# 'Ideal' Gases: Anaesthetics in the Heart of the Twentieth Century

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## 1. Introduction

By 1920 only three gaseous anaesthetics were widely used – nitrous oxide, diethyl ether (ether) and chloroform. The toxicity of chloroform was acknowledged, nitrous oxide did not induce deep anaesthesia, and ether was extremely inflammable, so in the 1920s there were good reasons to search for new anaesthetics. While my concern is with gaseous anaesthetics, I recognise that there were parallel developments in two related fields, that of topical or local anaesthetics, typified by the natural product cocaine and a host of synthetic substances, and injectable anaesthetics starting with opiates, then barbiturates and leading to modern materials such as propofol (2,6-diisopropylphenol).

## 2. Theories of anaesthetic action

Hans Meyer[1] noted that the anaesthetic substances were soluble in both fatty and aqueous media, proposed a general theory of anaesthesia based on the partition or distribution coefficient as a critical determinant. Meyer enunciated the following three principles that underpinned his theory:

- all chemically inert substances that are soluble in fats and fatty materials will produce narcosis;
- the line of action is in the nerve cells;
- the comparative strengths of substances depend on their solubility in fatty material and in water, that is, on the distribution coefficient.

Charles Overton arrived at the same idea independently. Some years after completing his PhD research on cell permeability studies, Overton first presented his theory of narcosis in a lecture to the Society for Natural History in Zurich in October 1898, in a paper published the following year[2] and in his book[3] which included a full exposition. Although his contribution to the theory of narcosis was recognised in the term 'Meyer-Overton theory', the details were not widely accessed although some excerpts of his work (and Meyer's) were published in translation in 1963.[4] A full translation of Overton's book, commissioned by the US Environmental Protection Agency, and accompanied by remarks by modern authors was published in 1991.[5]

According to the Meyer-Overton theory the anaesthetic substances interacted in reversible ways with fatty membranes and thus mediated their effects on consciousness. Since it was not possible to predict the distribution coefficients of potential anaesthetic substances, the

[1] H. Meyer, 'Zur Theorie der Alkoholnarkose. Erste Mitteilung. 'Welche Eigenschaft der Anästhetica bedingt ihre narkotische Wirkung?', *Naunyn-Schmiederbergs Archiv für experimentelle Pathologie und Pharmakologie* (1889), **42** (2-4), 108-118.
[2] E. Overton, title, *Viertlejahrsschrift der Naturforschenden Geselleschaft in Zurich* (1899), **44**, 88-135.
[3] C.E. Overton, *Studien über die Narkose zugleich ein Beitrag zur allgemeinen Pharmakologie* (Gustav Fischer, Jena, Switzerland, 1901).
[4] B. Holmstedt and G. Liljestrand, *Readings in Pharmacology* (Pergamon Press, Oxford, 1963), pp. 147-154.
[5] R.L. Lipnick, ed., *Studies of Narcosis* (Springer, Netherlands, 1991).

Meyer-Overton theory was not helpful in guiding researchers to structures of organic molecules that might deserve further investigation. Winterstein[6] provided a detailed critique of the theory, showing that the relationship did not hold when a broader range of chemically inert substances was tested, and other researchers also concluded that the Meyer-Overton theory was 'not entirely satisfactory' but was the best available and had gained widespread acceptance.[7] Addressing the apparent inconsistency, Henderson and Brown postulated three types of anaesthetic action: '(a) due to changes in the anesthetic in the body; (b) due to secondary effects produced in metabolism; (c) inherent in the anesthetic.' In their view only the last of these might be correlated with physical parameters, while the others could account for toxicity but the lack of predictive value remained a serious obstacle to the search for new anaesthetics. Nicholas Franks at Imperial College, London, discovered that binding by anaesthetic agents to soluble proteins, and consequent competitive antagonism, was likely to be the true mechanism of anaesthetic action.[8] Reviewing the progress that followed his initial discoveries, Franks[9] observed that although there were many exceptions the Meyer-Overton theory survived because it had 'beguiling simplicity' and was not inconsistent with developing ideas of the lipid bilayer nature of nerve membranes.

