

Epilogue

To understand a patient, one listens, looks, touches and measures – and using that knowledge and experience, and the experience of others, a diagnosis is made. Only with the correct diagnosis can the correct treatment be started. The rest is just fine-tuning – but let's start at the beginning.

“Medical training in the 1960s was still, almost completely, rote learning – primarily because the mechanisms of many pathologies and pharmacological agents were only crudely known, so the ability to deduce, for example, the action of a drug from its structure was limited. The anatomy of many drug receptor sites was unknown. Or, to put it another way, the only receptors taught were the α and β adrenergic receptors and the acetylcholine receptor. Rote learning is not everyone's preferred method of learning – memories fail and mnemonics multiply.

As a young house surgeon having to make diagnoses I decided I needed some help – the memory is weaker now but the first diagnostic algorithm related to determining the likely nature of breast lumps. From the past experience of others it was possible to use age as a differential piece of evidence, together with mobility and size – no need to go into greater detail but it gave me a method for systematically giving an order to the possible diagnoses. This was for personal use only.

After a digression, twelve months vocational training as a general practitioner, I realised that general practice was not for me and that I had to search for another specialty. Anaesthesia was an option but a vacancy was also advertised with ICL – a large computing company, they were looking for a medical developer/advisor – I was fresh out of the shell but I applied for it. Fortunately, I believe, the interview for the training post in anaesthesia in Nottingham came first; I took it.

Being in the right place at the right time is good; Nottingham had just acquired a medical school and the academic departments were expanding fast. At interview, I was bold enough to ask if I could be involved in research. In retrospect this was an extraordinary request; that had to wait until examinations had been passed.

Feeling a bit of a dropout, after 'failing' general practice, the books were hit hard and the first exams passed within six months. Some

studies were undertaken under the tutelage of Tom Healy – an enthusiastic, ambitious and very amusing raconteur – a good introduction to scientific methodology, basic statistics on computers and paper writing. Computing didn't really come to have importance until consultant status was achieved, closely followed by a senior lectureship in Nottingham.”

The professors of anaesthesia that have been the subjects of the two volumes of “*British Academic Anaesthetists*” have been instrumental in many aspects of the development of anaesthesia in the UK and abroad (and provided me with textbooks and examination experience). This is only one way of telling the story and it must be remembered that there were a large number of other researchers behind the ‘head’ of the departments.

The references appended to each section name many of these people and their contribution should not be underestimated. Others are not included in the references; these are the multitude of laboratory workers, technicians, pharmacologists, statisticians, graphic artists and not forgetting the secretaries. Before word processors existed all submitted papers were typed and retyped and retyped. Cut and paste and auto-correction did not exist.

In the writing of these stories I have had the privilege of communicating with many of these researchers and without exception they have always been helpful and very interested in the ‘stories’ of their contemporaries. “I was too busy to know what everybody else was doing”.

It has been suggested that I should have integrated the work completed by A in the UK, with similar work by B in USA or C in Germany. Life is too short and I will leave that to someone else.

Other names have been suggested as subjects for the book; again, life is too short. I have no doubt that there are really important productive, innovative, highly knowledgeable people that I have omitted, I can think of a couple at least, but the line has been drawn and here it is.

Volume 3 is left to someone else. One advantage of writing a history based book is that it is less likely to become out of date than a book on pharmacology!

Michael Harrison 2015

ADDENDUM

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Michael Harrison trained in anaesthesia in Nottingham, starting in 1971; mentored by Tom Healy. In 1975 he was lecturer in anaesthesia in Sheffield under Prof. Andrew Thornton. He became a consultant in Nottingham in 1977 and a senior lecturer in 1978.



When Tom Healy became professor of anaesthesia in Manchester Harrison became the acting head of department in Nottingham. After five years Harrison resigned his position and emigrated to New Zealand in 1987¹.

He was appointed senior lecturer in the Department of Anaesthesiology in the University of Auckland and again became acting head of the department, and Associate Professor, when Stephan Schug was appointed to the chair in Perth. He continued to work in this department when Alan Merry was appointed to the chair. In 2009 Harrison moved to Wellington.

Like so many others his first publication was a case report; "*Inhaled foreign body*" [1]. The foreign body was a spring from a Biro; tricky to extract but caused no respiratory distress.

