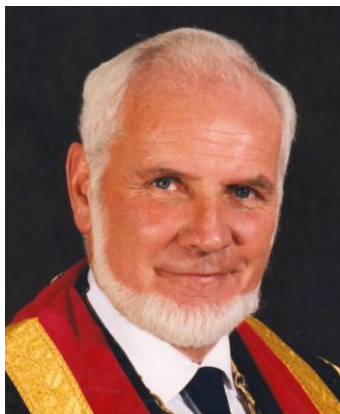


**Cedric Prys-Roberts**  
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From 1964 – 1967 Cedric Prys-Roberts was a research fellow with Senior Registrar status in Leeds, he worked with Dick Kelman<sup>i</sup> and Ronnie Greenbaum under the guidance of John Nunn; he moved to Oxford as clinical reader (1967 to 1976). He was in San Diego 1973-74 as a Professor of

Anaesthesia in the University of California. In 1976 he became Professor of Anaesthesia in Bristol<sup>iii</sup>. Cedric Prys-Roberts is probably most well known for his work on cardiovascular physiology and pharmacology, and especially the topic of hypertension and anaesthesia. He also investigated the effects of ventilation, beta-blocking agents and volatile anaesthetic agents on cardiovascular physiology.

His first two publications were in 1966 [1, 2]. The first publication, a letter to Anesthesiology, was with Greenbaum, Kelman and Nunn and was about a paradoxical decline in arterial oxygenation during hyperventilation; this had been brought to their attention by Markello<sup>iv</sup> and Laver and Slater<sup>v</sup> in previous correspondence in the journal Anesthesiology. The comments are summarized in a table where it is shown, with data from their own department in Leeds, that  $PA_{O_2}$  increases the (A-a) gradient as does the a/v difference and an increase in pH. A reference is made to a paper 'in press' (Haemodynamic influences of graded hypercapnia in anaesthetised man, B.J.A.); there is no paper with this title but there

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<sup>i</sup> GR Kelman, author of Applied Cardiovascular Physiology and Physiology: A Clinical Approach

<sup>ii</sup> Photograph courtesy of the Royal College of Anaesthetists and CP-R, see <http://www.rcoa.ac.uk/index.asp?PageID=1460>

<sup>iii</sup> J F Nunn. British Journal of Anaesthesia. London: Dec 1999. Vol. 83; pg. 916

<sup>iv</sup> Anesthesiology 27;334:1966

<sup>v</sup> Anesthesiology 27;335:1966

Are several papers in 1967 dealing with cardiovascular influences on gas exchange.

The 1966 paper, where CP-R was the primary author, was a comparison between in-vivo and in-vitro changes in acid-base status when either the anaesthetised patient or a blood sample was exposed to high and low levels of carbon dioxide. As expected there were differences; when plotted on a pH vs.  $[\text{HCO}_3^{-1}]$  mEq/litre graph the whole blood in-vivo slope was less steep than the whole blood in-vitro. However, the plasma-in-vitro plot was even less steep. The explanation for this, citing the work of many others, was that intra-cellular buffering mechanisms (very high compared with other body fluids) come into play; so tonometric measurements do not reflect holistic physiological changes.

*My [CP-R's] main research object was to differentiate the cardiovascular and gas exchange effects of changes of CO<sub>2</sub> levels, both up and down, from the mechanical effects of IPPV.....[With Dick Kelman he] developed blood gas analysis techniques and the dye-dilution method for cardiac output measurement..... [floating] fine (non-ballooned) catheters into the right ventricle and on into the pulmonary artery to sample true mixed venous blood. [1, 3, 4] ..... No one had previously measured true mixed venous blood (during anaesthesia or intensive care) (Pvo<sub>2</sub> and Cvo<sub>2</sub>) and [they] applied these measurement techniques in patients in intensive care (under John Ablett) with tetanus, fat embolism, and severe pulmonary trauma.”<sup>vi</sup>.*

1967 was a big year for CP-R as he had twelve publications as joint author with Greenbaum, and Kelman et al. [3, 5-15]

## Hypertension

Let's first deal with CP-R and hypertension. *“During the period 1967 to 1972 I became very interested in the problem of hypertension in relation to anaesthesia, as a result of discussions with Sir George Pickering – then Regius Prof of Medicine, and I set up a whole series of human studies during anaesthesia and surgery, that ran in parallel with the animal work”. These studies took place at the Churchill Hospital (Oxford). Pickering was not involved in the design or setting up of the studies.* <sup>vi</sup>.