## 3. Hydrocarbons leading to cyclopropane

Ethylene and acetylene had been investigated in the late nineteenth century and found to be effective anaesthetics but they did not become established in the repertoire of the anaesthetist until the 1920s.[10] The use of acetylene (CH≡CH) became more common, mainly in Germany, after Hermann Wieland,[11] in Freiburg, reported extensively on its use and it was marketed as Narcylen. Wieland was led to experiment with acetylene by noting the facility with which nitrous oxide dissolved in blood and could therefore be transported to sites of (unspecified) action. 'The proof of this hypothesis', he wrote, 'was shown by the experiments with other gases such as acetylene that dissolved even more easily in water'.[12] Note was taken by the anaesthetists in other jurisdictions[13] but acetylene was mainly used in Germany. Wieland had generated acetylene from the reaction of calcium carbide and water, purifying it before use in anesthesia. Since acetylene had industrial uses in lighting and welding it was available

[6] H. Winterstein, *Die Narkose in ihrer Bedeutung für die allgemeine Physiologie* (Springer, Berlin, 1919), pp. 203-228.

[7] V.E. Henderson and W.E. Brown, 'The theory of anesthesia and the problem of toxicity', *Journal of Pharmacology and Experimental Therapeutics* (1926), **29**(1), 269-278.

[8] N.P. Franks and W.R. Lieb, 'Do general anaesthetics act by competitive binding to specific receptors?', *Nature* (1984), **310**, 599-601. This is now the accepted mechanism and several specific receptors have been identified. C.J. Weir, 'The molecular mechanisms of general anaesthesis; dissecting the $GABA_A$ receptor', *Continuing Education in Anesthesia, Critical Care & Pain* (2006), **6**(2), 49-53.

[9] N.P. Franks, 'Molecular targets underlying general anaesthesia', *British Journal of Pharmacology*(2006), **147**, S72-S81.

[10] F. Shipway, 'Acetylene, ethylene and propylene', *Lancet* (1925), **205**, 1126-1130.

[11] H. Wieland, 'Über den Wirkungsmechanismus betäubender Gase, des Stickoxyduls und des Azetylens', *Naunyn-Schmiederbergs Archiv für experimentelle Pathologie und Pharmakologie* (1922), **92**, 96-152.

[12] My translation, from C.J. Gauss and H. Wieland, 'Ein neues Betäubungsverfahren', *Klinische Wochenschrift* (1923), **2**(3), 113-158.

[13] T. Brand, 'Narcylen (acetylene gas) anesthesia', *Norsk Magazin for Lagevidenskaben*, August 1924, abstracted by T. Batrud, *Current Researches in Anesthesia and Analgesia* (1925), **4**(1-6), 128. T. Brand, 'Acetylene-oxygen anesthesia in gastric surgery', *Current Researches in Anesthesia and Analgesia* (1926), **5**, 329-331. C.H.S. Horwitz, 'A new general anaesthetic', *Lancet* (1923) (1), 619. Anonymous, 'New anesthetics: ethylene and acetylene', *Journal of the American Medical Association* (1923), **80**(19), 1383-1384).

commercially but that material had to be cleansed of small quantities of acetone with which it was stored under pressure.[14]

V.E. Henderson at the University of Toronto was drawn into work on anaesthetics by W. Eason Brown, an anaesthesiologist at Toronto General Hospital, who had joined the department of Pharmacology in 1922 and by George Lucas, a young chemist he hired to pursue the work. They wrote about their experience with ethylene as an anaesthetic and related their findings to those of other researchers.[15] Their intention was to increase the efficiency of nitrous oxide for general anaesthesia by adding other substances to it, but their reasons for choosing ethylene were not explicit. In the event, they found ethylene to be more potent than nitrous oxide, producing rapid and effective anaesthesia in animals and humans when administered in mixtures containing 10-15% oxygen. They generated ethylene by pyrolysis of ethanol vapour over aluminium oxide at 350$^{o}$ but later used cylinders supplied by a manufacturer. Although Brown and Henderson published further work on ethylene[16] they ceded the research field to others and ethylene, on grounds of odour and flammability, never became a major anaesthetic.

