BJA
British Journal of Anaesthesia

Volume 126, Number 2, February 2021

British Journal of Anaesthesia, 126 (2): 343–347 (2021)
doi: 10.1016/j.bja.2020.10.020
Advance Access Publication Date: 24 November 2020

EDITORIALS

Seventy-five years since the birth of the Liverpool anaesthetic technique

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Keywords: general anaesthesia; Liverpool anaesthetic technique; medical history; neuromuscular blocking drug; T. Cecil Gray

Seventy-five years ago, just after the end of World War II in 1946, T. Cecil Gray (Fig. 1) was a general practitioner in downtown Liverpool, giving anaesthetics in a bombed-out community and at local rundown hospitals. Although working in very basic and challenging conditions at that time, he managed to describe one of the most important contributions to clinical anaesthesia of his generation: the concept of balanced general anaesthesia, which became known as the Liverpool anaesthetic technique.[1]

In 1926, the term 'balanced anaesthesia' had been introduced by Lundy,[2] at that time based at the Mayo Clinic (Rochester, MN, USA), who had combined two anaesthetic agents, a barbiturate and an inhalational agent, to alter the level of consciousness to apply regional anaesthesia to block pain. Lundy's concept of 'balanced anaesthesia' was different from that created by Gray and Halton,[1,3] but Gray and Halton undoubtedly based their concepts on Lundy's original description. Gray and Halton had also read the revolutionary article by Griffith and Johnson[4] from Montreal in 1942 that described use of small doses of 'Intocostrin', a natural product from the South American rubber plant *Chondrodendron tomentosum*, to 'take the edge off muscle tone' during abdominal surgery. It is important to note that all the patients in the Canadian series were still allowed to breathe spontaneously.

On March 1, 1946, T. Cecil Gray delivered the lecture 'A Milestone in Anaesthesia' at the Royal Society of Medicine in London where he introduced the early principles of his concept. At that time, Gray and Halton[1,3] considered that balanced anaesthesia should aim to reduce the dose of i.v. barbiturate and potent inhalational agent by adding the neuromuscular blocking drug d-tubocurarine, a purified derivative of Intocostrin, and i.v. pethidine (which was also used with an antihistamine intramuscularly as premedication) to the technique. Gray and Halton emphasised that anaesthetists should abandon the concept of using only one type of anaesthetic, usually an inhalational agent, to produce the desired effects at the expense of progressively deepening depression of the CNS. The selective use of different types of drugs, each producing one desired effect, allowed the use of the lowest possible dose of each agent.[1,3] Thus, a light plane of narcosis without movement or reflex response became possible. This became known as the Liverpool anaesthetic technique and is now, 75 yr later, still the basic concept of general anaesthesia.

Fig 1. T. Cecil Gray when he was a member of the Board of Faculty of Anaesthetists, Royal College of Surgeons of England in the 1960s (reproduced with kind permission of the Royal College of Anaesthetists).

The Liverpool anaesthetic technique

The first report in 1946 actually consisted of three different techniques based on the duration of the surgical procedure. For short procedures, after premedication with 'morphia' and atropine, anaesthesia was induced with a mixture of Pentothal 0.5 g and tubocurarine 15 mg injected i.v. rapidly. After 2–3 min, when respiration became shallow or ceased, an airway or tracheal tube was inserted. For longer surgical procedures, small doses of Pentothal (0.1 g) and tubocurarine (2–4 mg) were given incrementally throughout the procedure as the reaction of the patient to stimuli and the demands of the surgeon dictated. When necessary, an anaesthetic vapour (cyclopropane or diethyl ether) was used to maintain anaesthesia. In the third technique, tubocurarine was only used as an adjuvant to inhalational anaesthesia. Intermittent injection of a total dose of tubocurarine 15–30 mg was utilised to produce relaxation if necessary while still keeping the patient in a light plane of anaesthesia. Artificial ventilation was always maintained by hand, and whichever of the anaesthesia techniques was used, it was stressed that oxygen had to be supplied preferably by means of a closed circuit.[1]

From 1946 to 1960, the Liverpool anaesthetic technique evolved significantly (Table 1). Over these years, this entirely new concept was frequently criticised, but Gray[5,9,10] never missed an opportunity to respond to such criticism and, when appropriate, to adapt the technique accordingly. He was assiduous in his attention to detail in this respect.