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<sup>vi</sup> Personal communications from CP-R – all italicized text verbatim.

There are seven publications titled 'Studies of anaesthesia in relation to hypertension, I-VII' covering a period of 15 years, 1971 – 1986.

The first (1971), 'Cardiovascular responses of treated and untreated patients' [16], covered the whole sequence of anaesthesia from induction to recovery in normotensive, untreated hypertensive and treated hypertensive patients. The anaesthetic used was standard at the time, nitrous oxide and halothane in oxygen. Twenty-five percent of the hypertensive patients had significant decreases in blood pressure that led to ischaemic changes on the ECG. Other hypertensive patients whose blood pressure was well controlled behaved in a similar manner to the normotensive patients. The bottom line was that "untreated high arterial pressure constitutes a serious risk to patients undergoing anaesthesia and surgery, and therefore anti-hypertensive therapy should not be withdrawn prior to anaesthesia without a compelling reason."

Paper two (1971) in the series concentrated on the haemodynamic consequences of induction and endotracheal intubation in the hypertensive patient [17]. In this study five different agents were used to induce anaesthesia and the effects on the ECG and cardiovascular parameters were observed. Neuroleptanalgesia (phenoperidine and droperidol) caused the least hypotension (propanidid and diazepam were worst) but the protection against hypertension, tachycardia and dysrhythmias was only marginally better than the other agents (methohexitone, thiopentone). It was recommended that prophylactic beta-blockade should be used to protect the patient against hypertensive crises during laryngoscopy and intubation. An interesting aspect of this paper is the use of cusum analysis and a Manhattan graph to indicate where significant episodes of dysrhythmia occurred. (*The use of the cusum originated in the tetanus papers from Oxford*).

No.3: (1971) Pulmonary gas exchange during spontaneous ventilation [18]. Patients were allowed to breathe spontaneously during nitrous oxide and halothane anaesthesia. Minute and alveolar ventilation were depressed more than was expected compared to the changes in oxygen uptake and carbon dioxide production. This resulted in a moderate hypercapnia. This effect was short lived

after cessation of the anaesthetic. Although the dead space was reduced because of intubation the VD/VT was increased, the tidal volume being halved. There was no evidence of progressive pulmonary dysfunction. The bottom line of this paper was that during anaesthesia, in hypertensive elderly patients, changes in cardiovascular function were far more serious than changes in pulmonary function.

No. 4 (1972): The effects of artificial ventilation on the circulation and pulmonary gas exchanges [19]. The cardiovascular responses during artificial ventilation using a nitrous oxide, muscle relaxant technique ( $\pm$  halothane) were studied; during (severe) hypocapnia (PaCO<sub>2</sub> of 23 mmHg) without halothane the mean arterial blood pressure fell about 30% - 40% from preoperative values, with halothane (1%) between 40% and 50%, the untreated 'hypertensives' being the more hypotensive. This was principally due to decreases in cardiac output as the systemic vascular resistance increased in all patients. Electrocardiographic evidence of myocardial ischaemia was seen in half of the treated patients and in all the untreated patients. There was oxygen desaturation of mixed venous blood but pulmonary venous admixture did not change significantly.

No.5. (1973) Adrenergic beta-receptor blockade [20]. The significant part of this paper is the oral administration of practolol for 48h before anaesthesia in a group of treated hypertensive patients; this was in addition to their normal medication. The patients maintained a higher arterial pressure intra-operatively; the cardiac output was higher and systemic vascular resistance lower. The response to laryngoscopy and intubation was attenuated and ischaemic changes and dysrhythmias significantly reduced, from 38% to 4%.

No. 6. (1984) Cardiovascular responses to extradural blockade of treated and untreated hypertensive patients[21]. Mean arterial blood pressure changes were greater in the untreated hypertensive group of patients... for comparison the untreated hypertensive patient having a lumbar epidural had a 42% drop and the treated hypertensive patients 22%...combinations of falls in systemic vascular resistance and cardiac output. Three of the five untreated patients required intervention to maintain perfusion.

