From Serendipity to Science:

How Anaesthesia Contributed to the Origins of Pharmacology

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Introduction

Successful inhalational anaesthesia for dental and surgical procedures was achieved by William E. Clarke and by Crawford W. Long (1815–78), both of whom who used ether in 1842, and by Horace Wells (1815–48) who used nitrous oxide in 1844;[1 2] but it was William Morton's successful demonstration with ether vapour in October 1846 which convinced the influential Boston surgeons and which then led to the rapid adoption of ether vapour worldwide during 1847.[2] However the introduction of these agents was not the result of scientific experimentation but of empirical observations derived from the recreational inhalation of ether by medical students and others ('ether frolics') and the 'laughing gas' demonstrations of itinerant showmen.[2]

That anaesthetic activity might be related to chemical composition and structure was suspected in the late 1840s, after which the search for new anaesthetic agents was increasingly based on scientific principles. However progress was limited until the 1860s when advances in chemistry enabled recognition of structure-activity relationships. Thereafter work on the development of new anaesthetic agents made significant contributions to the genesis of the new specialties of experimental and clinical pharmacology.

The Search for Better Anaesthetic Agents

Because the use of ether and of nitrous oxide posed some difficulties in clinical practice, their discovery prompted an intensive search for the 'ideal' anaesthetic agent. Initially this search was, like the original discovery of anaesthesia, based largely on trial and error.

James Young Simpson

Chloroform, which largely replaced ether as an anaesthetic, was just one of many compounds with which the Edinburgh surgeon Sir James Young Simpson (1811–70) and his colleagues experimented during 1847, using themselves as the experimental subjects. However, the selection of these agents was based not on their chemical composition or structure but on their physical properties, particularly volatility. Simpson also chose those compounds with a 'more fragrant or agreeable odour'.[3] Other substances selected by Simpson using the same criteria proved less satisfactory, either because something with a fragrant odour might still prove irritant to the bronchial mucosa or because of other side effects.[4 5]

Of the researchers who subsequently took a more scientific and systematic approach to the search for potential new anaesthetic agents, some chose compounds on the basis of their physical properties but others now looked at compounds which had similar chemical compositions. Those who chose this second option were hampered by what was then only an embryonic knowledge of chemical formulae and chemical structure. To understand the problems which they faced it is first necessary to consider the limitations of their understanding.

Barriers to Pharmacological Progress during the Early Years of Anaesthesia

The study of chemistry had made rapid advances during the first half of the nineteenth century. After Antoine Lavoisier (1743–94) and his colleagues had shown that chemical compounds were combinations of elements and had calculated the relative weights of the elements in a number of compounds, the conceptualisation of chemical compounds was completely changed by the atomic theory of John Dalton (1766–

1844). Attention now switched from the weight of each element in a compound to the number of atoms in a molecule. This new focus made it potentially possible to relate composition to structure and both composition and structure to pharmacological activity.[6] The earliest studies which attempted to make such relationships were those made between 1839 and 1848 by James Blake (1814–1893), an English student of François Magendie (1783–1855).[7] Working with inorganic compounds, Blake found relationships between chemical composition, molecular weight and physiological activity.[8-10] However, similar investigations with organic compounds were to prove much more problematic.

In the 1830s Jean-Baptiste Dumas (1800–84) had shown that hydrogen atoms in candle wax or in acetic acid could be replaced with chlorine atoms to produce a new compound with physical properties which remained very similar to those in the original compound. Having shown that atoms of apparently opposite electrical charge could substitute for each other in this way Dumas formulated his 'Law of Substitution', initially expounded in 1834 and expanded, in the light of further work by Laurent and Gerhardt, as the 'Theory of Types' in 1839. From this he deduced that there were circumstances in which the properties of a compound could depend more on the number and position of its constituent atoms than on the actual nature of those atoms.[6 11] This was to have implications for those who subsequently synthesised chemically related compounds while searching for new anaesthetic agents.

By the time that Dumas had formulated his theory it had already become apparent that a chemical formula could not in itself provide a satisfactory basis for the classification of organic compounds. The recognition of isomers, which had the same formula but different properties, and of isomorphic compounds, which had different formulae but similar properties, showed that a simple chemical formula did not necessarily predict structure or action.[6] Such then was the state of chemical knowledge when the scientific search for new anaesthetic agents begun.