As the novelty of introduction of d-tubocurarine into clinical practice passed, the drug gradually was used not merely as an aid to anaesthesia, but became an integral part of major anaesthetic procedures. Preventing laryngeal and bronchial spasm, muscle relaxation allowed much easier intubation of the trachea. In addition, Gray and Halton[3] stated that the synergistic action of anaesthetic agents meant that 'if a correctly balanced anaesthesia is maintained, patients after long abdominal and thoracic operations are awake, in good vasomotor equilibrium, free from nausea, and able to exert their respiratory function to the full'. With this technique, patients were also thought to experience a much more rapid recovery from anaesthesia and a smoother postoperative convalescence.[3]

After publishing his initial ideas in the *Proceedings of the Royal Society of Medicine* with John Halton, another well-established Liverpool anaesthetist,[1] several further papers from Gray[5] and his colleagues over the following years considered different adaptations of the technique using neuromuscular blocking drugs with various anaesthetic agents. In 1950, Rees and Gray[6] described the use of low concentrations of methyl-n-propyl ether instead of diethyl ether to produce analgesia (Table 1). At this stage, Rees and Gray still did not consider the use of potent inhalational agents to be unacceptable. They stated that methyl-n-propyl ether might have value when given with a neuromuscular blocking drug in balanced anaesthesia to complete the essential triad of muscle relaxation, narcosis (unrousable unconsciousness), and analgesia.[6] Of particular note, this was the first time the concept of

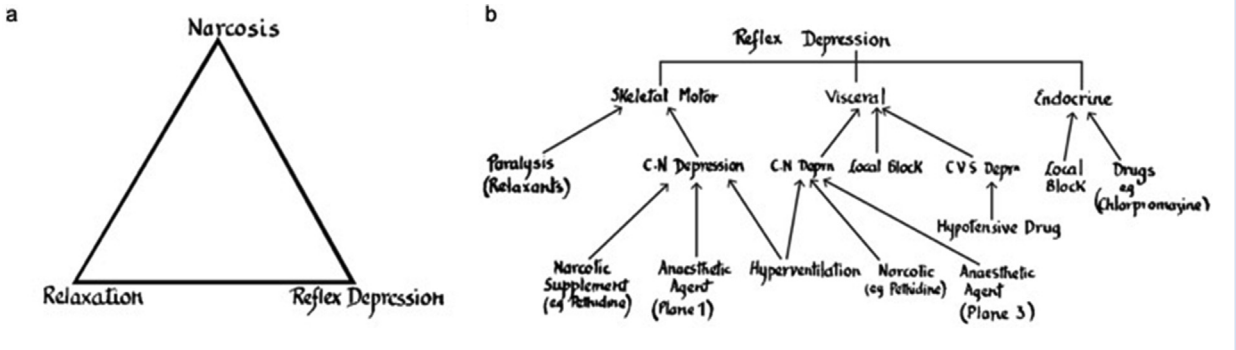

Fig 2. **(a)** The "more accurate" triad (according to T. Cecil Gray) of general anaesthesia in which analgesia was replaced by reflex depression. **(b)** A detailed schematic classification of the reflexes and the available methods of producing their depression. Reprinted with permission from Springer Nature: *Irish Journal of Medical Science*. Gray TC. A reassessment of the signs and levels of anaesthesia. *Ir J Med Sci* 1960; 35: 499-508.[11]

Table 1 From 1946 to 1960, the Liverpool anaesthetic technique was to evolve significantly. The component parts and role of the individual drugs used over the years are shown. NMBD, neuromuscular blocking drug; dtc, d-tubocurarine.