Instead they turned to propylene, which they found possessed anaesthetic properties, as did methane, although only at higher concentrations.[17] Brown suggested that higher hydrocarbons might be better anaesthetics but this does not seem to have been followed up, and there was more to learn about $C_3$ hydrocarbons. Cyclopropane was found to be a good anaesthetic.[18] Researchers were unable to conduct a partition experiment with it, but instead they determined separately the solubilities of cyclopropane in water and olive oil, which were in ratio 1:64.4 and that compared favourably with ethylene 13.2, ether 2.5 and acetylene 2.1.

As a result of further work by Ralph M. Waters of the University of Wisconsin,[19] cyclopropane was introduced to practice from 1933 in the United States and Australia, but not in Britain. A number of deaths of patients under anaesthesia in Toronto hospitals at about that time made doctors unwilling to experiment with cyclopropane,[20] which Exhibited toxic effects when it was used in high doses. In addition, the constant danger of explosion in the operating theatre made doctors cautious about its use. The explosion risk, shared by other inflammable agents like diethyl ether and acetylene, was heightened when electrocautery was introduced into surgery in the late 1920s and when electronic monitoring devices later became common.

## 4. **Rare gases**

[14] For safety reasons compressed acetylene is dissolved in acetone (later dimethylformamide) which is absorbed on a porous medium. E. Almqvist, *History of Industrial Gases* (Springer, Boston, 2003), pp. 242-243.
[15] W.E. Brown and V.E. Henderson, 'On ethylene as an anaesthetic', *Archives internationales de pharmadynamie et de thérapie* (1923), **28**, 257-264.
[16] W.E. Brown and V.E. Henderson, 'Experiments with anaesthetic gases', *Journal of Pharmacology and Experimental Therapeutics* (1926), **27**, 1-8.
[17] W.E. Brown, 'Experiments with anesthetic gases propylene, methane, dimethyl ether', *Journal of Pharmacology and Experimental Therapeutics* (1924), **23**(5), 487-496.
[18] D. Gavrus, 'Envisioning cyclopropane: scientific product or medical technology?', *Scientia Canadensis* (2010), **33** (1), 3-28.
[19] R.M. Waters, 'Cyclopropane anesthesia', *Journal of the American Medical Association* (1934), **103**(13), 975-983.
[20] G.H.W. Lucas, 'The discovery of cyclopropane', *Current Researches in Anesthesia and Analgesia* (1961), **40**(1), 15-27.

Experience with deep-sea divers and other humans working under increased pressures of nitrogen gas showed that nitrogen has narcotic (= anaesthetic) effects, and this led to the investigation of other chemically inert gases. The noble – at that time regarded as inert – gases from Group 8 of the periodic table naturally attracted attention, although it was known that helium had only a very small narcotic effect.[21] The solubility of the gases in water increased with increasing atomic weight and so it seemed likely that higher members of the group might have interesting properties.

Argon, twice as soluble in water and in fat as nitrogen, was found to have approximately twice the narcotic effect.[22] Referring to the Meyer-Overton hypothesis that the fat-water solubility ratio is an important determinant of anaesthetic effects, Lawrence *et al.*[23] brought together the relevant data for solutions in water or corn oil or olive oil (Table 1) and confirmed that mixtures of oxygen and xenon (but not krypton) produced physiological effects when animals were exposed to recirculating gas mixtures with removal of carbon dioxide by soda-lime.

**Table 1. Solubility ratios for chemically inert gases**
(n/a indicates data unavailable)

| **Inert gas** | **Oil/water solubility ratio** | |
|---|---|---|
| | **22°C** | **37°C** |
| Nitrogen | 3.5-4.2 | 4.7-5.2 |
| Helium | n/a | 1.7 |
| Neon | n/a | n/a |
| Argon | 4.0 | 5.3 |
| Krypton | 7.5 | 9.6 |
| Xenon | 14.5 | 20.0 |
| Radon | 110 | 125 |

Krypton and xenon were investigated further in the early 1950s, the former having 'no significant narcotic properties' while xenon was about as effective as ethylene,[24] and 'although it may not by virtue of its cost of manufacture prove to be a satisfactory agent commercially, it may materially assist in solving one of the important theoretical problems of anesthesia'. The main use of xenon as an anaesthetic seems to have been in Russia, where it was also used in training athletes for low-oxygen conditions until this practice was banned by the World AntiDoping Agency in June 2014.