The Search for new Anaesthetic Agents before 1859

Robert Glover

Although he did not realise at the time that he was working with potential anaesthetic agents, the earliest systematic pharmacological experiments with such compounds were those published by Robert Mortimer Glover (1815–59) in 1840–2, some five or six years before the advent of clinical anaesthesia. Glover was born near Newcastle and studied in Edinburgh, Geneva and Paris before returning to work in Newcastle.[12] James Young Simpson was one of the examiners for his MD thesis in which Glover described his studies with compounds of bromine, iodine and chlorine and for which he won the Gold Medal of the Harveian Society in 1842.[13] In his systematic studies of what were at that time described as the 'physiological properties' of the bromide and chloride of olefiant-gas (ethylene in modern terminology), and of bromoform, chloroform, and iodoform, Glover not only described the narcotic and anaesthetic properties of chloroform but he also recognised that 'exact and beautiful chemical relationships subsist between chlorine, bromine, iodine and their compounds' and he noted the 'striking resemblances in the leading characters among members of the group.' Later however, in 1848, he attributed some very different properties to iodoform when it was given topically or orally.[14] In his original experiments Glover had administered the compounds intravenously and intraperitoneally. Although he smelt the injected chloroform on the breath of his experimental animals he did not try giving it by inhalation. Many of the animals died because he used such large doses. It did not therefore occur to Glover that the anaesthetic properties of some of the compounds might be of clinical relevance. However there is no doubt that his studies with these related compounds represent the earliest systematic pharmacological experimentation with compounds which have anaesthetic properties.

Glover described the composition of compounds in terms of the type and number of atoms which he believed them to contain. As was common at this time, he assumed an atomic weight of 6 for carbon, and so he gave the formula of chloroform as C_2HCl_3 instead of $CHCl_3$ and that of Dutch Liquid (ethylene dichloride or 1,2 dichloroethane) with additional carbon and hydrogen atoms as $C_4H_6Cl_2$ instead of $C_2H_4Cl_2$. In 1848 he was still using an atomic weight of 6 for carbon, writing iodoform as C_2HI_3.

After Simpson had introduced chloroform into clinical practice, Glover claimed priority for the discovery of its anaesthetic action and he criticised Simpson for not having acknowledged his contribution.[15] Simpson replied that, as a clinician, he did not read reports of animal experiments and had therefore missed Glover's paper in 1842. However, it is curious that Simpson should not have recalled examining Glover's thesis which formed the basis of that paper. Glover was a brilliant polymath who lectured and published extensively on many different subjects, but his short life was blighted by addiction to opiates and chloroform. He died from an accidental overdose of chloroform which he was using as a sedative.[12]

Marie Jean Pierre Flourens

Flourens (1794–1867) was a French physician and physiologist who carried out pioneering experiments on the localisation of brain function.[16] Soon after the discovery of the anaesthetic effects of ether, he began using this agent as an investigative tool in his work on the functions of the medulla oblongata. Initially he used sulphuric ether and subsequently compared its effects with those of hydrochloric ether (ethyl chloride in modern terminology) and then nitric ether. He found that the effects of hydrochloric ether appeared more quickly and disappeared more rapidly than those of sulphuric ether, and that nitric ether was invariably fatal.[17] Having compared these three ethers he subsequently wrote that his experience with hydrochloric ether had led him to try chloroform, with the implication that it was the chlorine in hydrochloric ether which led him to experiment with chloroform.[18] Whatever his exact reasoning, Flourens was the first to demonstrate the anaesthetic property of chloroform, in March 1847, some seven months before Simpson's discovery.

Perhaps more importantly, Flourens had used a systematic and logical approach in comparing the effects of three ethers and in his choice of chloroform as a potential anaesthetic agent. However, Flourens simply noted the fact of his discovery but did not pursue it because it was not relevant to his own programme of research. As regards the potential clinical use of such agents, he did note that ether was 'both remarkable and fearsome.'[17]

John Snow

The immense scientific contributions of the London doctor John Snow (1813–58) in the fields of anaesthesia and epidemiology are well known.[19] Snow was conscious of the empirical background to the introduction of anaesthesia and, as late as ten years after it was first used, he wrote that the discovery of the anaesthetic agents which were in use at that time was due 'to a number of accidental circumstances rather than to any systematic and well-regulated investigation.'[20] Snow had pioneered the use of scientific investigation in the study of anaesthesia, most notably in his ground-breaking series of eighteen papers published in the London Medical Gazette between 1848 and 1851.[21] As Ellis has noted, the calibre of Snow's science as displayed in these papers is outstanding.[22] He understood the significance of saturated vapour pressure and showed how it varied with temperature. He anticipated the concept of pharmacokinetics and he also showed that the quantities of inhalational agents needed to produce anaesthesia were inversely proportional to their solubility in blood.