Year	Induction agent	Inhalation agent	NMBD	Analgesic	Reversal drug	Other drugs	Other interventions
1946[1]	Pentothal or Kemithal (thialbarbital)	Cyclopropane Diethyl ether Nitrous oxide	dtc	Pethidine, Morphine	Pyridostigmine		
1946[3]	Pentothal (thiopental)						
1947[5]	Thiopental		dtc				
1950[6]	Thiopental	Methyl-n-propyl ether Nitrous oxide		Morphine			
1952[7]	Thiopental	Nitrous oxide	dtc	Pethidine			Apnoea
1954[8]	Thiopental	Nitrous oxide	dtc	Pethidine			
1957[9]	Not specified	Nitrous oxide			Neostigmine		Hypothermia
1959[10]	Thiopental	Nitrous oxide	dtc		Neostigmine		Hyperventilation
1960[11]	Thiopental	Nitrous oxide Cyclopropane	dtc	Pethidine	Neostigmine	Local field block (mepivacaine/lidocaine) Mepivacaine or lidocaine Chlorpromazine	Hyperventilation

balanced anaesthesia had been viewed as a triad.[6] Increasingly, the effects of these three aspects of the Liverpool anaesthetic technique were being considered to be ideally produced by specific drugs with a selective mode of action that did not include potent inhalational agents, but only 70% inspired nitrous oxide.

At this stage, the method of anaesthesia had evolved into induction of anaesthesia with thiopental or Kemithal (thialbarbital), a short-acting barbiturate,[12] and use of d-tubocurarine and nitrous oxide in oxygen in a primed anaesthetic circuit with pethidine as an analgesic to reduce the response to noxious stimuli (Table 1).[6–8] After 6 yr of development, by 1952, the classic description of the Liverpool anaesthetic technique had truly been born.

Controlled ventilation

In 1952, Gray addressed another important aspect of the technique. He discussed the possible benefits of reducing the dose of neuromuscular blocking drug and the potential benefits of apnoea during anaesthesia produced by hyperventilation.[7,10] Control of breathing had not been discussed in detail in the earlier papers. He postulated that this approach could be protective against postoperative pulmonary and cardiovascular complications, which, at that time, was a startlingly controversial proposition. He suggested that apnoea could protect patients from the trauma of surgery, and thus should be added as a fourth element to the triad of narcosis, muscle relaxation, and analgesia.[7,8] This technique became known, certainly in Liverpool, as the anaesthetic tetrad, although this new term never received the same international recognition as the original triad.

Reversal of residual neuromuscular block

By the early 1950s, use of a neuromuscular blocking drug during anaesthesia was becoming an increasingly common technique around the world. However, the seminal paper by Beecher and Todd[13] suggested that anaesthetic deaths were more common in patients who had received a neuromuscular blocking drug during anaesthesia than in those who had received regional analgesia or who had breathed spontaneously using a potent inhalational agent. Healthy patients were developing severe postoperative respiratory complications after neuromuscular blocking drug use. Griffith and Johnson[4] had suggested that pyridostigmine should be available whenever Intocostrin was used, but they had not had reason to administer it in their series of patients. Gray and Halton[1] made very little mention of the use of an anticholinesterase in their original report, only administering pyridostigmine to three of more than 1000 patients. But, Gray was quick to respond to the report by Beecher and Todd, and by the mid-1950s, neostigmine was being given routinely in large doses (5 mg to adults) as part of the Liverpool anaesthetic technique.[14] This was a major factor in the subsequent success of the technique.

Stress response

In 1953, Gray lectured at the opening of the Dublin University Biological Association. By then, he had already taken another step in the evolution of his concept by stating that his technique gave a considerable degree of control of physiological responses to surgical injury and the relief of pain.[8] Although often critical of other techniques, Gray[8,9] was showing interest in French publications, which reported that hypothermia and artificial hibernation could possibly play a role in the defence against the stress of surgery. In the further evolution of his concept, Gray[9] became convinced that modern anaesthesia could be summarised by only one word: 'control'. This approach lasted until 1957 when he reported on the possible benefits of hypothermia and its physiological effects in relation to safer control of the circulation, which is imbalanced by the stress of surgery.[9] This was one of the earliest clinical considerations of a stress response produced by anaesthesia and surgery.