An interesting outcome of the discovery of the anaesthetic action of xenon was Linus Pauling's interest in the phenomenon and his decision to look more broadly at other anaesthetic molecules because 'their chemical properties are such that it is impossible to believe that they produce narcosis by taking part in chemical reactions involving the formation and breaking of ordinary chemical bonds.' Because many substances fitted the Meyer-Overton criterion of fat-water partition without exhibiting anaesthetic action, he sought

[21] H.J. Taylor, 'The use of helium in diving', *Chemical Society Lecture, 4th June, 1953*.
[22] A.R. Behnke and O.D. Yarborough, 'Respiratory resistance, oil water solubility and mental effect of argon compared with helium and nitrogen', *American Journal of Physiology* (1939), **126**, 409-415.
[23] J.H. Lawrence, W.F. Loomis, C.A. Tobias and F.H. Turpin, 'Preliminary observations on the narcotic effect of xenon with a review of values for solubilities of gases in water and oils', *Journal of Physiology* (1946), **105**, 197-204.
[24] S.C. Cullen and E.G. Gross, 'The anesthetic properties of xenon in animals and human beings with additional observations of krypton', *Science* (1951), **113**, 580-582.

a more specific physical mechanism and proposed that this might involve 'hydrate crystals of the clathrate type'.[25] A similar theory was put forward, at about the same time, by Stanley Miller.[26] Unsuccessful experiments undertaken in Pauling's laboratory with brine shrimp and goldfish, and the consideration that such clathrates could form only under conditions that were far from physiological, meant that the theory gained little purchase and had almost no predictive value, although Pauling himself never entirely relinquished the idea.[27]

## 5. **Elaborating the Ether Structure**

The structure of one of the oldest anaesthetics, diethyl ether was the starting point for the exploration of anaesthetic properties of a range of aliphatic ethers that began in the 1920s. The American anaesthesiologist Chauncey Leake[28] noted that 'there has not yet been a systematic effort to determine whether or not there is any relation between chemical constitution and physiological action … of a relatively large series of related compounds'. His proposal was to bring together the structural elements of two known anaesthetics, diethyl ether and ethylene, and so to test divinyl ether ($CH_2$=CH-O-CH=$CH_2$) and some related compounds. This approach, he claimed, 'involves the climax of the scientific method – the ability to predict in a reasonable manner that a certain proposition will be true on the basis of observed phenomena and a workable theory'. He also noted the general tendency for higher members of a homologous series to exhibit greater toxicity, which directed attention to small molecules as those most likely to have useful properties.

Leake mentioned oil-water partition coefficients of the ethers he investigated and noted that 'if the partition coefficient may be taken as an index of anesthetic efficiency, then, divinyl ether meets our expectations'. From this we might conclude that he was aware of the Meyer-Overton theory but regarded it as providing a check on experimental results but not something with predictive value. Although divinyl ether was an effective anaesthetic it was degraded by exposure to light and air. This problem was partly overcome by addition of a small amount of ethanol as a stabilizer, and the product achieved commercial success for a few years under the name 'Vinethene' which was used in dental and other minor surgery and obstetric cases.[29]

Thinking along the same lines as Leake, John C. Krantz at the University of Maryland felt that ethyl vinyl ether 'represented more completely a cross between the two anesthetic molecules than does divinyl ether' and accordingly investigated its properties.[30] Before then, however, he had introduced another 'hybrid' molecule, combining the ether link with the structure of a recently introduced hydrocarbon anaesthetic, cyclopropane. The research group investigated cyclopropyl alkyl ethers[31] and then alkenyl ethers[32] which were found to be more