No. 7. (1986) Adrenergic responses to laryngoscopy [22]. Noradrenaline and adrenaline were measured during induction of anaesthesia and during laryngoscopy in normotensive and hypertensive patients. After induction of anaesthesia noradrenaline levels decreased; however, laryngoscopy was associated with a moderate rise in the normotensive patients but a marked increase in the hypertensive group with also an increase in adrenaline levels.

As indicated previously these studies took place over fifteen years with a variety of authors; of note are Meloche, Greene, Foex, Dagnino and Harvey. These papers are the 'skeleton' on which all the other papers about hypertension and anaesthesia hang; in chronological order they are [23-35].

A 2004 article by Howell, Sear and Foex<sup>vii</sup> (a meta-analysis) analysed 30 studies and demonstrated an odds ratio for the association between hypertensive disease and perioperative cardiac outcomes of 1.35 (1.17–1.56). This, although statistically significant, was considered not clinically significant, as there is "little evidence for an association between admission arterial pressures of less than 180 mmHg systolic or 110 mmHg diastolic and perioperative complications." They also commented that where patients have higher blood pressures, deferring surgery might not change the perioperative risk. They also commented on the fact that many preoperative blood pressure readings are 'stressed' readings and do not reflect the 'true' preoperative arterial pressure.

*"One of my most consistent interests in the field of hypertension, since long before I met George Pickering, has been the management of patients with phaeochromocytoma. Over the many years I anaesthetized more than 70 patients with various types of phaeo. The two late papers, one my BJA review (193) and the paper with the late John Farndon (198) (Prof of Surgery [Bristol] and a great expert on phaeochromocytoma) deserve to be mentioned.....also relevant was the paper on measuring the degree of beta-adrenoceptor blockade in humans (31) – a technique that stemmed from the need to do dose-response curves in the animal beta-blockade studies."*

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<sup>vii</sup> Hypertension, hypertensive heart disease and perioperative cardiac risk. British Journal of Anaesthesia. 2004;92(4):570-583 (a review)

## **Other cardiovascular studies**

### **Tetanus**

During 1968/69 four publications on tetanus appeared [36-39]. The first, in the Lancet, with Kerr, Corbett, Crampton Smith and Spalding, was a retrospective study of 82 patients with tetanus; it was argued that the high death rate was possibly due to fluctuating overactivity of the sympathetic nervous system and not just due to the hyperexcitability of motor neurones. They noted the marked range of blood pressure and heart rate variability and also the 24h catecholamine values (from nine patients); these varied from 70 -1100 mcg/day, the normal value being 450mcg/day. Carbon dioxide production was also raised. A comprehensive discussion of the thoughts of other workers in the field is presented; the final sentence presenting their view that all the signs are probably due to overactivity of the sympathetic nervous system.

The second paper was a prospective study of 21 patients admitted to the Oxford Respiration Unit between 1966 and 1968. These patients were studied in detail. The observation was that tetanus involves an overall increase in sympathetic activity with marked exacerbations when stimulated. Once again high catecholamine levels were measured..."the more severe the sympathetic overactivity the more likely is death to occur unless specific therapy is employed".

The remaining two papers at this time were on the treatment of the sympathetic overactivity, one in the Proceedings of the Royal Society of Medicine and one in the Lancet. In the latter article the management of four patients was described...chlorpromazine was found to be ineffectual, general anaesthesia (nitrous oxide, halothane and trichloroethylene, separately) were helpful but had to be discontinued because of toxicity. However, a combination of propranolol and bethanidine (blocks adrenergic transmission at postganglionic nerve endings) proved satisfactory. All patients survived.