Tom Healy encouraged 'bench' research and at that time the laboratory was a converted bathroom in the Nottingham General Hospital; the University Hospital was being built. It was fortunate that it was a bathroom as the first studies were significantly wet [2, 3]. The first assessed intravenous administration sets for particulate contamination,

¹ John Nunn actually got that wrong! J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916.

requiring litres of saline for flushing, and the second tested some blood warmers and required a steady flow of water at 4°C. No matter what care was taken water always seemed to find the floor.

The next bench study was one using an automatic flow interruption bronchoscope [4]. A venturi device was used to ventilate a model lung and the 'oxygenation' was assessed when the model lung was altered by varying resistance and compliance. The more difficult it was to ventilate the lung the higher the oxygen concentration in the ventilated gas - there was less entrainment.

These were relatively easy studies to perform whilst still having significant clinical duties.

In 1975 Harrison moved to Sheffield as lecturer which was a natural progression but it was not a very productive one [5, 7]. It did, however, introduce him to the art of writing - the lecture notes prepared for the primary examination course became the backbone of the "*Aids to Anaesthesia; the Basic Sciences*"².

An innovation was published in 1976 "*A double-lumen tube connector*" [6]. This was a simple device that allowed the isolation of one lung and suction access with a simple slide mechanism³.

One clinical study in Sheffield was a dental sedation study; "*I.v. flunitrazepam and i.v. diazepam in conservative dentistry. A cross-over trial*" [10]; this was not published until 1980.

Back in Nottingham in 1980 an unexpected opportunity arose. A team of engineers and physicists had produced what was considered the first nuclear magnetic resonance imaging machine for humans. Harrison was asked to supervise the first patients through the device - "*Just in case...*" The research space looked like a ship's engine room with cooling pipes, a large Faraday cage and, of course, a very large magnet. The utilitarian appearance was softened with a few mobile patient screens borrowed from a ward. Of course nothing happened but the experience of seeing an ECG trace traversing the screen diagonally in response to the

² This was before the AIDS epidemic!

³ It was taken up by a manufacturer - a more sophisticated prototype was made, a cylindrical valve mechanism. The core when warmed up by exhaled gas expanded and completely froze the mechanism.

magnetic field was intriguing [11]. This may be the first anaesthetic communication about MRI scanning.

That same year was the first of a multifaceted theme on the development of a decision support system for anaesthesia and the use of artificial intelligence system to enhance anaesthesia monitoring. The story is outlined below.

In 1978, or thereabouts, two Zenith (Heathkit) computers were bought with 64K of RAM – magnificent! They cost about £2000 each. Once they were turned on there was a green screen and a c:>! What next!? Harrison had no idea how to drive the machine but 'playing' with it and learning Basic – a very linear simple language – eventually allowed programs to be written – these were clumsy but over time became more and more complex.

Using the computer to assist decision making was an early goal and with the help of Frank Johnson (computer whiz and physicist in the orthopaedic department on the opposite side of the corridor) started to create an algorithm for an advisory program to create an anaesthetic recipe for different types of patients with different co-morbidities and surgery. Frank wrote in FORTRAN, which was really frustrating because Harrison was unable to tweak it – and with its complex IF-THEN rules it really needed a lot of tweaking. The answer was a parallel program in Basic, with a simpler structure. These both eventually worked well [12, 13]. The first was presented at an ARS meeting (and was met with some scorn by Prof. Jimmy Payne).

The computers were taken to Sheffield for others to use, for evaluation. In 1980 computer crashes were common. An aluminium 'mask' was put over the keyboard to restrict the keys that could be used. One important point from this evaluation was that the users wanted (needed) explanation for the advice being offered. With two colleagues (Ron Jones and Brian Pollard) the skeleton of the algorithm was turned into a book – *A Rule Based Guide to Anaesthesia Management*.

At that time there was a great upsurge in work on expert systems – de Dombal had published his paper on diagnosing appendicitis

with the intention of reducing the incidence of negative laparotomies⁴. Shortliffe's book on identifying bacteria and the treatment of infection⁵ was out and the Edinburgh artificial intelligence unit headed by Michie were marketing a software package called ExpertEase⁶ – a workshop was held in London - Harrison attended – the only medic there.