However, Snow's interests were mainly concerned with establishing the physical and clinical principles of anaesthetic action. As such, he was primarily interested in the physical properties of anaesthetic agents, particularly their volatility and solubility, and in their physiological and clinical effects. In 1848 he experimented with sixteen individual agents including chloroform, ether, nitric ether (ethyl nitrate), bisulphuret of carbon (carbon disulphide), benzin (benzene), bromoform (tribromethane), bromide of ethyle and Dutch Liquid, but his investigations with these compounds served primarily as a means of furthering his main areas of interest. He did not therefore classify them according to their chemical compositions but by the physical characteristics of their solubility in blood and their volatility.[21] It was for this reason that he gave what he believed to be the chemical formulae of only three of the compounds which he investigated in 1848.

That is not to say that Snow ignored chemical composition. Having initially rejected Dutch Liquid, 1,2-dichloroethane ($C_2H_4Cl_2$), as a suitable agent for anaesthesia he then investigated the 'monochloruretted chloride of ethyle' (1,1-dichloroethane, CH_3CHCl_2). He gave this uneventfully to twenty-two patients but thereafter was

unable to obtain supplies of sufficient purity.[23] He synthesised bromoform ($CHBr_3$) in order to compare it with chloroform. Although he found it more pleasant to inhale than chloroform, his experiments were limited to himself and two mice, probably because it was expensive to make.[21] This was fortunate because it was subsequently found to cause renal and hepatic damage.

When Snow chose to investigate amylene in 1857, he was certainly aware that its composition was similar to that of benzene with which he had experimented in 1848. He wrote that he knew in advance that 'there could be no doubt of amylene causing insensibility when inhaled.'[20] He used amylene on 238 occasions but gave it up after he experienced a second death.[24] Thereafter he never tried to synthesise other compounds in the benzene series and, indeed, he had only worked with amylene after he became aware of its existence. He did however synthesise amyl chloride ($C_5H_{11}Cl$) at about the same time as he started to investigate amylene but found that, because of its low volatility, it induced anaesthesia only very slowly and with some difficulty.[25]

As Snow was also working at a time when the atomic weight of carbon was still usually considered to be 6 rather than 12, he gave the formulae of Dutch Liquid as $C_4H_4Cl_2$ (instead of $C_2H_4Cl_2$) and of amylene as $C_{10}H_{10}$ (instead of C_5H_{10}).

Thomas Nunneley

The Leeds surgeon Thomas Nunneley (1809–1870) combined a busy clinical practice with research into anaesthesia, toxicology, physiology and ophthalmic anatomy. He published his anaesthetic researches in 1849. Like Snow he began by recognising that the use of anaesthetic agents had hitherto been 'mainly, if not altogether empirical, - not founded upon any rational basis.' He set himself the ambitious task of answering, by experimentation, six questions. Five of these were essentially physiological or clinical. However, the first question on his list was pharmacological, namely, whether the property of inducing anaesthesia was limited to the few agents already in clinical use, or whether there might be a large number of such compounds; and, if so, 'whether these substances are characterized by any similar composition or chemical alliance, and have a common modus operandi upon animal bodies?'[26]

From a knowledge of the existing anaesthetic agents Nunneley hypothesised that anaesthetic activity might be found in other hydrocarbons which incorporated either oxygen or chlorine. Clearly aware of the work of Dumas, he also speculated that a chlorine atom, for example, might be replaced by one of 'iodine, nitrogen, sulphur or some other element, the new compound in property being analogous, if not identical, with the old.' He described how this was 'in some degree an extension of the beautiful theory of substitution, now so generally admitted amongst chemists, applying the same doctrine to the therapeutic and physiological properties, as has so long been known to prevail in their chemical qualities.' He was also keen to compare isomers, to investigate some pure hydrocarbons and at least one carbon compound, bisulphuret of carbon, in which the hydrogen had been replaced by sulphur.[26]

For their time Nunneley's ideas represented a most erudite and insightful train of thought. In the event he was not able to investigate all his chosen compounds because some could not be obtained or were too unstable or too irritant. Others were unsuitable because they lacked volatility or solubility. Even so, he investigated thirty four substances, usually singly but sometimes in combinations. As he investigated these thirty-four substances in only 363 experiments using five different routes of administration (inhalation, intravenous, oral, rectal and topical) in eleven different species of animal, it is perhaps surprising that Nunneley should have felt able to draw any valid conclusions.