[25] L. Pauling, 'A Molecular Theory of General Anesthesia', *Science*, 1961, **134**, 15-21.
[26] S.I. Miller, 'A Theory of Gaseous Anesthetics', *Proceedings of the National Academy of Sciences of the United States*, 1961, **47**, 1515-1524.
[27] B. Marinacci, ed., *Linus Pauling in His Own Words* (Simon & Schuster, New York, c. 1995), pp. 225-228.
[28] C.D. Leake and M-Y Chen, 'A preliminary note on the anesthetic properties of certain unsaturated ethers', *Current Researches in Anesthesia and Analgesia* (1931), **10(**1), 1-2.
[29] F.M. Marvin, 'Clinical use of Vinethene', *Current Researches in Anesthesia and Analgesia* (1935), **14**, 257-262. L.F. Anderson, 'Newer anesthetic agents', *American Journal of Nursing* (1937), **37**(3), 276-280.
[30] J.C. Krantz Jr., C.J. Carr, R.D. Musser and M.J. Sauerwald, 'Anesthesia. XXVIII. The anesthetic action of ethyl vinyl ether', *Journal of Pharmacology and Experimental Therapeutics* (1947), **90**, 88-94.
[31] J.C. Krantz Jr., C.J. Carr, S.E. Forman and W.E. Evans Jr., 'Anesthesia. I. The anesthetic action of cyclopropyl methyl ether', *Journal of Pharmacology and Experimental Therapeutics* (1940), **69**, 207-220. J.C. Krantz Jr., C.J. Carr, S.E. Forman, E.E. Evans Jr. and H. Wollenweber, 'Anesthesia. IV. The anesthetic action of cyclopropyl ethyl ether', *Journal of Pharmacology and Experimental Therapeutics* (1940), **72**, 233-244.

effective than diethyl ether. Difficulties were experienced in measuring the oil-water partition coefficient directly by equilibrating the distribution between the two phases, and new methods were introduced but there was poor agreement between data obtained by the Leake and Krantz groups, not that it seemed to matter since effect anaesthetic agents had been discovered by more traditional approached of structure variation.

## 6. Halogenated hydrocarbons after chloroform

Ethyl chloride,[33] trichloroethylene[34] and mixtures containing methyl chloride and ethyl bromide[35] were investigated for their anaesthetic properties. All were toxic to some degree, but trichloroethylene especially so since it was converted to highly toxic dichloroacetylene (Cl-C≡C-Cl) when exposed to soda lime in the recirculating system.[36] All four chlorinated methanes were found to possess anaesthetic activity. Of these, dichloromethane (methylene chloride, $CH_2Cl_2$) was the most favoured but a later review made a strong case that the real anaesthetic material was a chloroform present as an impurity.[37] Pure dichloromethane was later found to have the disadvantage that in the body it was converted to carbon monoxide which reduced the oxygen-carrying capacity of the blood.

## 7. Fluorinated substances as anaesthetic gases

The development of organo-fluorine chemistry in the 1930s offered new opportunities for development of analogues of know anaesthetics, but none of dichlorofluoromethane ($CHCl_2F$) and chlorodifluoromethane ($CHClF_2$)[38] decafluorobutane and decafluorocyclopentane[39] were suitable and more extensive studies showed that while a number of small fluorine-containing molecules exhibited some degree of anaesthetic activity they also had pronounced toxicity.[40]

In Britain, Imperial Chemical Industries (ICI) had prepared many fluorine compounds and investigated possible uses for them as refrigerants, foam-forming agents and aerosols and it

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[32] J.C. Krantz Jr., C.J. Carr, S.E. Forman and H. Wollenweber, 'Anesthesia. VI. The anesthetic action of cyclopropyl vinyl ether', *Journal of Pharmacology and Experimental Therapeutics* (1942), **75**, 30-38. J.C. Krantz Jr., C.J. Carr, A.G. Horney and W.E. Evans, 'Anesthesia. IX. The anesthetic action of isopropenyl vinyl ether', *Journal of Pharmacology and Experimental Therapeutics* (1943), **79**, 179-185.

