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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].

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

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

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 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]

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

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 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 Boththner 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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[iv] http://www.syc1999-2008.co.uk/ Thanks to Dr Douglas Russell

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