In the same year, Loder,[15] following the development of the Liverpool anaesthetic technique, noted that a light plane of

anaesthesia with muscle relaxation was not able to block autonomic reflexes during major abdominal surgery, and that even pethidine was of little value. Loder[15] found that adding infiltration of local anaesthetic to the sympathetic plexus to block some autonomic responses was beneficial during light anaesthesia. At the same time, Woodbridge[16] (Greenfields, MA, USA) discussed the changing concepts of the depth of anaesthesia. He expressed the need to block undesirable respiratory, circulatory, and gastrointestinal reflexes.[16] Woodbridge suggested that, because the word *anaesthesia* actually means full sensory block without any indication of sleep, reflexes, or muscle relaxation, the Greek word 'nothria' or the English word 'torpor' to define this state of mental and motor inactivity with insensibility and absence of reflexes was more appropriate. However, his views did not receive universal acceptance. Also in 1957, Young[17] suggested that the three components of Gray's technique were a triangle where the overlapping actions of several anaesthetic drugs met in the centre, producing narcosis, analgesia, and muscle relaxation.

Awareness

As the Liverpool anaesthetic technique was practised more widely, Gray reluctantly had to take cognisance of reports of awareness in patients receiving this increasingly popular technique. Hutchinson[18] (1960) reported on awareness during surgery and studied its incidence, which was estimated at 1.22% (8 out of 656 patients). In this retrospective analysis, it became apparent that it was possible for immobile patients to be in a state of awareness during surgery performed using such techniques. Inadequate nitrous oxide concentration, lack of hyperventilation, and use of neuromuscular blocking drugs were considered most likely to be responsible. Fortunately, the incidence of awareness was low (1.22%), but it was concluded that every possible effort must be made to ensure complete unconsciousness during general anaesthesia to protect patients from physical and mental suffering.[18] The unacceptable incidence of awareness was ultimately a major cause of the demise of the classical Liverpool anaesthetic technique.[14]

Reflex depression

Another important step in the evolution of the Liverpool anaesthetic technique was made in 1959. Gray was invited to lecture on the depth of anaesthesia at the inaugural meeting of the Faculty of Anaesthetists of the Royal College of Surgeons in Ireland. For the first time, he suggested that the accepted triad of general anaesthesia should be reconsidered. The term *analgesia* had proved to be unsatisfactory, and for the first time, Gray[11] modified the triad to narcosis, muscle relaxation, and *reflex depression* (Fig. 2a). His lecture was published in 1960 with the title, 'Reassessment of the signs and levels of anaesthesia'.[11] Gray suggested that the word *analgesia* is confusing and could lead to irrational use of high doses of potent analgesic drugs. Furthermore, Gray[11] stated, somewhat controversially, that when a patient is 'narcotic' or under anaesthesia, the patient cannot be aware of pain, although analgesia means freedom of pain. Gray concluded that reactions observed during anaesthesia, which in a conscious state might be painful, are the result of reflex stimuli. Therefore, a more accurate triad of general anaesthesia would be narcosis, muscle relaxation, and reflex depression (Fig. 2a).[11]

Gray[11] gave an extensive description of all the possible reflexes, which 'the anaesthetist desires to depress' and how, at that time, this could be effected. He classified three major reflexes that are triggered by the stress of surgery (Fig. 2b). The first group of reflexes was described as skeletal motor reflexes that consisted of involuntary movements and contractions resulting from surgical stimuli, such as peritoneal irrigation. These reflexes could be depressed by the combination of neuromuscular blocking drugs, local motor nerve block, and central nervous depression induced by potent anaesthetic agents. The second group of reflexes was described as visceral reflexes, such as the vasovagal responses to trauma. These reflexes could be depressed by potent anaesthetic agents and more selectively by local blockade of the mediastinal and splanchnic ganglia. This could also be achieved by the use of ganglion-blocking agents that block the efferent side of the reflex arc. Gray[11] suggested that there was no evidence that narcotic drugs, such as pethidine, have any selective effects on these reflexes. The third group of reflexes was the endocrine responses to surgical injury. These reflexes could be depressed by application of field blocks or agents with an anti-hormonal action, such as chlorpromazine. However, Gray[11] rightly questioned that interfering with the responses of the pituitary–adrenal axis to injury is appropriate, as evidence seemed to suggest that these responses are protective.

