John B (Iain) Glen
BVMS, DVA, PhD, FRCA, DVMS (Hon).

Iain (Gaelic for John) grew up on the Island of Arran in Scotland. He graduated in veterinary medicine in 1963 and after a year in Kenya doing tropical veterinary medicine returned to Glasgow and spent a year as a House Surgeon in the Small Animal Surgery Department. He became Assistant Lecturer in Veterinary Surgery (Anaesthesia) in 1965.

At this time the Royal College of Veterinary Surgeons (RCVS) had decided develop veterinary anaesthesia as a speciality, a Diploma in Veterinary Anaesthesia (DVA).

In Glasgow, Sir William Weipers, Professor of Veterinary Surgery, made contact with the medical anaesthetist Professor Alex Forrester at the Royal Infirmary and obtained his agreement that Iain could attend classes for anaesthetists preparing for Fellowship examinations. Two veterinarians who had specialised in veterinary anaesthesia, Dr Lesley Hall and Dr Barbara Weaver, became foundation Diplomates and Professor T. Cecil Gray was the medical examiner when he was the first to obtain the RCVS DVA by examination in 1968.

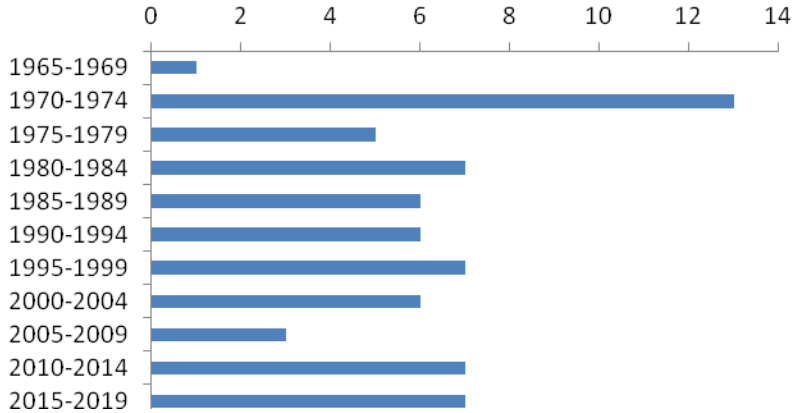
At that time general anaesthesia in most animal species consisted of premedication with acepromazine, induction with

intravenous thiopental and maintenance of anaesthesia with halothane.

In 1982 he gained a PhD titled “Studies on the pharmacology of injectable anaesthetic agents” [71].

He joined Imperial Chemical Industries (ICI) Pharmaceuticals Division in 1972; which later became part of Astra-Zeneca (the result of a merger between Swedish Astra AB and the British Zeneca Group which was formed following a demerger from the parent ICI Company in 1993).

In terms of numbers of publications the most prolific year was 1973 with a total of five; 1974-1976 and 1981-1983 were lean periods.



Glen’s first publication, in 1966, was on the subject of the identification of sublingual duct defects by sialography [1]. This was the first of several publications involving the salivary tract. [1,4,5,8].

Salivary tract pathology

Sialography was used in the investigation of eight dogs with fluid filled sub-mandibular swellings previously designated as developmental branchial cysts [1]. A defect in one or both sublingual salivary ducts was found in 7 cases and in the remaining case, no recurrence followed removal of a sublingual gland.

Cortisol utilization by salivary glands, kidneys and adrenals of various mammals was the subject of a 1970 publication [4]. It was found that 11β-Hydroxysteroid dehydrogenase activity was localized in salivary gland ducts, renal collecting and convoluted tubules and in the adrenal cortex of some species. There was no obvious relationship between the levels of enzyme activity in these organs.

In 1971 Glen and Lawson described a new surgical technique for the treatment of keratoconjuntivitis sicca in the dog [5].

SUMMARY.—A detailed description of the isolation of the parotid papilla and of the technique of suturing the papilla into the conjunctiva is given. This technique differs from those described previously in that the whole operation is performed through a single incision on the lateral aspect of the face, and a lateral canthotomy is not required.

A year later a series of fifty consecutive cases of salivary mucocoeles in dogs were investigated [8]. Sialography demonstrated sublingual salivary gland, or duct defects in forty cases with a normal mandibular sialogram in seven of the remaining 10 cases, normal mandibular sialograms were obtained on the affected side. This completes this collection.

Following Glen's first publication in 1966 was an investigation into the non-invasive measurement of blood pressure, it was the first of three [2] 1970), [9] 1972 and [14] in1973.