He recognised that he had given only a 'partial answer' to the question of whether substances with anaesthetic properties are characterised by 'any similar composition or chemical alliance.' He also recognised that some of his experiments may have been compromised by the presence of chemical impurities. Nevertheless he felt able to draw some very definite conclusions on the basis of evidence which, by modern criteria would be regarded as merely suggestive rather than definitely conclusive, but which were justifiable by the standards of the age in which he worked.

Having excluded nitrous oxide and hydrogen sulphide on the grounds that, although they caused insensibility, they did not 'produce that condition of the system which is understood by the term anaesthesia', he concluded[26] that:

1. All true anaesthetics contain carbon.
2. The more effective agents also contain either hydrogen or chlorine and that, in those compounds which contain only carbon and hydrogen, the greater the proportion of carbon to hydrogen the more powerful the anaesthetic effect.
3. Anaesthetic activity could also reside in some combinations of carbon and hydrogen with oxygen, chlorine, iodine, bromine, nitrogen and perhaps some other elements; and, having implied that Dutch liquid was more potent and quicker acting than chloroform, he attributed these properties to its smaller content of chlorine.[26]
4. Substances of similar chemical composition were likely to have similar physiological actions, provided that they also had similar physical characteristics; but where this proviso did not apply, as with chloroform and iodoform, then there was no similarity of physiological action. He also believed that the same proviso applied to 'substances which are isomeric or nearly so.'

Nunneley's reasoning was occasionally incorrect because of the defective design of his experiments. Moreover many of his chemical formulae were incorrect because of the limited knowledge of organic chemistry in 1849. Those for carbon monoxide, carbon dioxide and carbon disulphide were given correctly but those for chloroform, sulphuric ether, hydrocyanic acid, alcohol, Dutch liquid (ethylene chloride or 1,2 dichloroethane) and carbon tetrachloride were all based on an atomic weight for carbon of 6 or less. As late as 1867 he gave the formula of carbon tetrachloride as C_4Cl_4.[27] He could never, therefore, have had an accurate understanding of the chemical structure of most of the chemicals with which he experimented. Nevertheless his conceptualisation of the possible relationships between chemical composition and anaesthetic effect (and possibly also of the concept of a relationship between structure and effect) was far in advance of his contemporaries in the late 1840s.

Charles Ozanam

Charles Ozanam (1824–1890) was the son of a doctor and the brother of Frederic Ozanam, the distinguished professor of foreign literature at

the Sorbonne. He worked as a senior intern at hospitals in Paris and then in Lyon before returning to work in Paris where he was also senior librarian at the Academy of Medicine.[28]

In 1856, seven years after Nunneley's paper but without any mention of his work, Ozanam wrote that 'All the volatile or gaseous carbon compounds are endowed with anaesthetic power; the more carbon in the compound the more it possesses this power.'[29] Ozanam also believed, mistakenly, that all carbon containing anaesthetics were converted by the body into carbon dioxide and carbon monoxide which were the active anaesthetic agents.[30]

He stated repeatedly that oxygen was a specific antidote to carbon anaesthesia. [31 32] According to Ozanam, 'oxygen and carbon are the two poles of life. Oxygen invigorates the blood, excites the organs and the nervous system; it is the hyperaesthetic par excellence' whereas 'carbon arrests the vital signs, darkens the blood, hinders the circulation and paralyses the nervous system; it is the anaesthetic *par excellence*.'[33]

Ozanam repeated many of his assertions in several papers but never provided any convincing evidence to support his assertions.[34-37] By 1862 Ozanam had turned his attention to homeopathy and appears to have given up both research and practice in orthodox medicine.[38 39]

Louis Scoutetten

Louis Scoutetten (1824-90) was a French military surgeon based at Metz. Scoutetten did not undertake any experimental research but his analysis of the work of others was more perspicacious than that of Ozanam. He reviewed papers written by Ozanam, Nunneley and others and concluded that, if their findings were correct, 'it would be sufficient to know the formula of a carbon compound to determine, a priori, its anaesthetic power.'[40]

Whereas Nunneley had simply posed the question of whether anaesthetic agents 'are characterized by any similar composition or chemical alliance',[26] Scoutetten now explicitly suggested that this information, if correct, could be used to predict the anaesthetic potency of a compound whose chemical formula was known.