[33] M.J.P. Flourens, 'Note touchant l'action de l'ether sur les centres nerveux', *Comptes rendus hebdomadaire des Sêances de'l Academie des Science* (1847), **24**, 340-344.

[34] K.B. Lehmann, V. Behr, L. Quadflieg, M. Franz, G. Herrmann, A.H. Knoblauch, K. Gundermann and H. Würth 'Experimentelle studien über den einfluss technisch und hygienisch wichtiger gase und düampfe auf organismus XVI-XXIII' *Archiv für Hygiene* (1911), **74**, 1-60.

[35] G.B. Rolland and F. Robinson, 'Somnoforme', *Journal of the British Dental Association* (1902), 23, 321-333.

[36] Recirculating systems only became common when cyclopropane was introduced but thereafter they were commonly employed with all anaesthetics. Production of toxic products by interaction anaesthetic gases with strong bases in the recirculating system was observed with trichloroethylene and also with sevoflurane, a fluoroether that was introduced later in the twentieth century. The use of less aggressive bases to remove carbon dioxide made these systems compatible with trichloroethylene and other gases.

[37] W.S. Sykes, *Essays on the First Hundred Years of Anaesthesia* (Churchill Livingstone, Edinburgh, 1982), Vol 3, pp. 153-167.

[38] H.S. Booth and E.M. Bixby, 'Fluorine derivatives of chloroform', *Industrial and Engineering Chemistry, Industrial Edition* (1932), **24**, 637-641.

[39] H.C. Struck and E.B. Plattner, 'A study of the pharmacological properties of certain saturated fluorocarbons', *Journal of Pharmacology and Experimental Therapeutics* (1940), **68**, 217-219.

[40] B.H. Robbins, 'Preliminary studies of anesthetic activity of fluorinated hydrocarbons', *Journal of Pharmacology and Experimental Therapeutics* (1946), **86**, 197-204. G. Lu, J.S.L. Ling and J.C. Krantz Jr., 'Anesthesia. XLI. The anesthetic properties of certain fluorinated hydrocarbons and ethers', *Anesthesiology* (1953), **14**, 466-472.

was recognized that the properties that made fluorocarbons valuable in these applications might also make them suitable as anaesthetics. Seeking a theoretical rationale for anaesthetic action, the research leader linked anaesthetic efficiency to chemical potential[41] but active research had to wait until after World War 2. 1,1,1-Trifluoro-2-bromo-2-chloroethane ($CF_3$-CHBrCl, Fluothane, Halothane), sometimes called the 'first designer anaesthetic' was synthesized in 1953.[42] A range of fluorinated compounds was synthesized by Dow Chemical Company in the late 1950s and submitted for testing at Abbott Laboratories, leading to the discovery of 1,1,1,2-Tetrafluoro-2-bromoethane ($CF_3CHBrF$, Teflurane). It had a solubility ratio of several hundred and differed from Halothane only by substitution of F for Cl.[43] While Halothane took a dominant place in the market, Teflurane was marketed for a time but was found to cause cardiac irregularities and its use was abandoned.

The interest in fluorine-containing moieties converged with that for aliphatic ethers when trifluoroethyl vinyl ether was investigated and found to be to a potent anaesthetic.[44] Several values of the oil/water solubility ratio, in the range 91-100, suggested that according to the Meyer-Overton theory it should be more potent but in fact its potency was similar to that of diethyl ether. It was marketed under the trade names Fluoromar and Fluroxene and was widely used until competition with other fluoro-ethers and Halothane restricted its use.[45] Research at Dow Chemical Company, referred to above, also produced a large number of fluorinated substances, among which was one judged to be suitable for clinical use (Methoxyflurane, $CH_3$-O-$CF_2$-$CHCl_2$) and it was market successfully from 1960. Research to identify other fluoro-ethers with useful anaesthetic properties continued. Ross C. Terrell of Ohio Medical synthesized over 700 compounds in a search for the 'ideal anesthetic' that commenced in 1960, eventually discovering Enflurane, Isoflurane and Desflurane,[46] while Sevoflurane came from researchers at Travenol Laboratories (Table 2).[47]