The government of the day was promoting artificial intelligence development and a specialist department in Nottingham was set up. The language used was Prolog – a programming language whose structure gobbled up memory at a phenomenal rate. Projects were needed to use as test beds – Harrison was approached and they used a part of the anaesthetic 'recipe' algorithm from the FORTRAN program to use with this language. They only used the premedication section but this turned out to be quite a feat – Harrison was just the medical advisor [14].

The situation at this time was that programming was a specialist activity, that computer memory was a significant factor (and speed – the FORTRAN program took two minutes to run). Computer hardware was still 'brittle' for routine use and I/O errors and floppy disc incompatibility common.

At this time, the 1980s, interested anaesthetists were writing their own programs on the basic home computers then available, BBC, Sinclair and so on. The journal *Anaesthesia*, for a short time, carried a description of programs that anaesthetists had written; Harrison was the editor for that section but this didn't last long – the fad faded.

Monitors for anaesthesia were also under investigation – each physiological variable had its own measuring device and these devices were festooned on the anaesthetic machine – commonly referred to as a Christmas Tree. The user interface, which is the appearance of the monitor screens, of the values of the different variables was investigated with a variety of different layouts and icons. Some were good, some not

⁴ de Dombal FT, Leaper DJ, Staniland JR, McCann AP, Horrocks JC. Br Med J. 1972;2(5804):9-13

⁵ MYCIN was developed in the 1970s at Stanford University; a doctoral dissertation of Edward Shortliffe

⁶ Professor Donald Michie, MA, D Phil, D Sc, FZS, FRSE, FBCS, FAAAAI 1974 - 1984 Director, Machine Intelligence Research Unit, Edinburgh.

so good. Understanding some of them was not intuitive and required varying degrees of relearning.

The concept may have had its origin in the medical bay of Starship Enterprise and it was this - for each variable there would be three zones, high, normal and low. These three zones were of uniform size, completely independent of the scales. For example the scale for blood pressure went from 40 – 200 mmHg, temperature from 34-42°C but the high, normal, low zones were all the same size [23].

This had the advantage that if any variable was high, or low, they were easily spotted above or below the normal zone. In the computerised form, 3D histograms were displayed for each variable and as time passed the histograms receded into the background as new values appeared in front. Imagine an anaesthetic where all variable were within the normal range, the top surface of the histograms would resemble a plateau, any high or low values become mountains or valleys. In one 3D diagram, all the variables were displayed over the whole duration of the anaesthetic – an integrated display.

However, this was the only integration – the screen or printout – all the monitors were separate so each had to have cabling from their output sockets to an A-D converter. This was complex and a professional company did the job – not exactly charlatans but they certainly made a meal of it. It worked – this was the first time that real-time data collection and processing had been achieved in his studies. Lessons learnt – displays must be intuitive and programmers essential for real-time analysis.

Harrison's move to New Zealand was completed in 1987 and, being ignorant of NZ geography, both national and local, he was extremely pleased to see the medical school with its facilities just across the road from the hospital.

Around this time HP programmable calculators were popular and it was thought that the collecting of blood pressure data could be automated and, through a network of connections Harrison was put in touch with an engineer who was working for Trutest, and later Fisher and Paykel. He helped programming the device. The idea was that basic statistics for the collected data would be updated automatically as new data came in. This would be good for specialist units – for example

neurosurgical patients might have a different data set to orthopaedic patients. When the engineer moved to F&P, contact was lost and the HP hand-held computer ended up in a drawer.

This however started a connection with the Auckland University Department of Engineering – one of their previous graduates had gone on to do medical training and it was through this link that the next big step took place. Harrison had once again reached a point where his computing skills were quite inadequate for what he wanted to do and was about to 'throw in the towel'. Andrew Lowe wanted to do a medical based PhD and had been told about Harrison's work on monitoring – in engineering terminology 'fault detection'. Lowe changed everything and started a very productive era of research, development and publications.

For the next three years, on and off, afterwards the duo worked together, with Lowe's engineering supervisors Brian Mace and Richard Jones. During that time Harrison was introduced to fuzzy logic, neural networks and belief and plausibility, and the rules of evidence.