However, unlike Nunneley and Ozanam, Scoutetten concluded that the premise was incorrect. The difference of opinion was, in part, due to different methodology. In general, all three investigators accepted the orthodox chemical formulae of the time whereby carbon, for example, was given an atomic weight of 6 and the formula of chloroform was therefore given as C_2HCl_3. However, Scoutetten also calculated the carbon content of a compound using the pre-Daltonian methodology which expressed it as a percentage of the compound's weight rather than according to the number of atoms of carbon which were contained in the compound. Nunneley and Scoutetten also differed in their assessment of the anaesthetic potency of various agents. For example, Nunneley considered that Dutch liquid was more potent than chloroform whereas Scoutetten regarded chloroform as 'the most potent anaesthetic which we possess.' All three also included in their comparisons many compounds which would not now be considered as anaesthetics. Scoutetten was right to question some of Nunneley's conclusions, as well as the more dogmatic assertions of Ozanam, even though some of his own assumptions were to prove incorrect. Nevertheless, all three deserve credit for attempting to link chemical content with pharmacological action with the implication, made explicit by Scoutetten, that a knowledge of the former might be used to predict the latter.

Advances in Chemical Theory

Men like Nunneley and Scoutetten evidently had an intuitive suspicion that there must be a relationship between the composition and the structure of a chemical and also between composition or structure and its pharmacological actions; but as long as they lacked accurate information on atomic weights they could not make satisfactory correlations and, even when accurate compositions were known, the Type Theory was not in itself sufficient to allow prediction of relationships between composition and structure or between structure and action. However, the Type Theory did pave the way for new concepts such as valency which were to make such correlations possible.[6 11]

Valency

By 1850 the work of August William Hofmann (1818–1892) and Alexander Williamson (1824–1904) had expanded the Type Theory by showing that amines could be regarded as substitutes of ammonia and alcohols and ethers as substitutes of water.[11]

By 1852 this work had led Williamson to make the visionary suggestion that:

'[Formulae] may be used as an actual image of what we rationally suppose to be the arrangement of constituent atoms in a compound, as an orrery is an image of what we conclude to be the arrangement of our planetary system.'[41]

In the same year Edward Frankland's (1825–99) studies of organo-metallic compounds led him to conclude that there was a limit to the number of radicals which could attach to each atom in an element.[42] What he initially described as 'combining power' was investigated further in 1857-8 by August Kekulé (1829–96) and Archibald Scott Couper (1831–92). Working independently, they described, almost simultaneously, the characteristic number of atoms with which particular elements could bind, a concept which became known as valency.[43- 45] Both men also suggested the existence of carbon-carbon bonds, a concept of crucial importance to organic chemistry in general and to anaesthetic research in particular. Kekulé later postulated the existence of polymers based on these bonds and Couper went on to propose structural formulae for organic molecules, formulae in which lines were used to represent the bonds which connected atoms.[6]

The Russian chemist Alexander Butlerov (1828–1886) is often credited with introducing both the phrase and the idea of 'Chemical Structure' in 1861. However a plausible case can be made that he was anticipated by the concept of tetravalent chain-forming carbon atoms put forward by Kekulé and Couper in 1858, even though they may not have expressed the concept as explicitly as did Butlerov.[11]

The pioneering work of Frankland, Kekulé and Couper was extended in 1864–5 by Alexander Crum Brown (1838–1922), whose formulae were the first to represent, clearly and satisfactorily, both the valency and the linking of atoms in organic compounds.[46 47] At this time both Crum Brown and Frankland were still cautious about attributing spatial implications to

formulae[11] which is an indication of how remarkably prescient Williamson's analogy with the orrery had been thirteen years earlier.

Understanding of the concept of valency was hampered by the multiplicity of terms which were used to describe it. What Frankland had termed 'combining power' in 1852, Kekulé then called 'basicity' in 1857 and 'atomicity' in 1861. He used both these terms indiscriminately until he changed to 'valenz' in 1867. Other terms included 'degree of affinity' (Couper 1858), 'equivalence' (Odling 1858), 'atomic-fixing capability' and 'quantivalence' (Hofmann 1865) and 'atomic value' (Williamson 1869).[11] It was even longer before consistency and clarity was achieved in textbooks.

