

Stanley A Feldman

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"He gave up his biochemistry thesis on the metabolism of the woodlouse to study medicine in 1950"ⁱ. After qualifying in 1955 he trained in anaesthesia at Westminster Hospital, was a Research Fellow in Washington (1957-8) and became senior lecturer at the Postgraduate Medical School in 1962 and visiting professor at



Stanford University, California. In 1990 he became the Magill professor at Westminster retiring in 1995ⁱⁱ; amongst many other appointments. His main interest was neuromuscular clinical pharmacology-physiology. However, he also published a few articles on equipment related topics.

Equipment:

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

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

ⁱ Introduction to "Panic Nation"

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

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

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

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

Clinical anaesthesia

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

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

ⁱⁱⁱ <http://www.medilexicon.com/medicaldictionary.php?t=94812>

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

Neuromuscular blockade

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

The neuromuscular studies fall into three main categories.

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

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

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

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

^{iv} Mushin WW, Wien R, Mason DF and Langston GT. Lancet 1949; 1:726

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

1970 A new theory of the termination of action of the muscle relaxants. It is not very often in medical journals that one finds the title of a paper including the phrase "a new theory of...". This paper in the Proceedings of the Royal Society of Medicine is an abridged article on the "Recent advances in muscle relaxants". Between 1905 and 1969 various hypotheses had suggested that the site of action for curare/acetylcholine was presynaptic/ synaptic/postsynaptic. Paton and Zaimis (1952 and 1961)^v proposed a competitive type of block – in this paper they, Feldman and Tyrrell, tested the view that the degree of paralysis was dependent on the blood/ECF concentrations and that lowering the concentration would decrease the effect. This was found to be incorrect. They used the isolated forearm technique and with curare and gallamine showed that when the tourniquet was released (significantly lowering the drug concentration in the blood) the block still persisted. This implied strong binding at the receptor site. The effect of decamethonium (a depolarising agent) wore off very quickly suggested a weak binding with receptors. However if the decamethonium stayed in contact with receptors for a long time then they formed a strong enough bond to produce a curare like-effect (a Phase II block). These studies, and others with tetanic stimulation suggested that it really wasn't a competitive block but that acetylcholine displaces curare from the receptor site and the 'reversal' depended on the quanta of Ach around the receptor site.

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

^vPaton WDM & Zaimis EJ (1952) *Pharmacol Review* 10;59. Paton WDM (1961) *Proc.Roy.Soc.* B154;21.

^{vi} Appiah-Ankam J and Hunter JM. *Critical Care and Pain*, 2004;4:2-7

How can these contradictory views be resolved?

- 1971 Factors influencing action of muscle relaxants.
- 1972 The effect of non-depolarizing muscle relaxants on cholinergic mechanisms in the isolated rabbit heart.
- 1972 The dual action of suxamethonium on the isolated rabbit heart.
- 1976 Affinity concept and action of muscle relaxants.
- 1976 The effect of blood flow upon the activity of gallamine triethiodide.
- 1976 Effect of hypothermia on neuromuscular block induced with a gallamine.
- 1978 Muscle blood flow and rate of recovery from pancuronium neuromuscular block in dogs.
- 1979 Plasma concentrations of pancuronium and neuromuscular blockade after injection into isolated arm, bolus injection and continuous infusion.
- 1980 Clinical importance of affinity constant.
- 1987 Etiology of failure of reversal of neuromuscular block.
- 1993 The effect of residual receptor occupancy on sensitivity to repeated vecuronium.
- 1993 Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration.
- 1994 Curare modification of suxamethonium blockade.
- 1995 The effect of dose and the rate of stimulation on the action of rocuronium.

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

- 1963 Prolonged paresis following gallamine.
- 1969 Diagnosis of non-depolarizing block.
- 1970 NB68, A new steroid muscle relaxant.
- 1970 Interaction of diazepam with the muscle-relaxant drugs.
A description of the effect of diazepam on gallamine and suxamethonium; the duration of the former was enhanced, the latter reduced – possibly due to action at a presynaptic site [21]. This was published in the British Medical Journal which is not renowned for its anaesthetic related content.
- 1970 Diazepam and muscle relaxants.