The final paper on the topic of tetanus was in 1980 and was titled 'Diagnosis of tetanus', *"...this was a minor letter to the Lancet describing the failure of the normal swallowing reflexes as an aid to the early diagnosis of tetanus."*

## **Haemodynamic studies on an animal model**

*“The most important early papers were those with Gersh and Hahn, resulting from my [CP-R’s] development of an animal model in which to study true haemodynamic events on a beat-to-beat basis using implanted LV pressure transducers and electromagnetic flowmeters to derive LV  $dp/dt$ , aortic flow and stroke volume, stroke power and aortic input impedance. These techniques all had to be validated [40, 41] before being applied to the first comprehensive studies of the effects of halothane on the circulation [42-44]. These were groundbreaking studies at the time, and formed the basis for the next 8 years of work.”<sup>vi</sup>*

## **Haemodynamic studies in the dog (haemorrhage, beta-blockade and anaesthesia)**

Ignoring the first canine paper [5] on the effects of higher oxides of nitrogen (1967) we will move on to the effects of beta-blockade, anaesthesia and hypovolaemia. Most of this dog work was done over a four-year period 1973-77. The first [45] was an abstract in the Proceedings of the Anaesthetic Research Society at the Royal Postgraduate Medical School, Hammersmith Hospital. It addressed the anxiety of anaesthetists that patients on beta-blocking drugs might have impaired physiological responses to blood loss. Under halothane or N<sub>2</sub>O anaesthesia dogs, that had had a myocardial infarction, were bled to up 25% of their blood volume; firstly without beta-blockade and then after beta-blockade with practolol. It was shown that the blood loss was as well tolerated in the treated state as in the untreated state, however, this was not so with propranolol. It was shown that each set of animals had an equivalent degree of beta-blockade. This was published in full in 1976 [46].

There were two papers in 1974 [47] with Foex, (beta-blockade and pCO<sub>2</sub> levels) and with Roberts and Foex [48](interactions of beta-blockade, halothane and hypoxaemia). In the first it was shown that hypo-, or hypercapnia, during halothane anaesthesia caused a fall in heart rate, cardiac output, and myocardial contractility with an associated increase in systemic vascular resistance, and this was greater with N<sub>2</sub>O. This confirmed findings in a human study in 1968 [4] and it was advised

to control pCO<sub>2</sub> levels when studying the effects of beta-blockers. The second publication, another ARS abstract, was converted to a full paper in 1976 [49]. The bottom line was that “no adverse haemodynamic effect of the combination of propranolol, halothane and hypoxia was demonstrated”.

The 1975 paper [50] in the B.J.A. is a more searching exploration of the effects of PCO<sub>2</sub> levels on myocardial contractility, and does not involve beta-blockers. They were particularly interested in determining “the mechanism whereby cardiac output and stroke volume decreased during hypocapnic hyperventilation”. It was discovered that myocardial contractility and ventricular filling changes little but that the left ventricle fails to maintain its output against an increased systemic load. During hypercapnia the increase in stroke volume and cardiac output seen must have been due to a reduction in systemic vascular resistance. A reference to the previous 1974 paper suggests that these were the same dogs as used in the beta-blocker study.<sup>viii</sup>

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<sup>viii</sup> *“It would have been difficult for you to work out the inter-relationships between the various people who worked with me during the Oxford years (interrupted while I was away in San Diego 1973-74). Foëx’s DPhil thesis (1969-72) was on the haemodynamic effects of changes in Pco<sub>2</sub>; Tom Clarke’s DPhil thesis (1971-74) was on dilutional anaemia and the role of the sympathetic nervous system; and John Roberts’s DPhil thesis (1971-74) was on haemorrhage and beta-adrenoceptor blockade. The latter two were partly stimulated by George Biro, a Canadian physiologist on sabbatical with us. The various published papers took second place in importance to the publication of the theses, thus there was a considerable delay (4-6 years) in the actual publication of many of the papers .....The Horan papers (1977) were not part of a thesis, and were thus published more quickly, but they were the result of me having worked with enflurane and isoflurane in San Diego, and bringing back supplies of the drug that were not clinically available in the UK at that time. It was logical to repeat the halothane related study (49) with enflurane (53) and isoflurane (54).*

*A particularly relevant paper.....was [ref.] 141 ..... and part of Clarke’s work. Tom was a medical student at the time and did his DPhil as an intercalated degree, and then became an anaesthetist much later.”*



In 1976 there were three publications; a study of beta-adrenergic stimulation in anaemic animals [51] – the heart responding well – at least a two fold increase in  $dp/dt$ ; Horan presented an abstract on enflurane/beta-blockade/blood loss to the ARS [52] and the full paper on beta-blockade/blood loss/myocardial infarction as mentioned previously[46].