Atomic Weights and the Periodic Table

The confusion was compounded by the continuing uncertainties over the correct values for atomic weights. All the concepts necessary to calculate atomic weights (Dalton's atomic theory, Gay-Lussac's law of combining volumes and Avogadro's concept of molecular gases) had been available since 1820. However, the work of Amedeo Avogadro (1776–1856) was not generally accepted until it was resurrected by Stanislao Cannizzaro (1826–1910) in 1858 and then further publicised at a conference organised by Kekulé in Karlsruhe in 1860.[11]

Even then many distinguished chemists continued to use outdated values. For example Edward Frankland, who had been professor of chemistry at Owens College in Manchester since 1851 and a Fellow of the Royal Society since 1853, only converted to the true values of carbon (12) and oxygen (16) in 1866.[48]

It was the advent of the periodic system of classification which ultimately enforced the universal acceptance of true atomic weights.[48] Classifications of the elements using both atomic weights and valency had been proposed by Odling (1864), Williamson (1864), Miller (1866) and Frankland (1867). However none of these London-based chemists recognised that there was a periodicity as atomic weight increased, and this limited the value of their classifications. It was the publication of the Periodic Table of Dmitri Mendeleev (1834–1907) in 1869 and the further observations of Lothar Meyer (1830–1895) in 1870 which finally persuaded the influential German chemist Herman Kolbe (1818–1884) and others to convert to the true atomic weights.[11]

Even when the correct formula of a compound was known, isomerism could still cause problems in determining structure.

Absorbing the new knowledge

It was some years before textbooks of chemistry incorporated the new knowledge and, in consequence, doctors and chemists continued to use incorrect formulae. A survey of the most popular textbooks of chemistry such as those by George Fownes (1815-49) and Henry Watts (1815-84), both of which went through multiple editions,[49 50] shows that it was only from 1863 onwards that correct chemical formulae were given consistently and, as already noted, it was well into the next decade before there was consistency about the terminology of the concept which became known as valency.

It is evident that anyone searching for new anaesthetic agents on the basis of chemical composition in the mid to late 1860s would have been faced with a plethora of conflicting information. He would have had to keep up to date not only by reading textbooks but, more importantly, by studying current issues of journals. Even then he would have met with conflicting opinions and, if his researches were to be successful, he would have needed both the intellect and the intuition to determine which of those opinions was the most probable. One such man was Benjamin Ward Richardson.

Sir Benjamin Ward Richardson

Richardson was not only a physician and scientist of renown but also a founder and editor of several journals, a humanitarian who was also concerned with animal welfare, a playwright and a poet.[51] In the field of anaesthesia he introduced the ether spray as an effective and practical means of producing local anaesthesia in 1866.[52] He sought to reduce the mortality associated with chloroform by finding safer methods of administration, by improving techniques for resuscitation and by discovering new and safer anaesthetic agents.[53]

Between 1864 and 1871 Richardson introduced fourteen new anaesthetic agents (Table 1). More important, by far, than the anaesthetic agents themselves was the manner of their discovery. The

use of the agents was transitory. Only two of them, methylene bichloride and methylene ether, achieved any degree of popularity and even that was relatively short-lived; but the discovery of those agents during the mid-late 1860s and the early 1870s was a significant advance in the new specialty of experimental pharmacology. The approach of James Young Simpson to the discovery and mode of use of new anaesthetic agents had been largely one of trial and error. John Snow had introduced the scientific approach, primarily to the physiology of anaesthesia but also, when he tested a series of chemically related compounds, to the pharmacology as well. Nunneley's experimental approach was pharmacological but somewhat haphazard. However, it was Richardson's systematic methodology which truly exemplified the scientific approach to what became recognised as the discipline of experimental pharmacology.

