merits of new agents which, in this case, is really about the properties of desflurane. Its sympathetic autonomic effect makes it less than perfect.

1995: “The organ toxicity of inhaled anesthetics” [83]. This was in an Anesthesia and Analgesia supplement devoted to the pharmacology of sevoflurane; it has 143 references and covers all aspects of the subject. Sevoflurane compared favourably, it was thought that there was a low rate of metabolism because of its low tissue solubility and that the metabolic processes did not produce reactive metabolites.

1995: “Serum fluoride concentration and urine osmolality after enflurane and sevoflurane anesthesia in male volunteers” [84]. The study involved giving the anaesthetics for a variety of MAC hours (minimum alveolar concentration x duration). There was an 18-h post-anaesthesia period of fluid deprivation during which the serum fluoride concentration was measured. Sevoflurane resulted in the greatest serum fluoride concentration which reached a peak in the 9-MAC-hour group. There were no significant differences between enflurane or sevoflurane anaesthesia and it showed that prolonged administration of enflurane or sevoflurane is not associated with impaired renal function.

And finally, the ‘thorn in the foot’ of sevoflurane -

1996: “Sevoflurane degradation by soda lime in a circle breathing system” [85] Compound A, a vinyl ether, is the end product sevoflurane degradation by soda-lime. Using gas chromatography and a flame ionisation detector Compound A concentration was measured. “It ranged between 10 to 32 ppm in the inspiratory limb and 7 to 26 ppm in the expiratory limb.” The temperature of the soda lime and the end-tidal concentration was positively correlated with the amount of Compound A.
Smoking
1984: “Smoking and anesthesia: preoperative abstinence and perioperative morbidity” [32]. This seems like a discussion document. What are the risks of stopping smoking in the short period before operation? Carbon monoxide and nicotine elimination, improved ciliary beating and reduction in sputum volume may enhance well being. “There are no proven disadvantages to the respiratory system from stopping smoking in the short term, and it seems unwise to sacrifice proven advantages for a theoretic consideration that sputum may become "stickier" and more difficult to clear.”

1985: “Smoking before surgery: the case for stopping” [42]. This was an editorial type article. Its conclusion was that “...roughly six weeks after stopping smoking patients may expect an improvement in pulmonary function, a reduction in postoperative respiratory morbidity, and a return towards normal immune responses. If, however, patients cannot be persuaded to stop smoking for this period (or permanently) considerable benefit will still accrue from the improvement in cardiovascular function brought about by even 12 to 24 hours of abstention from smoking - a factor of particular importance in patients with ischaemic heart disease.”

1993: “The effectiveness of preoperative advice to stop smoking: a prospective controlled trial” [74] The advice was ineffective. However, it did reduce the amount of tobacco consumed. But more than a sixth of all patients smoked within an hour of surgery.

Analgesics
1981: “Prevention of rigidity during fentanyl-oxygen induction of anesthesia” [4]. Patients undergoing coronary artery surgery were given 2500µg of fentanyl for induction of anaesthesia and rigidity occurred (hampering manual ventilation) but was ameliorated if pancuronium was given at the same time.

1984: “Naproxen pharmacokinetics in the elderly” [34]. Plasma clearance/bioavailability was found to be less in the elderly than in a
younger group and the fraction unbound was doubled; this relates closely to the toxic effect. Significant dose reduction was advised.

1985: "Parenteral aspirin for pain relief in day-case dental anaesthesia. A randomised double blind placebo controlled trial" [40]. Patients received either lysine acetylsalicylate intravenously or a placebo. Patients given lysine acetylsalicylate had better recovery overall but there were no statistically significant differences in pain scores. This was accompanied by a "Comparison of infusions of morphine and lysine acetyl salicylate for the relief of pain after surgery" [37] and "Comparison of infusions of morphine and lysine acetyl salicylate for the relief of pain following thoracic surgery" [44]. Lysine acetyl salicylate provided analgesia equal to morphine. There was less drowsiness, nausea and vomiting. There were no untoward side effects.

1994: “Comparison of desflurane and fentanyl-based anaesthetic techniques for coronary artery bypass surgery” [79]. This was a comparison between desflurane and fentanyl vs. high dose fentanyl. With desflurane the mean arterial pressure was maintained during incision and sternotomy but decreased afterwards. Fentanyl maintained arterial pressure during induction but it increased at incision. Heart rate was lower with desflurane than fentanyl prior to cardiopulmonary bypass. Vasodilators were needed more in the fentanyl group.

1998: “Comparison of remifentanil in combination with isoflurane or propofol for short-stay surgical procedures” [87]. Two hundred and fifty patients were studied; they were given either a remifentanil with isoflurane, or remifentanil with a propofol infusion. There were differences but the differences were clinically insignificant (author’s interpretation).