Following these studies was a set of three papers [49, 53, 54] all including the phrase “Haemodynamic interactions/responses....”.

The first: “Haemodynamic interactions of high-dose propranolol pretreatment and anaesthesia in the dog. II: The effects of acute arterial hypoxaemia at increasing depths of halothane anaesthesia.” I have been unable to find Haemodynamic interactions...I. *“It got lost by Foëx and Roberts while I was away.”* “Cardiac performance was enhanced in both groups during acute hypoxia. No adverse haemodynamic effect of the combination of propranolol, halothane and hypoxia was demonstrated.”

The second; "Haemodynamic responses to enflurane anaesthesia and hypovolaemia in the dog, and their modification by propranolol." It would appear from their results that enflurane resulted in greater adverse cardiovascular changes when compared with halothane...blood pressure, cardiac output, myocardial contractility all fell and were more marked with beta-blockade. Blood loss was tolerated poorly.

And the third, "Haemodynamic responses to isoflurane anaesthesia and hypovolaemia in the dog, and their modification by propranolol." Their bottom-line statement was that “The haemodynamic response to hypovolaemia during isoflurane anaesthesia was not modified by propranolol”.

To complete this animal work there are two publications that used goats, the first [55] studied the pulmonary and myocardial effects of Althesin and the second [56] assessed pulmonary arterial impedance during a halothane /N<sub>2</sub>O/O<sub>2</sub> anaesthetic at different level of CO<sub>2</sub>. Impedance did not seem to change, however pulmonary vascular resistance increased with hypercapnia and right ventricular work increased, it decreased with hypocapnia.

The last comment on cardiac output in dogs was in 1999 [57], "Metabolic regulation of cardiac output during inhalation anaesthesia in dogs" which was a comment on a paper by Scheeren, Schwarte and Arndt, *Acta Anaesthesiol Scand* 1999; 43: 421-430.<sup>ix</sup>

Another large section of CP-R's work was around the subject of drug infusions.

## **Infusions**

Prys-Roberts had worked with Althesin (with Foex and others) from 1972 [55, 58]... *but in 1977 he and Sear started work on Althesin infusions. John Sear was his first PhD student.* The first two described here [59, 60] and concerned various rates of infusion of Althesin, together with nitrous oxide. . . some patients breathing spontaneously some being artificially ventilated. There was a dose dependent decrease in arterial blood pressure due to a reduction in systemic vascular resistance but heart rate and cardiac output were increased. The accompanying paper showed that there was "an approximately linear relationship between the plasma concentration of alphaxalone and the rate of infusion of Althesin".

In 1980 CP-R wrote an article in *Acta Anaesthesiologica Belgica* on "Practical and pharmacological implications of continuous intravenous anaesthesia" [61] where it was suggested that there was a need for an index comparable to MAC for inhalational agents, we, in 2011, are still waiting for such an index.

In 1981 another couple of papers with Sear [62, 63] compared Althesin infusions with that of minaxolone...the latter having a slower recovery time; it was suggested that this was due to its water-solubility and a larger volume of distribution. Minaxolone did not last; "*it was withdrawn because it caused excitatory effects during induction, and because it was shown to be potential carcinogen in rats.*"

1983 was a very busy year with eight publications [64-71], three of these studying Althesin; one showed that Althesin diminished the baroreflex sensitivity

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<sup>ix</sup> " *This had very little to do with the Oxford dog studies, but was related to the much earlier work in Leeds in which we correlated cardiac output, a-v O<sub>2</sub> content difference, and VO<sub>2</sub>.*"

which allowed lower arterial pressures without tachycardia, another defined the equipotent doses needed to suppress the initial response to the surgical incision when used in premedicated patients with nitrous oxide and the third discussed hypersensitivity reaction to the agent. There was one more study of Althesin in 1984 [72] on how age influenced the infusion rate – the ‘old’ age group requiring less; Althesin was withdrawn in the same year.