Blood pressure measurement

The technique of using inflated cuffs for indirect blood pressure measurement was found to be applicable to anaesthetised dogs [2]. He showed that for accuracy the width of the cuff should be 2.5 cm wide for dogs less than 12 kg and 3.75 cm wide for heavier dogs.

In 1972 he assessed the systolic pressure, using the indirect method, in standing horses with cuffs applied to the tail, and found a mean value of 140 mm Hg [9]. The technique was sufficiently sensitive to detect changes in pressure caused by sedation with acetylpromazine. The indirect readings were slightly lower than values in the literature for intra-arterial measurements.

Further work was completed in 1973[14]. A comparison of direct and indirect measurements of systolic pressure was undertaken in 50 dogs; an infant sphygmomanometer was used for the indirect pressure measurement. An attempt was made to correlate accuracy with the size of cuff and foreleg circumference - it was more closely correlated with weight.

Before describing Glen's major contribution to anaesthesia, the development of ICI 35868, Diprivan/propofol, there are a few more minor publications to cover.

Carbon dioxide

Carbon dioxide was a normal part of the practice of [human] anaesthesia; there was always a carbon dioxide cylinder on the back of the anaesthetic machine. It was used primarily for the stimulation of breathing post-surgery at a time when hyperventilation was part of an anaesthetic technique (the "Liverpool Technique" combined the use of a muscle relaxant, nitrous oxide and hyperventilation). This is no longer the case, there was, to my limited knowledge, at least one death due to the accidental flow of CO_2 over a prolonged period. In abattoirs it has been used as a form of anaesthesia pre –slaughter. Carbon dioxide anaesthesia was first investigated, in animals, by Henry Hill Hickman in 1823.

This paper by Glen [6] outlined the technique used for pre-slaughter anaesthesia – in brief 12% CO_2 cause loss of consciousness, 30% percent produced anaesthesia and acidosis, 65-85%. CO_2 was used with air and so hypoxia was a contributory factor to unconsciousness. This may also have been part of the Liverpool technique as hypocapnoea leads to cerebral vascular constriction.

In 1972 real-time carbon dioxide monitoring was not available but a lot of work was being done towards this goal. In this paper [10] fifty-two comparisons were made between tracheal end-tidal carbon dioxide tension (PET CO_2) and simultaneously measured arterial carbon dioxide tension ($paCO_2$) in 22 anaesthetised dogs. The mean arterial to end-tidal carbon dioxide tension gradient was 3.2 mm Hg, (range -6 and +13 mmHg. No anaesthetic technique was associated with the larger gradients.

CO_2 may have been investigated for anaesthesia in humans, but not for euthanasia. In this 1973 study [13] euthanasia of 11 adult cats and 20 kittens was carried out in a U.F.A.W. Euthanasia Cabinet and the times to loss of consciousness, respiratory arrest, and death noted. Animals in a wire mesh cage were lowered to the floor of a cabinet which had been primed previously with CO_2. Concentrations of CO_2 greater than 60% caused loss of consciousness within 45 seconds, respiratory arrest within 5 minutes. Lower concentration took longer.

It was considered that CO_2 provided a suitable alternative to chloroform for use by non- veterinary personnel employed by Animal Welfare Societies.

Scavenging systems

In the 1970s (and prior) exhaled gas from patients was exhausted through the expiratory valve which was in many cases just below the nose of the anaesthetist holding a mask in place. This 1980 paper [23] reflects the moves towards a cleaner environment.

With a minimum fresh gas flow of 1 litre per minute per mask anaesthesia was maintained with an inspired concentration of 1.5-2% halothane. The apparatus they described reduced the vapour concentration in the operator's breathing zone to 5 ppm, previously 250 ppm had been recorded.

Four years later design modifications were made [26]. It was found that the halothane vapour concentration in the operator's breathing zone depended on the design of the oronasal mask. A concentration of halothane less than 1 ppm was achieved.

Neuroleptanalgesia

A combination of droperidol and fentanyl (Thalamonal Vet) produced satisfactory conditions for the performance of minor surgery [3 (1970)]. This early publication described its use in dogs.

Thalamonal Vet facilitated short painful procedures and with the use of Nalorphine animals could be quickly returned to waiting owners.

For examinations 1 ml/40 lbs (18kg) was used but for minor surgical procedures where analgesia was important a dose of 1 m1/20 lbs was required. Intramuscular injection was valuable when treating vicious dogs.

There was a high incidence of side effects; spontaneous movements, increased sensitivity to noise, occasionally insufficient analgesia or sedation and respiratory depression.
'Neuroleptanalgesia in the dog', published in The Veterinary Annual in 1973 [11] was a more general description of the technique.