1999: “Alpha-2 and imidazoline receptor agonists: Their pharmacology and therapeutic role” [88]; another dexmedetomidine on isoflurane requirements in healthy discussion document; a review. This was the opening for the "Effects of volunteers. 1:Pharmacodynamic and pharmacokinetic interactions" [89]. Dexmedetomidine is an alpha 2-
adrenoceptor agonist. Volunteers were given isoflurane preceded by an infusion of dexmedetomidine on three occasions. The high dose dexmedetomidine group responded to a tetanic stimulus at half the isoflurane concentration at which the placebo group responded. Dexmedetomidine also decreased the heart rate and arterial pressures. Cognitive dysfunction persisted for several hours after anaesthesia.

1999: “Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 2: Auditory and somatosensory evoked responses” [90]. Auditory and somatosensory evoked responses were measured after doses of dexmedetomidine at various end-tidal isoflurane concentrations. Some evoked parameters increased as isoflurane concentration decreased, some increased. The changes seen suggested that dexmedetomidine has a different action to that of volatile agents “…at least for effects on the cortex”. It could have other potentiating effects such as N₂O and opiates, or indeed an isoflurane-like activity at subcortical levels.

2001: “Effect of dexmedetomidine on propofol requirements in healthy subjects” [91]. Dexmedetomidine or a placebo was infused and forty-five minutes later propofol was infused, both in a systematic way. Dexmedetomidine reduced propofol requirements, as measured using behavioural endpoints, and therefore the dose should be reduced when using dexmedetomidine.

**Review or review-type articles**

“Anaesthesia and demyelinating disease” [2]
“Clinical comparison of inhalation anaesthetic agents” [16].
“The anaesthetic management of the Eisenmenger syndrome” [26]
“Neuromuscular transmission and its blockade. Pharmacology, monitoring and physiology updated” [41]
“The priming principle: how does it work and should we be using it?” [58]. This was followed by a letter (“The priming principle: early development”) [62] explaining that the earliest indication of the possibility of ‘priming’ was by the Nottingham team of Hussain, Healy and Birmingham in 1979.
“Desflurane and sevoflurane: inhalation anaesthetics for this decade?” [61]
“Inhalational agents - an update” [71]
“The organ toxicity of inhaled anesthetics” [83]
“Alpha-2 and imidazoline receptor agonists: Their pharmacology and therapeutic role” [88]

Case reports

1981: “Cardiovascular and hormonal responses to electroconvulsive therapy. Modification of an exaggerated response in an hypertensive patient by beta-receptor blockade” [9]. Propanolol attenuated the marked rise in blood pressure, heart rate and plasma catecholamines. The latter increased 15x, three times more than that expected to produce a cardiovascular response. The RPP was 16000 with β-blockade, 35000 without, and so attenuation with β-blockers was recommended with heart disease.

1981. The positive inotropic mechanism of insulin was unclear. In animal experiments it had been shown that glucose-insulin-potassium mixtures enhanced subendocardial perfusion and so this may have been a factor.

1981: “Cardiovascular responses and changes in plasma cation levels associated with infusion of hyperosmolar urea solutions” [11]. A hyperosmolar urea solution used to decrease brain volume caused hypotension and decreasing levels of ionized calcium. This was studied using dogs. There were significant reductions in arterial pressure, systemic vascular resistance, hematocrit, and levels of plasma sodium and ionized calcium. Cardiac output, right atrial pressure, arterial pO₂ and pCO₂ and plasma potassium all increased. These were considered important effects.

1982: “Severe hypertension and flushing in a patient with a non-metastatic carcinoid tumour. Hypertension and flushing with a solitary carcinoid tumour” [14].
1983: “Reversal of biliary sphincter spasm with low dose glucagon during operative cholangiography” [18].

1983: “Fatal pulmonary embolism secondary to limb exsanguination” [21].

1984: “Vasomotor disturbance at unilateral cordotomy” [25].

1984: “Anaesthetic considerations in patients with paroxysmal supraventricular tachycardia” [29]; case reports of three patients.

1984: “Sleep apnoea following cervical cord surgery” [35].

1985: [43] a case report summed up by its title “Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium”.


1986: “Generalized grand mal seizure after recovery from uncomplicated fentanyl-etomidate anesthesia” [50].

1989: “Postoperative hypotension associated with enalapril” [59].

1991: “Resistance to atracurium in a patient with an increase in plasma alpha 1 globulins”. It was thought that this was due to binding of the drug to the protein [67].

1993: “Sinus arrest during cholecystectomy” [73].

1994: “Spontaneous oesophageal haematoma: a review of the difficult diagnosis” [75].
Books

Clinical Cardiovascular Medicine in Anaesthesia: Fundamentals of Anaesthesia and Acute Medicine, 1997, by Pierre Coriat and Ronald M. Jones

Fundamentals of Anaesthesia and Acute Medicine, 2001, by Ronald M. Jones and A.R. Aitkenhead

Pharmacology of the Critically Ill, 2001 by Gilbert Park, Maire Shelly, Ronald M. Jones and Alan R. Aitkenhead

At least a third of Ron Jones’ publications were reviews, letters, comments or case reports. The substantial work was about fade during neuromuscular blockade and the early work on desflurane and dexmedetomidine.

References


77. McNicol, P.L., et al., Patterns of coagulopathy during liver transplantation: experience with the first 75 cases using