Also in 1983 were two papers on the use of opiate infusions [64, 66] (fentanyl and alfentanil), as one might expect there was depression of the carbon dioxide response curve, the recovery from alfentanil being quicker than that from fentanyl. “The infusion after operation provided adequate analgesia at a cost of depression of carbon dioxide responsiveness to 50% of its value before operation, but only moderate effects on minute volume and PaCO<sub>2</sub>.” A further two papers on Alfentanil with nitrous oxide [73, 74] were published in 1984 and 1987 respectively.

The one study in 1983 where the named hypnotic has stood the test of time was [68] "Haemodynamic effects of infusions of diisopropyl phenol (ICI 35 868) during nitrous oxide anaesthesia in man." The blood pressure fell, as did cardiac output; the systemic vascular resistance increased during surgery (was this due to inadequate analgesia?) but decreased without surgery. Over the next twenty years there were another 21 papers involving propofol [75-95], some involving alfentanil.

Of particular interest are the following:

1. A manual infusion scheme [81] .....1988
2. Computer controlled infusion [84].....1989
3. Interaction between fentanyl and propofol using a computer-controlled infusion of propofol [85] .....1990
4. The effects on the EEG [91, 92, 95] ....1994 - 2004

The manual infusion scheme [81] was created by modifying a computer algorithm that was designed to achieve a particular blood concentration of propofol. A loading dose was followed by a series of infusions of reducing dosage. They reported increased cardiovascular stability and that “The quality of induction and maintenance of anaesthesia was satisfactory in every patient”.<sup>x</sup> The computer controlled infusion [84] was set to achieve and maintain a blood concentration of propofol 3  $\mu\text{g ml}^{-1}$  as rapidly as possible. The concentrations in the blood were close to the set target but were up to 20% higher in those patients being artificially ventilated.

Interaction between fentanyl and propofol using a computer-controlled infusion of propofol [85]? There didn’t seem to be one...except for the fact that those who had fentanyl had more satisfactory anaesthetic conditions. *“(Some clinicians had suggested, without any evidence, that fentanyl (infused simultaneously) would have an additive effect on that of propofol).”*

The effects on the EEG [91, 92, 95]: In the first paper in 1994, with Forrest and Tooley, he studied the changes in the Median Power Frequency (MPF) during propofol infusions over a range of conscious states. They derived MPF values for the suppression of response to verbal commands, the eyelash reflex and venepuncture. They also measured propofol concentrations. “The dose required for 50% suppression of MPF was 7.1 (6.2-8.0)  $\text{mg kg}^{-1} \text{h}^{-1}$ ”.

The second paper, with Tooley and Greenslade, reported the effects of propofol alone on the first 100 ms of the auditory evoked response (AER). The complex processing allowed them to derive the relationships between the blood concentrations of propofol, features of the AER and response to eyelash stimulus and venepuncture. The mid-latency Nb provided a confident prediction of the

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<sup>x</sup> “This paper was repeatedly misinterpreted because anaesthetists thought that we designed the manual infusion scheme for clinical applications – it was originally designed as a means of achieving stable blood concentrations of propofol (Diprivan in those days) for our haemodynamic studies (while we were working to get the computer controlled infusion working).”

likelihood of eyelash response; a sensitivity of 100% and a specificity of 96% and an overall correctness of 98%. The Na wave was the most successful when determining the response to venepuncture.<sup>xi</sup>

The third paper, Tooley being the common denominator, reported an investigation into the effects of an alfentanil/propofol infusion and electrode placement on mid-latency auditory evoked response (MLAER). Data were collected from two electrode sites and the results compared with the previous study where propofol was used alone. As one might intuitively expect the infusion rate of propofol required was significantly lower than using propofol alone. Nb latency was again the best MLAER discriminator of unconsciousness. The vertex-inion electrode site gave the best protection against artefact.