Dissociative anaesthesia, a 'cousin' of neuroleptanalgesia, was described in two publications. The use of ketamine in cats [12] concluded that rapid and reliable immobilisation could be achieved with low doses but even at high doses, which were associated with prolonged recovery; satisfactory operating conditions could not be consistently attained. A general review of veterinary applications of dissociative anaesthesia was published in Proceedings of the Association of Veterinary Anaesthetists, also in 1973 [15]. It is associated with catalepsy, catatonia, analgesia and amnesia, and

phencyclidine, ketamine and tiletamine have been used in monkeys, pigs, and cats.

'The effects of some analgesic and neuroleptic drugs on the spasmogenic actions of substance P on guinea-pig ileum' in 1978 [19] was a laboratory based study. Substance P was thought to be a neurotransmitter associated with pain sensation at the spinal cord level. It was envisaged that analgesic activity might be related to Substance P antagonism such that this model could be used to search for a specific antagonist to Substance P. A range of peripherally acting analgesics and opioid agonists were studied but none were found to be specific antagonists of Substance P.

Some general pharmacology

The following papers resulted from work done when Glen moved from Glasgow to head the Anaesthesia and Analgesia Project Team at ICI Pharmaceuticals Division in Cheshire.

In '77 Glen reported a method for the evaluation of the speed of onset of i.v. anaesthetics in mice [16]. It involved the determination of the median hypnotic dose (HD50), plotting the mean induction time over a range of doses against the logarithm of the dose and comparing the induction times at 1.25 HD50. 1–s injection induction times were similar with thiopentone and Althesin. Those with methohexitone, etomidate and propanidid were marginally longer and ketamine and pentobarbitone were obviously slower.

Adverse reactions to intravenous agents are a constant hazard. Reactions to Cremophor-containing anaesthetic agents

Althesin and propanidid (Epontol) were reported to be more frequent than with thiopentone. The mini-pig was studied to determine the possible role of Cremophor [20]. A second injection of Cremophor EL or Althesin and propanidid (Epontol) produced a high frequency of adverse responses. No abnormal responses were seen using thiopentone. When propanidid and the steroids in Althesin were solubilised in a non-Cremophor formulation no reactions were observed with the second administration of propanidid but some reactions were still seen with the Althesin steroids. This model could then be used to search for an alternative non-Cremophor formulation of propofol whose anaesthetic properties had been first observed in 1973

This was preceded, in 1978, by a section in "Adverse Response to Intravenous Drugs", 129-135 [18].

Propofol

ICI 35868, Diprivan/Propofol is a drug that is used probably millions of times a day for the induction of anaesthesia. Below is the story of its early investigation and use.

Clinical use is dependent on knowledge of efficacy, side effects, pharmacokinetics and mode of administration. Much of this work was a collaborative effort but Glen's contribution was significant, as a veterinarian and as a scientist with ICI (Imperial Chemical Industries).

The first publications on propofol were in 1980.

James R and Glen JB - "Synthesis, biological evaluation and preliminary structure-activity considerations of a series of

alkylphenols as intravenous anaesthetic agents" [24]. 2,6-diethylphenol was found to have anaesthetic activity in mice and so a series of alkylphenols was examined and evaluated in in mice and rabbits. 2,6-diisopropylphenol was selected for further evaluation based on the optimum balance between potency, speed of onset and freedom from excitatory effects. This introductory paper paired nicely with "Animal studies of the anaesthetic activity of ICI 35868" [21]. This new i.v. anaesthetic, which was unrelated to barbiturate, eugenol or steroid agents, was studied in a range of animal species. It was a rapidly acting agent which produced anaesthesia of short duration and without excitatory side-effects. In the mouse ICI 35868 was 1.8 times more potent than thiopentone. Recovery was rapid even after repeated administration; there was no tissue damage, greater reflex depression and more profound e.e.g. changes. It was compatible with a wide range of drugs used for anaesthesia. This was a great start.

In 1984 it was reported that an aqueous soya bean emulsion formulation of ICI 35 868 with 2,6-diisopropylphenol had anaesthetic properties in rats, mice and mini-pigs similar to those of the Cremophor formulation [25]. In dogs there were no untoward effects with the new emulsion whereas the Cremophor formulation increased plasma histamine concentration. Similarly in the mini-pig, but with the Cremophor formulation anaphylactoid responses occurred after a second injection. It was suggested that the emulsion formulation might produce less pain on i.v. injection

Also in 1984 a review of the outcomes associated with three different formulations was published [27]. The

formulations contained 10% Cremophor EL, 10%Synperonic PE 39/70 or an aqueous emulsion in soya bean oil.