Table 1. General anaesthetic agents introduced by B.W. Richardson[54]

Agent	Date
Amyl chloride	1869
Amyl hydride	1867
Butyl chloride	1869
Butyl hydride	1867
Ethyl hydride	1867
Methylic alcohol	1864
Methyl bromide	1867
Methyl chloride	1867
Methylic ether	1867
Methylene bichloride	1867
Methylal	1868
Hydramyle	1871
Methylene ether	1870
Methylic-ethylic ether	1867

Richardson's Early Studies in Pharmacology

Like James Blake, Richardson also worked initially with inorganic compounds. In 1860 he showed that lethal injections of potassium chloride or sodium chloride in frogs could cause osmotic cataracts, but equivalent doses of potassium iodide or sodium iodide did not.[55]

He then turned his attention to organic compounds. Building on the early pharmacological studies of Magendie and Claude Bernard, Richardson went on to exploit the recent advances in organic chemistry which, by the 1860s, had led not only to the discovery of valency and all that stemmed from that discovery but also to much improved methods for purifying the active principles of many drugs and of determining their chemical composition.[56]

As a close friend of Snow, Richardson had observed Snow's orderly approach to the investigation of any potential new anaesthetic agent: how first he would ascertain its boiling point and then the points of saturation of air with its vapour at different temperatures; then the quantity needed to produce anaesthesia in animals, followed by the quantity required to cause their deaths, either by a rapidly administered large dose or by a cumulative dose given over a longer period; and finally, if these preliminary results had been promising, he would test it on himself.[57] Richardson also applied a systematic approach, but his choice of agents for investigation was based primarily on their chemical composition, which could now be more accurately determined, as well as on their physical and other chemical properties.[58-61] His initial pharmacological experiments with organic compounds had not been directly concerned with anaesthesia but with investigating the physiological consequences of various substitutions in the amyl compounds (amyl nitrite, amyl chloride, amyl iodide, amyl acetate and amyl alcohol), though he may have chosen to start with the amyl series because amylene was already known to be an anaesthetic.[62] He then went on to study the analogous methyl, ethyl and butyl compounds. By this means he was able to show, for example, that a marked vasodilatation and increase in heart rate was associated with the nitrite, but not with the other salts of these compounds, and that the extent and duration of the effects increased with the molecular weight of the compound. Thus amyl nitrite ($C_5H_{11}NO_2$) was more active than was

methyl nitrite (CH_3NO_2). These experiments allowed Richardson to establish a relationship, albeit a very simple one, between chemical composition and pharmacological activity. As has been noted, however, composition is not synonymous with structure. Richardson did recognise that structure, and not just composition, could be important. For example, he showed that both chloral and what he believed to be its isomer (but which may have been a polymer) had the same pharmacological effects,[63] but that two other isomers, methyl acetate and ethyl formiate ($C_3H_6O_2$) had very different actions, the former causing a deep stupor with no muscular activity and the latter causing much less stupor but considerable muscular activity.[64]

A more definite transition from 'composition and activity' to 'structure and activity' relationships had already been made by Crum Brown in collaboration with Thomas Richard Fraser (1841–1920) when they showed that the quaternary ammonium compounds of alkaloids such as strychnine, codeine and morphine all possessed curare-like activity and that the pharmacological effects of the parent alkaloid were either lost completely or very greatly diminished.[65] Crum Brown also presented the work at a meeting of the British Association for the Advancement of Science in 1868 where Richardson was fulsome in his praise for it.[64 66] However this compliment does not seem to have been reciprocated. Indeed, when Fraser listed pioneers of experimental anaesthetic pharmacology in the lower animals in 1881, Richardson's name was conspicuous by its absence.[67] The style in which Richardson wrote his papers may not have appealed to Crum Brown and Fraser. Richardson was apt to mix pure science and clinical practice and, as one of his obituarists noted, he was sometimes unable to curb his imagination.[68] In particular, he was prone to speculate excessively on the possible clinical implications of some of his laboratory findings. By contrast, Crum Brown and Fraser kept strictly to the matter under investigation.

Richardson's Pharmacological Studies of Anaesthetic Agents

After his initial pharmacological studies with organic compounds, Richardson used similar methodologies to investigate the structure-activity relationships of potential hydrocarbon anaesthetic agents.

Noting that Dumas had developed a 'law of substitution', Richardson wondered whether there might not be some analogous 'physiological law', which would make the investigation and application of medicinal remedies 'more sure and certain'.[58]

Bynum has identified three implications which stem from Richardson's suggestion.[56] Firstly, it presupposed the possibility of prediction in pharmacological research. Secondly, it assumed that only part of a molecule might be pharmacologically active and that such activity, whether beneficial or toxic, might be modified by small changes in the chemical composition of the molecule. Thirdly, and perhaps most importantly, it implied that it would be worth investigating whole families of related compounds, a principle which was to find widespread application in the field of experimental pharmacology.