A major part of Lowe's work⁷ was to write a program to connect a desktop computer to a GE/Datex-Ohmeda anaesthetic monitor. Between 1980 and 1987 the 'Christmas Tree' of monitors had largely disappeared and had been replaced with monitors that presented all the variables (most variables) in one box and on one screen. There were waveforms (ECG, arterial and carbon dioxide) and digital values as well. Lowe's software was made slightly more complex because of the need to pass on the data to an automated record keeping system.

With ethics committee and patient approval, many sets of data were captured and processed off-line.

Lowe's thesis covers the scope of this work that involved the theory of fuzzy logic, fuzzy courses (like navigation channels through which the variables pass for certain adverse events), determination of membership functions and rules of evidence – some very complex logic concepts intertwined with maths.

Papers were written about these concepts as applied to anaesthesia monitoring and, for the first time, using rules of evidence and

⁷ Lowe A. Evidential inference for fault diagnosis – Application to anaesthesia monitoring. PhD thesis, University of Auckland.

Mu values, different diagnoses were contemplated by combining the various parameters in different ways. These were primarily conceptual and the clinicians' assessments of events were used to correlate the diagnosis with the changes. As the medical advisor for the PhD work Harrison was the one to describe the interrelationships of the variables to, hopefully, detect the events. Fortunately, it is a feature of fuzzy logic systems that 'experts' are used to do this modelling of a system [40, 43-45, 47-49, 51-53, 59].

One triumph of this period was the modelling of malignant hyperpyrexia (MH). It is a rare condition and, after searching for all clinical descriptions of the onset of the condition, a relatively simple model was created using membership functions of fuzzy courses for blood pressure, heart rate, carbon dioxide concentrations and temperature, although temperature was not essential. Physiological variables were taken from a hand-drawn anaesthetic record⁸. The values were widely spaced in time so there had to be some interpolation. The software worked but the data were crude. A simulator centre provided further data but this was also crude.

A chance meeting with Neil Pollock a Palmerston North anaesthetic specialist with a major interest in MH, resulted in the receipt of an almost complete data set for a 'virgin' case of MH in Australia, neither the patient nor the anaesthetist was aware of the susceptibility to MH. The data came as several metres of print out, some interpolation was necessary but not much. Temperature was not recorded initially and so it was clear when the anaesthetist considered the diagnosis because temperature values suddenly appeared. The software worked perfectly, the diagnosis was made about nine minutes before the first temperature measurement [43].

Following the completion of Lowe's PhD there was some limited collaboration.

There were several projects underway at the same time but one is pertinent – what blood pressures were recorded during anaesthesia? Together with a colleague (Phil Guise) blood pressures were collected at five-minute intervals – they had to be recorded anyway for the

⁸ Rampton AJ et al. Br. J. Anaesthesia. 1984; 56:1443-1444

anaesthetic record. After collecting from many patients of all ages and a wide variety of surgery, a distribution curve for blood pressure under anaesthesia was created – *had this been done before – not sure?* A distribution curve for changes in blood pressure was also created [46]. This had been inspired by John Gleick's book *Chaos*, the plotting of the value of a variable against the next value. These were valuable data because it was then possible to 'predict', with some certainty, the range of blood pressure where the next blood pressure should lie and this would be the basis for future work.

Further progress was made when Harrison became a supervisor to a Master's student, Bhupendra Gohil, at the Auckland University of Technology (AUT). Fuzzy logic was used to diagnose hypovolaemia.

The aim, or one of the aims, of his work was to get a system working in real time; all Lowe's work had been done off-line. With Lowe's help, data was collected, as before, and there should have been an automated diagnostic alert system with the ability for the user to agree or disagree – unfortunately this did not eventuate. Gohil spent a huge proportion of his time developing artefact rejection mechanisms, an essential prerequisite to data processing. At the end of the day the program diagnosed acute onset hypovolaemia with an acceptable degree of agreement with clinicians [66-68, 73].

Age also is of importance in diagnostics – this was addressed [62]. The expectation was that both BP and HR would increase with age – counter intuitively the older person's HR, on average, went down probably due to the widespread use of beta-blocking drugs. This was presented at a meeting in Australia [62].