Respiration

Gray and Rees[7] had already suggested that apnoea should be regarded as a key component in protecting the patient from surgery and that the triad principle could be replaced by a tetrad, which included apnoea. After 1960, Robinson and Gray[19] continued investigating the effects of anaesthesia on respiration and examined the effects of hyperventilation on cerebral perfusion, suggesting that a higher pH, rather than hypoxia, might explain the anaesthetic effects. They speculated that hyperventilation with the use of a neuromuscular blocking drug may contribute to unconsciousness, a theory that has recently been reconsidered,[20] and that as hyperventilation produces EEG changes similar to potent inhalational agents, it can be used as a supplementary anaesthetic agent.[10,19] Robinson and Gray's[19] controversial observations on the cerebral effects of hyperventilation were suggested to show a reduction in the required dosage of anaesthetic drugs as a result of the production of general analgesia and from depression of other cerebral functions.

In their initial report, Gray and Halton[1] detailed the incidence of postoperative pulmonary complications in their study using the Liverpool anaesthetic technique. Interestingly, the incidence was around 12%, which is little changed in current practice, but was only a third of the incidence that had been reported before World War II using deep inhalational anaesthesia.[1]

Analgesia

The lack of adequate analgesia became increasingly recognised as another important deficit of the Liverpool anaesthetic technique. By 1960, anaesthetists were more convinced that high-dose opioids should be the standard method of care to block pain and other reflexes during general anaesthesia. Unfortunately, it would seem that Gray's[11] paper in 1960, in which he described reflex depression, was not widely recognised at the time.[14] However, reflex suppression, together with the stress of light levels of anaesthesia allowing rapid awakening, and controlled apnoea using neuromuscular blocking

drugs are important facets of the contribution of the Liverpool anaesthetic technique to present-day practice.[14,21]

Nausea and vomiting

Postoperative nausea and vomiting was a major concern associated with administration of diethyl ether, chloroform, and ethyl chloride, the main potent inhalational agents in use in the 1940s.[1] To produce satisfactory operating conditions for the surgeon, administration of high concentrations of these toxic agents often resulted in postoperative nausea and vomiting, which was a challenge to treat.[1–4] Gray recognised the advantages of barbiturates over the potent inhalational agents regarding this complication.[22] In 1963, Riding[23] supported the concept of a reduction in postoperative nausea and vomiting when the Liverpool technique was used. However, by 1973, Cronin and colleagues[24] were suggesting that postoperative nausea or vomiting remained a significant problem, occurring in nearly 50% of patients, and by this time, use of the technique in its unadulterated form was declining.

Conclusions

T. Cecil Gray undoubtedly made a significant contribution to modern anaesthetic practice. He was to travel the world and especially the British Commonwealth in the 1950s and 1960s, describing his technique.[25] A generation of anaesthetists went from these countries to Liverpool to learn the technique in detail. The concept of control in the Liverpool anaesthetic technique laid the foundations for the introduction of cardiac and neonatal anaesthesia and of intensive therapy. Its main facet was its applicability to all kinds of patients and all types of surgery. Many of his theories about the mechanisms of general anaesthesia were questionable and, at that time, unproved scientifically. Nevertheless, they showed remarkable foresight, and many are now the basis of modern anaesthetic research. Gray went on to make further contributions to clinical practice with the description 25 yr later of the train-of-four twitch technique.[26] He was also the Editor of the *British Journal of Anaesthesia* with W. Falkner Hill (Manchester) from 1948 to 1960. We salute his outstanding contributions on the 75th anniversary of the birth of the Liverpool anaesthetic technique.

Authors' contributions

All authors contributed equally to the writing of this paper.

Declarations of interest

JPM has received research grants from Merck Sharp & Dohme, USA; General Electric; Johnson & Johnson; and Medtronic, and is Treasurer of the European Society for Perioperative Care of the Obese Patient. JMH was Editor-in-Chief of the *British Journal of Anaesthesia* (BJA) from 1997 to 2005 and Chair of the BJA Board from 2006 to 2012. HDdB has received research grants from Merck, Sharp & Dohme, USA, and is member of the Executive Committee and Treasurer of the ERAS® Society.

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