In 1985 the adrenocortial function in rats during anaesthesia with etomidate, methohexitone or propofol was reported [28]. A reduced corticosterone response to ACTH was observed in rats anaesthetised with etomidate but not with the other two agents.

In the same year (1985) another review was published summarising a variety of studies concerning the general pharmacology of propofol [29]. There was no evidence of central anticholinergic or anticonvulsant effect in mice and no potentiation of anaesthesia was found 24 hours following pretreatment with phenelzine, amitriptyline, diazepam or alcohol. Oral propofol failed to induce anaesthesia. In pigs beta-adrenoceptor antagonists, atenolol or propranolol, were well tolerated. The arrhythmia threshold, after propofol, to adrenaline was greater than in cats anaesthetised with halothane; there was no ganglion blocking or alpha-adrenoceptor antagonist activity. Nor did propofol have any effect on ADP-induced platelet aggregation, whole blood clotting time, bronchomotor tone or gastrointestinal motility. There was only a slight reduction in sodium excretion and the response to ACTH was normal following a 90 minute infusion of propofol.

This was indicative of a very ‘clean’ drug.

Human clinical studies

Also in 1985 was a report, in man, of a randomised study comparing the effects of the emulsion formulation of propofol with those of Althesin containing Cremophor [30]. Plasma histamine concentration, immunoglobulin levels,

complement C3 and complement C3 conversion were measured. In only one volunteer, in the Althesin group, was there a relatively large increase in plasma histamine. There were no changes suggesting the possibility of an anaphylactoid response in propofol treated subjects.

By this time Glen had moved to the Medical Department at ICI to assist Dr Stark in the clinical evaluation of the emulsion formulation. Another 1985 paper, published in the Postgraduate Medical Journal, [31] reviews clinical results with the emulsion formulation obtained from studies on 1720 patients in 27 studies.

Drugs used during anaesthesia are often used in combination, particularly for infusions for total intravenous anaesthesia (TIVA). Gavin Kenny (see separate bibliography) was a keen advocate of TIVA and in 1992 work was presented with Taylor and Glen on the stability of a mixture of propofol and alfentanil [36]. It was concluded, after studying 40 patients, that propofol and alfentanil may be administered by infusion from a single syringe without diminished or delayed effect of the opioid.

In the same year Glen had work published with another two well known medical anaesthetists, John Sear and Pierre Foex [38]. Using graded infusion rates of propofol in dogs left ventricular global and regional function was assessed. Administration of propofol significantly reduced left ventricular preload, contractility was depressed (contributing to the induced hypotension), relaxation was impaired but the regulation of coronary blood flow was not affected.

1992 was a busy year as another paper [39] described the metabolism and elimination of propofol – see below in the pharmacokinetics section.

TIVA with Target Controlled Infusions

Three years later another TIVA based study was published with Russell et al [40]. This study, conducted by a group of anaesthetists with little or no experience of the use of propofol by infusion, compared manually controlled with target-controlled infusion using the Diprifusor system, and expressed a clear preference for the target-controlled system. Significantly more propofol was administered during both induction and maintenance with the TCI system but recovery from anaesthesia was not significantly prolonged. Bispectral index monitoring was used to determine the difference between manual and target controlled systems. In both groups the rate of propofol administration was adjusted without knowledge of the BIS value. The total dose of propofol in the target controlled group was an average of 9.9 (SD 1.6) mg $kg^{-1}h^{-1}$ compared with 8.1 (SD 1.0) mg $kg^{-1}h^{-1}$ in the manual group, $p< 0.0001$. The higher doses of propofol and lower BIS values occurred mainly at the start of anaesthesia.

Another paper, in 1995, with Sear studied propofol administered by a manual infusion regimen using two techniques [41]. In one body weight was a determinant of the dosage and the other where 70kg was used as standard; it used a three-step infusion method. Cardiovascular effects, recovery times and the apparent steady state blood propofol concentrations were similar. It was suggested that for the 60-90

kg weight range a standard dose infusion regimen would be a suitable starting point followed by titration of the infusion rate according to clinical response.

1995 was another busy year with a third major publication; it was pharmacokinetic so see below [42].