Whilst work continued with Auckland University of Technology and the University of Auckland other ideas were maturing in parallel. A conference in Plymouth in 2005, however, was really rewarding and resulted in four publications, and they were significant to the ultimate goal. The conference was on 'Pattern Recognition'.

There was a presentation by Paolo Lisboa about generating rules from the output of neural networks, the work of Terence Etchells who happened to be sitting next to Harrison. After discussion Etchells offered to analyse some data and the following day the kernel of a paper about rules governing the transfusion of blood, based on an audit of

anaesthetists in the Department of Anaesthesia at Auckland Hospital [60]. A paper on this topic had been accepted for publication in *Transfusion Alternatives in Transfusion Medicine* [63] but after a dialogue with the editor of *Anaesthesia*, explaining that this was a completely different approach, the paper was accepted. This was not 100% pertinent to the monitoring software but contact with Etchells was to prove very useful.

During the conference Chris Connor, a trainee anaesthesiologist in Boston, USA, made contact and it was arranged that he, and his wife, would visit NZ for Christmas and attend a research meeting there.

Another concept highlighted at the Pattern Recognition conference was about normalisation of data. After leaving the conference, a few days in the country allowed some consolidation on ideas regarding the application of normalisation methodology to alarm systems; there was a definite Eureka moment.

Connor was an engineering graduate from Cambridge in the UK, who went to the USA, worked for NASA and then completed an engineering PhD on a medical topic. With this experience he decided to cross credit and did medicine. After meeting for the first time at the pre-Christmas conference in Queenstown (NZ) they returned to Auckland. Connor enhanced the normalisation technique using Principal Component Analysis. With much editorial and reviewer support, it was published [69]. A subsequent paper extended the concept [73].

A belated MD thesis was accepted in 2007 “The enhancement of intra-operative diagnostics and decision-making using computational methods”⁹.

During this period other 'mini' projects were underway and formed part of the infrastructure for the final diagnostic software. Two anaesthetic trainees, Amber Chisholm and Dan Faulke, needed to complete projects for their College accreditation. Chisholm's project was significant in that it led to a major component of the final program although the subject matter of her project was completely unrelated.

Faulke's project was aimed at one particular piece of knowledge the software depended on – was the patient being ventilated (or to put it

⁹ <http://hdl.handle.net/2292/74>

more pedantically – were the patient's lungs being artificially ventilated?) or was the patient breathing spontaneously?

Chisholm: The death of a trainee by opiate overdose stimulated the search for some way of detecting the change in opiate usage in the operating room. Like units of alcohol, the various opiates used were converted to a common unit and data were collected from a set of colleagues; the historical data were collected from the dead trainee's records. A variety of statistical tests were unsuccessful but once again serendipity occurred in the contact with Davis Balestracci (a run chart guru). Using an 'adulterated' methodology it worked and was published [72] and a new technique for time series analysis was now available.

Faulke: To determine whether the respiration was 'spontaneous' or 'controlled' using only the respiratory rate, EtCO₂, and FiCO₂ was the goal. This information was needed because physiological responses are significantly different in these two modes of ventilation and for one index of blood volume status it was essential that the lungs were artificially ventilated. This being a classification problem, Etchell's skill was needed once more. In a diagnostic system an incorrect output is undesirable and so, to minimise this risk, the system tested separately for both 'spontaneous' and 'controlled' ventilation. If the two algorithms agreed, the output was accepted; if they did not agree the mode of ventilation was "unsure" [74].

During the collaboration with Lowe, an anaesthetic advisory system was created, and, as an aside, with the computer science department at the University of Auckland, a user interface was designed that could have been the public face of the diagnostic system [71]. However, user interfaces are like wallpaper – they could be of almost any design, but some are more user-friendly and intuitive than others.

The concept of 'change', rather than absolute values, brought a new direction to the fuzzy logic and a new Master's student – Mirza Baig [76-78].

What was wanted to know was: *When is a trend a trend? How many falls in BP are needed to be convinced that a true change is taking place?* When this question reached 'conscious' level the concept of using runs analysis surfaced, as in Chisholm's paper. The beauty about this technique is that the 'next' value has a 50:50 chance of going up or down,

two down in a row is 1:4, then 1:8 and then 1:16, for subsequent values in the same direction. This not only gave the probability of change but it was completely independent of units of measurement and, with time, reset itself to new values because of the moving window for the 'baseline' median value.