*“There was another series of studies by Alberto Gemal, a Brazilian on the mid-latency AER that resulted in a PhD (1999). These should have been published but (1) Gemal went back to*

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<sup>xi</sup> *“In [this] section it is important to understand what we were trying to do. Our primary aim was to develop a closed loop controlled infusion of drugs to maintain total intravenous anaesthesia. To that end we started to improve on the existing self-tuning control systems to accommodate the problem of oscillations in drug delivery resulting from a long lag-time between the measured variable (adequate anaesthesia – however measured) and the change in drug infusion – this is an inherent problem that required a very novel solution – two-steps ahead prediction with exponential forgetting of previous input variables. This was the basis of another PhD thesis by Roger Millard – the second of three medical physicists who worked with me in Bristol (the first was John Curnow, the third ..... being Mark Tooley). We used Millard’s various controller models to test the quality of control with intravenous drugs (phenylephrine or sodium nitroprusside) or inhalation anaesthetic (isoflurane) to control blood pressure (an easily measured variable). Another researcher (Edisio Pereira – a Brazilian) completed his PhD (1986) with me on this work*

*The studies on the EEG and AER were an attempt to correlate these indices of neurophysiological function with adequacy of anaesthesia (as you point out I was much against the concept of “depth of anaesthesia”). “*

Brazil ..... and (2) I retired and became more interested in trekking in the Andes and Himalaya! These studies showed that there were some derivatives of the MLAER that might be used as a controlled variable – they have not been published other than as a thesis in the University of Bristol.”

“Another very important paper you have missed altogether – not surprising as it would not appear in Index Medicus [96]. Mark Tooley, Frances Forrest and I in Bristol joined forces with Lionel Tarasenko’s group (Engineering Science) in Oxford. Tarasenko’s DPhil student, Mark Holt had had access to digitized EEG data from patients in the Oxford Sleep Laboratory, awake and during various stages of normal sleep. We had the same digitized EEG data from patients, awake and during infusions of propofol at two different levels. Holt used a very complex parametric model and statistical analysis of EEG pattern recognition and was able to show that anaesthesia produces a totally different EEG pattern to that of normal sleep, but that the awakening process involves REM sleep in both normal sleep and awakening from anaesthesia. Because Holt was a computer engineer he wanted the paper published in IEEE Proc.; and we have never published, let alone publicized, the results in an anaesthetic journal. BIS was just coming on the market when I retired, but I have never been very impressed with its use for controlling anaesthesia because the variability of the BIS signal at any specific concentration of propofol, for instance, is far too wide. It is easy to control any electrical signal that can be measured (accurately) at say 30 second to 1 minute intervals – but to control anaesthesia requires a far greater complexity of interactive input variables. It is a fascinating area to work on.

I should also point out that we used the infusion and anaesthetic controller to study sedation in our Intensive Care ward (refs 175,176,177,178 and 180).”

Before leaving this section on infusions we should consider the following papers [97-99]; in the first paper (1987) they used the self-tuning controller of Clarke and Gawthrop<sup>xii</sup>, which was used with a syringe pump delivering phenylephrine (a vasoconstrictor). The patients were undergoing lower abdominal surgery during epidural analgesia, which tends to drop the blood pressure. It proved very effective and was also used to produce controlled hypotension using sodium nitroprusside infusions.

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<sup>xii</sup> Clarke DW, Gawthrop PJ. Implementation and application of microprocessor-based self-tuners. Automatica 1981; 17: 233-244.

The next one in 1989 used the same controller but it controlled the administration of isoflurane, the vaporizer being controlled by an electric servomotor and clutch controlled by a BBC computer (it probably had only 128K RAM). The outcome (induced hypotension) in all study groups was “rapid, accurate, stable and reproducible” and equalled manual performance.

The final paper in this group compared the performance of the self-tuning algorithm when controlling isoflurane or nitroprusside. They were compared with another group of patients where hypotension was manually controlled using nitroprusside. They were unable to show any major differences.

There are many studies involving sophisticated techniques for the assessment of cardiorespiratory function and they are listed below, amongst other individual papers on a variety of subjects. To round off this bibliography is one article on monitoring for adequacy of anaesthesia; it displays his analytical thinking.

### **Anaesthesia – a practical or impractical construct?**

In this editorial in the British Journal of Anaesthesia, in 1987 [100], he attempted to clarify ‘our’ understanding of anaesthesia and questioned the validity of ‘depth-of-anaesthesia’ monitors; assuming that surgery is a noxious stimulus inducing a range of reflex responses.

The section below is a paraphrase of the main points.