- 1970 A new steroid muscle relaxant. Dacuronium-NB.68 (Organon).
[Dacuronium did not 'take-off'.]
- 1973 Paradoxical effect of halothane upon neuromuscular block with gallamine.
- 1974 Letter: Paradoxical interaction between halothane and pancuronium.
- 1978 Interaction of halothane and pancuronium bromide.
- 1981 Intubating conditions with ORG NC45. A preliminary study.
[ORG NC45 did 'take-off'; it was Norcuron, commonly known as vecuronium. This was a dosing study comparing two doses of ORG NC45 with pancuronium for tracheal intubating conditions at 60, 90 and 120 seconds. There was no statistical difference.
- 1984 Peritoneal closure and atracurium.
- 1984 Comparison of intubating conditions with atracurium, vecuronium and pancuronium.
- 1985 Competitive block - UK style.
- 1987 Vecuronium--a variable dose technique.
Vecuronium was given in doses ranging from 0.1mg/kg - 0.25mg/kg resulting in durations of action from 28-72 minutes - it was suggested that for long procedures a large initial dose had advantages.....[45]
- 1988 Reversal of muscle relaxants.
- 1989 Effect of rate of injection on the neuromuscular block produced by vecuronium.
Using a subparalytic dose of vecuronium, given by rapid injection or by infusion, it was shown that the rapid injection produced a higher peak concentration but the maximum block was similar [47].
- 1993 Resistance to decamethonium neuromuscular block after prior administration of vecuronium.
It was known prior treatment with small doses of non-depolarising reduces the effect of succinylcholine and so the effect was investigated using vecuronium and decamethonium. The effect was replicated - vecuronium doubled the dose of decamethonium required to produce the same effect. It was a nonparallel effect and so was not considered a simple agonist-antagonist effect [50].
- 1993 Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration
A study, using vecuronium, compared tetanic fade with twitch depression using both a systemic injection and an isolated forearm

- technique – there was less fade in the isolated forearm and it was suggested that twitch depression and fade "are independently mediated effects of vecuronium" [49].
- 1993 The effect of residual receptor occupancy on sensitivity to repeated vecuronium.
A combination of systemic doses of vecuronium and an isolated forearm suggested that the reduction in ED50 following repeated systemic doses was due to residual drug in the plasma, not at the receptor site [48].
- 1994 Rocuronium — onset times and intubating conditions. [Ro — rapid onset]
A comment on the assessment of 'intubation times' for doses of rocuronium; careful interpretation of the studies with different methodologies is essential. Feldman suggested that the rapidity of onset of the rocuronium block appeared to be a pre-synaptic effect and that 90s was 'closer' to the time when conditions were excellent for intubation and that this difference (cf. suxamethonium) had to be considered a matter of clinical judgement when airway protection was a necessity [51].
- 1994 Sensitivity to second dose of mivacurium.
By using systemic doses of mivacurium with and without an isolated forearm it was possible to show that there was increased sensitivity to the second dose in both situations and that this was therefore not due to a receptor effect of residual drug in the plasma [52].
- 1994 Curare modification of suxamethonium blockade
Giving tubocurare before suxamethonium resulted in a slower onset low intensity block; train-of-four fade was similar to tubocurare blocks and it was concluded that there were effective amounts of tubocurare in the neuromuscular junction within 30s of injection and that this affected the suxamethonium block [53].
- 1995 The effect of dose and the rate of stimulation on the action of rocuronium.
The time to complete neuromuscular blockade was found to be dependent on the rate of ulnar nerve stimulation and thus in studies of neuromuscular block duration stimulation rates have to be consistent [54].
- 1995 Priming studies with rocuronium and vecuronium.

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

1997 Tracheal intubation conditions after one minute: rocuronium and vecuronium, alone and in combination.

It was found that an ED95 dose of rocuronium combined with an ED95 dose of vecuronium produced better intubating conditions for intubation at 60s than twice ED95 doses or either drug – an obvious synergistic effect [56].

Miscellaneous

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

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

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

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

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

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

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

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

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

Books

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

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

Muscle relaxants by Stanley A. Feldman (1973)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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