The clinical problem is that of the balance between the early and late notifications – data came through at 10s intervals. Instead of taking a single variable (BP), as above, but two variables in parallel (BP and HR) as in an organised physiological response, the likelihood of four changes consecutively in two variables was $1:16 \times 1:16$ which is 1:256. This was seriously good. With three variables (BP, HR and pulse volume (PV, amplitude) the odds are 1:4096 that it would happen by chance, with four variables (BP, HR, PV and EtCO₂), 1:65000.

It could still be argued that these trends could take place but the actual changes could be very small. Blood pressure is the final product of many physiological factors – heart rate, heart contractility, blood volume, peripheral resistance – and this is why it is the primary monitored variable; if the blood pressure hasn't changed significantly the anaesthetist is unlikely to worry very much. To check for clinical significance of the automated diagnoses it was decided to detect for trending (combined runs analysis) and then check for a significant change in BP (using normalisation). Not only could acute onset hypovolaemia be detected but by using appropriate combinations of BP up, BP down, HR up, HR down, PV up, PV down, EtCO₂ up, EtCO₂ down a whole range of diagnoses were open to investigation.

The established 'alarms', or alerts for hypotension on monitors was 'crisp' rather than fuzzy. There were 30 definitions of hypotension in the literature. With Stephen Lo, another trainee, a survey was devised where the aim was to capture the blood pressure values at which the anaesthetists would intervene to prevent the blood pressure falling further. It took into account various pathologies and ages [86].

The software was modularised and had the potential capacity to diagnose hypovolaemia, a decrease in cardiac output secondary to hypovolaemia, a sympathetic response, the Cushing response, malignant hyperpyrexia and, as a highly specialised extra, the ability to detect failure to ventilate post cardiopulmonary bypass. The ability to detect the

failure to ventilate post cardiopulmonary bypass was assessed with David Cumin [80], the sympathetic response and hypovolaemia was assessed by Vincent Bonhomme (Belgium)[81, 88] and the ability to detect a fall in cardiac output secondary to hypovolaemia with Mathew Zacharias and Ross Scott-Weekly [89].

Publications of interest: (in Harrison's view!)

1979: Nasotracheal intubation [9]. A very clean and atraumatic technique – a bit fiddly but very clean.

1984/1990: [17, 30, 31] Maintenance of drug levels at the therapeutic threshold; Prediction of infusion rates: computer study and Prediction of infusion rates: Validation of a computer simulation using vecuronium.

This was the result of an insight that was developed with the help of Prof. Chris Hull's pharmacokinetic program and subsequent patient studies. The pharmacokinetic modelling saved the necessity for many interim patient studies.

1986: Remote monitoring using an induction loop [25]. This is the description how a patient's variables could be remotely monitored using hearing aid technology - decades before Bluetooth!

1989: Weight determined dosage of vecuronium bromide [28]. A simple study of how the duration of action of a muscle relaxant is far more consistent if the dosage is based on the fat free mass.

1999: Personality traits of anaesthetists and physicians: an evaluation using the Cloninger Temperament and Character Inventory (TCI-125) [42]. An interesting exercise; the one question that still remains unanswered is whether the personality determines the choice of specialty or the specialty moulds the personality.

Books:

- 1 Aids to Anaesthesia, Basic Sciences
- 2 Aids to Anaesthesia, Clinical practice
Harrison MJ, Healy TEJ, Thornton JA, Churchill Livingstone.
- 3 A Rules Based Guide to Anaesthesia
Harrison MJ, Jones RM, Pollard BJ, Butterworths
- 4 Anaesthesia for Uncommon Diseases
Pollard BJ, Harrison MJ. Blackwell scientific.
- 5 So you're going to have an operation
(A patient information book on anaesthesia)
- 6 Diagnostic alarms during anaesthesia. Harrison MJ, Low A, and
Gohil B. VDM Verlag 2009
- 6 British Academic Anaesthetists 1950-2000 Vol 1
ISBN 9780473200497
- 7 British Academic Anaesthetists 1950-2000 Vol 2
ISBN- 978-0-473-32137-6

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