In 1996 a collaborative study with Mirakhur (see his separate bibliography) et al compared total intravenous anaesthesia with propofol with isoflurane anaesthesia for major abdominal surgery [43]. Recovery from anaesthesia was significantly faster in the propofol group and there was significantly less nausea, 15.4% compared to 33.7% in the first two postoperative hours. There were no other significant differences.

Also in1996 a study involving the administration of propofol by target-controlled infusion (TCI) in patients undergoing coronary artery surgery [44]. Patients were anaesthetised using a continuous infusion of alfentanil and propofol. Arterial samples were analysed at specific times before, during and after bypass. The measured blood propofol concentrations were underestimated by the TCI system with a bias of +21.2% during pre-bypass and +9.6% during the bypass periods. The mean propofol concentrations required to induce and maintain anaesthesia before bypass were 0.92 μg/ml and 3.64 μg/ml respectively, while during and after bypass the concentration required to for anesthesia was 2.22 μg/ml. The overall quality and ease of control of anesthesia were considered as being good or adequate.

Drs Gavin Kenny and Martin White developed a computerised system for delivery of intravenous anaesthesia. It

allowed control of the drug's concentration within the patient. With AstraZeneca the Diprifusor® target-controlled infusion system was launched in 1996.

In 1998 Glen published "The development of 'Diprifusor': a TCI system for propofol" [46] and "Evaluation of the predictive performance of a 'Diprifusor' TCI system" [47].

The first was an explanatory review rather than a research report. Preferred pharmacokinetic parameters for propofol were selected using computer simulation and the selected model was included in a 'Diprifusor' module interfaced with a computer-compatible infusion pump. Clinical trials led to guidance on appropriate target concentrations for propofol to the point where they were included in drug prescribing information. Clinical studies indicated that the blood concentrations were 16% greater than the calculated values. This meant that titration of the target concentration was still required to produce a specific pharmacodynamic effect.

The second paper evaluated the predictive performance of the 'Diprifusor' TCI system in 46 patients undergoing major surgery. Three age groups were studied and arterial propofol concentrations were compared with values calculated by the target controlled infusion system.

Performance indices were similar in the three age groups but measured concentrations tended to be higher than calculated concentrations, particularly following induction or an increase in target concentration. The mean propofol target concentration during maintenance was lower in older patients, The control of depth of anaesthesia was good such that the predictive performance was considered clinically acceptable.

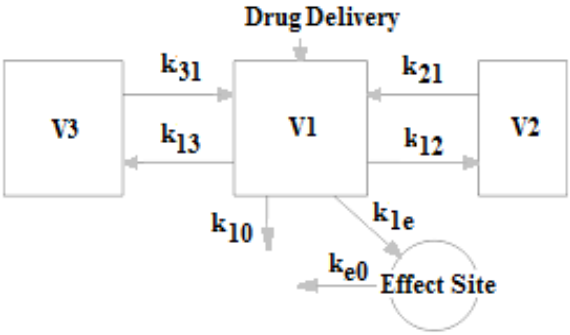
In 2001 Glen returned to veterinary assessment of a modified TCI system in dogs during dental surgery [49]
Predicted concentrations of propofol were compared with measured concentrations in venous blood samples. The performance of TCI systems were considered acceptable when the median prediction error was not greater than ±10 to 20% and the median absolute performance error not greater than 20 to 30%. The results fell within these and the optimal induction target was found to be 3 μg/ml, and maintenance targets of between 2.5 and 4.7 μg/ml propofol.

Sedation in intensive care had been a longstanding issue, with the use of opiates and benzodiazepine being common. Even though propofol infusions had been used for some time, and etomidate - which was problematic in its effect on the pituitary/adrenal axis; TCI propofol was studied in 2004 [54].
A multicentre study determined the range of target blood propofol concentrations, with opiates, for sedation in 122 adults using the Diprifusor system. Assessed with a modified Ramsay score a desired level of sedation was achieved for 84% of the sedation period. Different propofol targets were set for different groups of patient; postcardiac, brain injured and general ICU patients. Measured concentrations were close to values predicted by the Diprifusor and target range of 0.2-2.0 microg.ml^{-1} was proposed for propofol sedation in this setting.

Pharmacokinetics

The pharmacokinetic variables that determine distribution and elimination of drugs in the body are the foundations on which dosage is based, whether single dose,

repeated doses or infusions, which are, in essence, multiple tiny doses given at high frequency. Part of this is determining how the drug is metabolised and excreted.