1. Pain is the conscious perception of a noxious stimulus and so the state of anaesthesia can be defined as that in which, as a result of drug-induced unconsciousness, the patient neither perceives nor recalls noxious stimulation.
2. Anaesthesia is an all-or-none phenomenon - there cannot be degrees of anaesthesia, nor for that matter can there be variable depths of anaesthesia. The terms hypnosis and amnesia confuse the issue.
3. Analgesia is normally defined as diminished or abolished perception of pain in an otherwise conscious patient. There is little evidence at present to link the "anaesthetic" state induced by large doses of

opioids to receptor-mediated activity<sup>xiii</sup>.

4. Muscle relaxation...it is illogical to include muscle relaxation induced by neuromuscular blocking drugs as a component of the state of anaesthesia. Muscle relaxation is to satisfy the requirements of the anaesthetist for laryngoscopy and the surgeon for surgical access.
5. Noxious stimulation evokes a number of somatic and autonomic reflexes; they are particularly prominent when evoked by stimulation of abdominal or thoracic viscera. The continuation of noxious stimulation into the postoperative period also evokes a metabolic and endocrine response.
6. Suppression of both perception and recall of pain can be achieved with blood concentrations of either i.v. or inhalation anaesthetics which are too low to suppress the motor responses.
7. Suppression of the motor withdrawal reflex has been used as the basis of the main quantitative index of anaesthetic potency, the minimum alveolar concentration (MAC). It is therefore implicit, that the blood concentration of anaesthetic required to suppress the somatic motor response is higher than that required to induced unconsciousness, and by implication, perception of pain.
8. Greater concentrations of anaesthetics are required to suppress breathing responses to somatic noxious stimulation, than to suppress motor responses or to produce unconsciousness.
9. Sudomotor responses (sweating) are readily suppressed by low concentrations of volatile or i.v. anaesthetic supplements.
10. Haemodynamic responses occur even when anaesthetic concentrations are high enough to prevent sensory, motor and breathing responses.

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<sup>xiii</sup> Dodson, B. A., and Miller, K. W. (1985). Evidence for a dual mechanism in the anesthetic action of an opioid peptide. *Anesthesiology*, 62, 615.



Roizen, Horrigan and Frazer (1981)<sup>xiv</sup> introduced the concept of MAC-BAR as a correlate of MAC, being the alveolar concentration of an anaesthetic that would suppress haemodynamic and adrenergic responses in 50 % of patients. They found that the ratio of MAC-BAR to MAC was 1.45 for halothane and 1.60 for enflurane.

11. Hormonal responses are difficult to suppress by volatile anaesthetics, but can be partially suppressed by high doses of opioids and by regional blockade but only partially suppressed by beta-adrenoceptor blockade.
12. If one accepts the ranked order of responses to noxious stimulation then it is logical to consider anaesthesia as that state which ensures the suppression of the somatic and visceral sensory components, and thus the perception of pain.
13. Analgesia, muscle relaxation, and suppression of autonomic activity, are not components of anaesthesia. Rather they should be considered as desirable supplements to the state of anaesthesia as a means to enable surgery to be performed.
14. Any reliable indicator that the level of anaesthesia is adequate to ensure lack of awareness is highly desirable.
15. Methods have been described to achieve this, oesophageal motility, the EEG and its derived parameters and brain stem auditory evoked responses. These clearly demonstrate a dose-effect relationship for many anaesthetic agents, but do not answer that fundamental question: is it feasible to find some measure which will ensure that the patient will be unaware of, and will not recall, events and sensations during surgery?

An interesting editorial in its analysis of the difference between what the *state*

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<sup>xiv</sup> Roizen, M. F., Horrigan, R. W., and Frazer, B. M. (1981). Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision—MAC BAR. *Anesthesiology*, 54, 390.

of anaesthesia is and what is called 'anaesthesia', which includes the 'supplements' that make the *practice-of-anaesthesia*' a practical construct.

This is a large body of work and CP-R worked with many well-known anaesthetist-scientists, to name a few (in no particular order), Greenbaum, Kellman, Nunn, Foex, Sear, Hutton, Adams, and Edmonds-Seal...forgive me if I've missed you off.

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