**Table 2. Fluoro-ether anaesthetics**

| Anaesthetic name | Chemical structure | Introduction |
|---|---|---|
| Enflurane | $CHF_2$-O-$CF_2$-CHClF | 1973 |
| Isoflurane | $CHF_2$-O-CHCl-$CF_3$ | 1981 |
| Desflurane | $CHF_2$-O-CHF-$CF_3$ | 1992 |
| Sevoflurane | $CH_2F$-O-$CH(CF_3)_2$ | 1994 |

[41] J. Ferguson, 'The Use of Chemical Potentials as Indices of Toxicity', *Proceedings of the Royal Society B* (1939), **127**, 387-404.
[42] C.W. Suckling and J. Raventos, 'A new halohydrocarbon and methods of making the same', British Patent 767,779, 1957. C.W. Suckling, 'Some chemical and physical factors in the development of fluothane', *British Journal of Anaesthesia* (1957), **29**, 466-472.
[43] A. van Poznak, 'Methoxyflurane and Teflurane', in *Modern Inhalation Anesthetics*, ed. M. B. Chenoweth (Springer, Berlin Heidelberg, 1972), pp. 77-92.
[44] J.C. Krantz, Jr., C.J. Carr, G. Lu and F.K. Bell, 'Anesthesia. XL. The anesthetic action of trifluoroethyl vinyl ether', *Journal of Pharmacology and Experimental Therapeutics* (1954), **108**, 488-495. M.S. Sadove, R.C. Balogot and H.W. Linde, 'Trifluoroethylvinyl ether (Fluoromar®). I. Preliminary clinical and laboratory study', *Anesthesiology* (1956), **17** (4), 591-600. J.W. Dundee, H.W. Linde and R.D. Dripps, 'Observations of trifluorovinyl ether', *Anesthesiology* (1957), **18**, 66-72.
[45] L.E. Morris, 'Fluroxene', in *Modern Inhalation Anesthetics*, ed. M. B. Chenoweth (Springer, Berlin Heidelberg, 1972), pp. 93-102.
[46] W. Burns and E. Eger, 'Ross C. Terrell, PhD, an anesthetic pioneer', *Anesthesia & Analgesia* (2011), 113**(**2), 387-389.
[47] M.D. Larsen, 'History of anesthetic practice', in R.D. Miller, ed., *Miller's Anesthesia* (Churchill Livingstone, Elsevier, Amsterdam, 2010), 7th edition, 3-42.

All the fluoro-ether anaesthetics, as well as Halothane, can be responsible for some degree of liver damage and as a result their uses are carefully controlled.

## 8. Concluding remarks

Meyer and Overton's theory was widely referred to but did not provide a sure path to the development of new anaesthetic gases[48] and although researchers in the 1920s and 1930s measured partition coefficients and solubility ratios they were only paying lip-service to theory. Forman[49] has argued that the various lipid hypotheses, did not meet Popper's criterion that a scientific hypothesis should be falsifiable. Nonetheless, researchers proceeded to ring the changes in molecules and test them in animals against a number of criteria. And although it is three decades since it emerged,[50] neither has the receptor binding mode of action facilitated the discovery of new anaesthetics. Perhaps the fluorinated ethers now in use can be regarded as the long-sought 'ideal gases' for inducing the sleep that takes us away from the realm of pain and facilitates surgery of many kinds.

[48] M. Perouansky, 'The quest for a unified model of anesthetic action: a century in Claude Bernard's shadow', *Anesthesiology* (2012), **117**(3), 465-474.
[49] S.A. Forman, 'A paradigm shift from biophysical to neurobiological: the fading influence of Claude Bernard's ideas about general anesthesia', *Anesthesiology* (2012), **118**(4), 984-985.
[50] C. Grasshoff, U. Rudolph and B. Antkowiak, 'Molecular and systemic mechanisms of general anaesthesia: the 'multi-site and multiple mechanisms' concept', *Current Opinions in Anaesthesiology* (2005), **18** (4), 386-391.