In 1992 the major metabolite of propofol (propofol glucuronide, PG) was studied [39]. Bolus doses of 14C-PG were given to rats and dogs and 40 and 66% respectively were eliminated in the urine, 48 and 19% in the faeces. In the dog PG's plasma half-life was four minutes, and the elimination half-life was 80 minutes. Total body clearance was 1.8 ml/min per kg, and renal clearance about 20% GFR. Metabolites, mainly side-chain hydroxylation products, were evident in both species from 4 h after dosing. Intravenous doses of PG in mice had no hypnotic activity.

Not all models of a drug's distribution and elimination are equal and so in 1995 model selection for target controlled infusions of propofol was undertaken [42]. Patients received propofol TCI regimens but were randomly allocated to one of three parameter sets (Dyck, Marsh and Tackley), prediction errors were calculated. In the Dyck group the bias had a mean of 43%, Marsh -1% and Tackley -3%. The inaccuracy of the Dyck

group was 47%, the Marsh 29% and Tackley 24%. It was concluded that the Marsh and Tackley models had equally good performance within the range of 3-6 micrograms/ml. Clinically, the choice of pharmacokinetic model did not seem to make a difference.

Results obtained in in-vitro studies are assumed to have clinical relevance if the perfusing concentration is close to the measured blood concentration in vivo; this assumption was investigated in Wistar rats in 2001 [50]. Heart tissue:blood propofol concentrations ratio close to unity have been recorded in vivo in rats but tissue:organ bath ratios had not been measured.

Hearts obtained from Wistar rats were mounted in a Langendorff apparatus and perfused at 37°C with Krebs± Henseleit solution with propofol 10 mg ml±1, with propofol and bovine serum albumin 2% or with propofol and BSA 4% or intralipid. Propofol concentration in the heart and perfusate were measured after 75 minutes. In brief, in the absence of protein, "...propofol perfusate concentrations, equivalent to plasma concentrations in man, may achieve tissue propofol concentrations greatly in excess of tissue concentrations resulting from equilibration between blood and tissues in vivo."

Ten years after the introduction of the Diprifusor TCI system pharmacokinetic studies were still being reported; in 2007 Glen, with Thomson and Nimmo, determined the optimum k_{e0} value for use with the Marsh PK model for propofol in effect-site control mode [55]. If the k_{e0} is inappropriate the sedation may lighten or deepen over time. Sedation was measured using the visual reaction time. In the 64 patients aged 41 ± 11years; the inter-individual variation was marked; the

calculated median value for k_{e0} was 0.59/minute (95% CI 0.36 – 0.76).

Refining the TCI system continued in 2009 with the evaluation of four predictive models [56]. The Marsh model was implemented using the Diprifusor; the 'Schnider', 'Schuttler', and 'White' models were simulated using a computer. Data from a previous study with arterial propofol concentrations and patient characteristics was used. The overall assessment indicated that all four models were clinically acceptable. However, the analysis of bias at different phases of an infusion showed differences. It was suggested that evaluation of divergence should involve linear regression analysis of both absolute and signed predictive errors.

In 2010 Glen described a pragmatic approach to effect-site target-controlled infusion [58]. It was proposed to determine a suitable blood–brain equilibration rate constant for the Marsh pharmacokinetic model. This was based on the hypothesis that during target-controlled infusion, if the target concentration is set to the calculated effect-site concentration and a desired level of sedation is reached, sedation level should remain constant if the correct blood–brain equilibration rate constant (k_{e0}) is used.

With any group of patients pharmacokinetic constants are likely to vary widely from the average value used in a model. This work showed that changes in V1 could mimic changes in k_{e0} such that a wide range of apparent k_{e0} values would be required to achieve a stable effect in all patients. The k_{e0} value that provided a stable effect in the greatest number of patients might "differ from values determined in integrated PK/PD studies but may be more clinically useful."

The following year, 2011, there was another PK paper, this time with Nimmo et al [59], investigating the Marsh model for propofol with an alternative k_{e0} value. There were concerns about the appropriate combination of PK model and k_{e0} value and unwanted haemodynamic side-effects because of larger bolus doses of propofol. Eighty patients were studied in a double-blinded trial. They were randomly allocated to one of four models with different k_{e0} values. An initial target concentration of 4μg.ml−1 was set for each patient; the primary end-point was time to loss of consciousness. It was concluded that the Marsh PK model/k_{e0} 0.6 min^{-1} combination could be used to induce anaesthesia without excessive effects on blood pressure.

This 'hunt' for the k_{e0} was described in a letter to Anesthesia and Analgesia in 2013 [60]. It was a plea for 'pharmacokinetic authors' to report their findings correctly. It described the plethora of TCI systems. "... it is not sufficient to just describe the particular commercial device used as some of these provide a choice of pharmacokinetic model, k_{e0} or time to peak effect... In most cases, these research systems also offer the user a choice of models with different k_{e0}s. It is also important to note that these systems have evolved over the years as new information has become available" and therefore might not be directly comparable.

The hunt for the ke0 continued in 2014 with the Nimmo team again [61]. **"**A novel technique to determine an 'apparent k_{e0}' value for use with the Marsh pharmacokinetic model for propofol." This was because debate continued over the most appropriate blood-brain equilibration rate constant (k_{e0}) for use with the Marsh pharmacokinetic model. "Sixty-four patients

were sedated with incremental increases in effect-site target concentration of propofol while using six different k_{e0} values within the range 0.2-1.2 min^{-1}". Visual reaction time was used to assess the depth of sedation and an 'apparent ke0' value of 0.61 min^{-1} (95% CI 0.37-0.78 min^{-1}) had the greatest probability of achieving the desired clinical effect.

A follow-up paper in the same year with Nimmo et al [62] studied the induction of general anaesthesia with propofol and the influence of pharmacokinetic model and k_{e0} value, 0.6 min^{-1}. Speed of induction and side-effects were assessed with three other target-controlled infusion systems. Induction times were shorter with the Marsh model with a k_{e0} of either 0.6 min^{-1} or 1.2 min^{-1} than with the Marsh model in blood concentration control. The Schnider model produced induction times that were longer. There were no differences in blood pressure changes or frequency of apnoeas.

Another paper, in 2014 (a busy year), compared three pharmacokinetic models [63]. They compared the existing Diprifusor using the Marsh model and the Schnider model with a new modification of the Diprifusor model (White) that included age and sex information.

Computer simulation replicated the infusion profiles of an earlier study of 41 patients. "Bias with the White model (5%) was significantly less ($p < 0.0001$) than with the Diprifusor (16%) or Schnider (15%) models." None of the models accounted for all the inter-individual variation in propofol clearance but the improved performance suggests the White model has merit.

"One advantage of effect-site target-controlled infusion is the administration of a larger initial dose of propofol to speed

up the induction of anaesthesia", 2015 [65]. The influence of target concentration, equilibration rate constant (k_{e0}) and pharmacokinetic model on the initial propofol dose delivered was reported.

The induction dose is determined by the pharmacokinetic model parameters, the target set and the blood-effect time-constant k_{e0}. Computer simulations determined the k_{e0} values using three pharmacokinetic models for propofol for a particular induction dose. "With an effect site target of 4 $\mu g.ml^{-1}$ in a 35-year-old, 170-cm tall, 70-kg male subject, the k_{e0} values delivering a dose of 1.75 $mg.kg^{-1}$ with the Marsh, Schnider and Eleveld models were 0.59 min^{-1}, 0.20 min^{-1} and 0.26 min^{-1}, respectively." The predicted effect site concentrations using these k_{e0} values at loss of consciousness were close to those for maintaining anaesthesia.

History

Glen, later in his career, received requests from journal and text book editors for historical accounts of aspects of his work.

He started by contributing a section on the Discovery and Development of Propofol in a chapter on "Some examples of industry contributions to the history of anesthesia" published in 'The Wondrous Story of Anesthesia' [64] in 2014. Topics discussed by co-authors included a description of how high pressure cylinders made in the 1800s made the economical use of N_2O and O_2 possible. How Shukys, at Ohio Chemical/Airco, synthesized fluroxene, in 1953, and how Suckling, at Imperial Chemical Industries, synthesized

halothane in the 1960s. The first variable bypass vaporizer, Fluotec, was made in the 1950s when Edmonson and Jones organized Cyprane Ltd to make it, this indicated the concentration of anaesthetic delivered. Without these 'actors' anaesthesia would now be different.

This was followed in 2016 by a history of target-controlled infusion [66]. This review describes the pharmacokinetic principles of TCI, the development of TCI systems and technical and regulatory issues addressed in prototype developments. Readers who have got this far will know that it is the "technique of infusing IV drugs to achieve a user-defined predicted ("target") drug concentration in a specific body compartment or tissue of interest". This was a comprehensive history that included the following details: –

The first prototype TCI system was developed by Schwilden and Schuttler in Bon in 1979.

White and Kenny, at Glasgow University, developed an Atari-controlled propofol computer pump to deliver a targeted plasma concentration of propofol and later used an Ohmeda 9000 pump connected to a Psion Organiser, a hand-held computer. Later the Psion organizer was replaced by a customized backbar containing a dual microprocessor control system that served as the prototype for the Diprifusor module. It used two processors to solve the PK equations. Parallel calculations of plasma concentration based on the movement of the pump motor. This was done to ensure a double check on the infused volume to guarantee safety. If you are really interested in the history of this major development it's best to read the full text.

Another paper in 2016, with Absalom, Zwart, Schnider and Struys was on the subject of target-controlled infusion: a mature technology, in Anesthesia and Analgesia [67].

Target-controlled infusions had been used for more than two decades and non-approved TCI software systems had been used in almost 600 published studies. The first-generation pumps were approved in 1996 and an estimated 25,000 units had been sold. TCI systems were available in at least 96 countries and were used to administer propofol and opioids for IV sedation and general anesthesia. Non-approved software is commonly used in studies because the research software has greater flexibility than approved TCI systems. TCI devices had not received regulatory approval in the United States (2016). This means that TCI propofol and opioid infusions for sedation and anaesthesia was only possible using research software in IRB-approved research studies.

In 2017 Glen wrote a section about "The development and regulation of commercial devices for the administration of drugs by target controlled infusion". In 'Total intravenous anaesthesia and target controlled infusions: a comprehensive global anthology' [68]. This was a big book (824 pages), a combination of veterinary and human information. It was noted by reviewers (Short and Willemsen), on the positive side, that "...it breaks new ground as a reference source on a subject that is practiced widely but is often not truly understood ... It is a high-quality volume ... Those that take the time to read a good portion of it will be richly rewarded in their increased understanding of TIVA. It was pointed out, again, that TCI was not available in the USA.

In 2018 Glen was invited to write an article in JAMA about “The discovery and development of propofol”, when he had been awarded the 2018 Lasker-DeBakey Clinical Medical Research Award.

It covered the discovery and development of propofol, describing the systematic evaluation of related alkyl substituted phenols, mice given propofol recovered enough to balance on a horizontal rod very rapidly after regaining consciousness. There was a thirteen year delay because of the difficulty finding an acceptable formulation. Finally a formulation containing soybean oil and egg lecithin had the desirable properties. From then on work continued as described above. The article is an interesting read.

“Balancing tricks and mini-pigs: Steps along the road to propofol”, also published in 2018, covers similar ground but is a more personal record, including members of the team involved in the early development, Katie Hopkins, Sue Hunter, Kate O’Conner, Ron Stark, Sue Binks and Vera Dutka [70].

The following article “Try, try, and try again: personal reflections on the development of propofol” [71, 2019] is even more detailed regarding the process of developing a new drug, it is extremely interesting to read the inside story. As a New Zealander it was a little surprising to see a NZ connection – “...went to New Zealand with John Dundee to participate in the first launch meetings in Auckland and Rotorua, with results of a local study presented by Tony Newson”.

As Glen has written – “Drug development requires the involvement and assistance of a host of company experts and support staff. In particular I recognise the key roles played by Roger James, Steve Strong, Alec Jamieson, Sue Hunter, Ron

Stark, Katie Hopkins, Sue Binks, David Goodale, David Priaulx, David Kent, Hugh Adam, Ian Cockshott, and Phil Arundel."

Iain Glen was awarded a Fellowship of the Royal College of Anaesthetists, by election, in 2002.

Prizes and Awards

Lawson, Walley and Williams prize, 1963 (Veterinary undergraduate prize)

William Hunting Award, 1967 (Paper in Veterinary Record)

Zeneca received a Queens Award for Technological innovation for Diprivan in 1994

Frontiers Lectureship, US Society for Ambulatory Anesthesia (SAMBA), 2012.

Lasker~DeBakey Clinical Medical Research Award, 2018

Doctor of Veterinary Medicine and Surgery (Hon), Glasgow University, 2019

EM Papper Endowed Lecturer, Columbia University, New York, 2019

Henry Hill Hickman Medal, Royal Society of Medicine, 2020

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This body of work has been instrumental in an amazing change in anaesthetic practice and Glen's contribution has to be recognised. I am sure that it was not only clinical and pharmacological knowledge that were essential but I can imagine the bureaucratic hurdles were complex and required significant administrative skills.

In the author's view propofol, together with remifentanil and suggamadex, have revolutionised anaesthesia; they are drugs that are clean, very efficacious and provide extremely rapid recovery.

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PATENTS

Patent specification 1 472 793. Filed 28 March 1974. Inventors John Baird Glen and Roger James. This invention relates to a pharmaceutical composition which may be administered parentally to a warm-blooded animal for the production of general anaesthesia.