Richardson used quantitative methods in his systematic studies of the anaesthetic and toxic properties of various hydrocarbons. Although he did not discover any universal 'physiological law of substitution', he did show that toxicity, in this group of compounds, increased in proportion to the number of carbon atoms in a straight carbon chain until eventually a point came where the physical properties of the compound changed.[69] This discovery, which is sometimes known as 'Richardson's principle', found application in the synthesis of many alkyl compounds intended for use as drugs.[70] Lauder Brunton (1844–1916) described Richardson's research on the hydrocarbon anaesthetics as one of the first systematic attempts to connect structure and physiological action and as the bridge between the empirical studies of Simpson and the later research of Crum Brown and Fraser.[71]

Richardson showed that, among the chlorinated hydrocarbon anaesthetics, the anaesthetic property resided in the hydrocarbon moiety, whereas toxicity was related to the amount of chlorine in the molecule.[64 72] He reasoned that, as chloroform ($CHCl_3$) was safer than carbon tetrachloride (CCl_4), so methylene bichloride (CH_2Cl_2) would be safer than chloroform, and that methyl chloride (CH_3Cl) would be

safest of all.[73 74] He therefore synthesised and then tested methylene bichloride and methyl chloride.[75,76] Because methyl chloride is a gas, and was therefore regarded by Richardson as less convenient than a liquid for everyday clinical practice, he settled on methylene bichloride as an acceptable compromise between convenience and safety.

Desirable Attributes of Anaesthetic Agents

Richardson used his findings to describe what he regarded as the desirable attributes of a general anaesthetic which would be safe, convenient and suitable for both short and long operations.[72] He considered only liquids because he regarded both gases and solids as impractical for clinical use. Like Snow, he did not usually approve of mixtures of different agents because the constituents of some common mixtures, e.g. ether and chloroform, evaporated at very different rates, and he therefore considered that the ideal fluid should be homogeneous, stable and not easily decomposed by heat or light.[77] It should have a pleasant odour and should not cause muscular spasm or irritation of the respiratory or gastric mucosa. Its boiling point should not be too low, because fluids which evaporated at temperatures at or below that of the body had to be used, like gases, in large quantities and often with exclusion of some air. On the other hand, if the boiling point were too high, the substance remained too long in the body. Richardson thought a boiling point of 122°F with a vapour density of 40 and a solubility in blood of 1 part in 50 at body temperature would be ideal. Lauder Brunton (1844-1916) considered that, on *a priori* grounds, these principles were sound, but noted that they would have excluded the two best available agents, namely ether and chloroform![71] Richardson's requirement for a stable compound stemmed, at least in part, from his experiments with methyl iodide and methyl bromide. He found them to be good anaesthetics but was unable to prevent the formation of free iodine and free bromine which caused marked lachrymation, salivation and bronchial secretions.[75] Having reported that death sometimes occurred in animals which had been exposed to methyl bromide, Richardson was justifiably incensed when, twenty four years later, the vapour was used in man with the same fatal consequences:

'To practise first on human beings with agents so potent as these is the empirical method carried to recklessness, and ought really to come under the correction of law. In the case of the bromides, the administration is all the less excusable in that they have been tried, experimentally, and pronounced dangerous.'[78]

By the time that fluorine had been prepared in elemental form in 1886[79] Richardson had long given up work on the experimental pharmacology of anaesthetics but, given his concerns about the toxicity of chlorine, bromine and iodine, it is unlikely that he would have chosen to experiment with anything which was known to be as poisonous as fluorine. Were he alive today, he would probably not be surprised to learn that most modern volatile anaesthetics are methyl ethyl or methyl isopropyl ethers, but he would be taken aback when told that they all contain either chlorine or fluorine or both, and that another volatile anaesthetic, halothane, contains fluorine, bromine and chlorine.[80]

Prediction of Anaesthetic Properties

Richardson claimed that, if told the composition, weight, solubility in water, vapour density and boiling point of any substance, he could predict whether it had anaesthetic properties and, if it had, how much would be needed to produce narcotism and the time needed for induction of anaesthesia and recovery.[61] This was a bold claim but, at least as regards the liquid hydrocarbons, was probably a reasonably accurate one, and he did later restrict the claim to fluids, thereby excluding nitrous oxide, an agent for which he had always had a blind spot.[74] From first to last, Richardson regarded nitrous oxide not only as an inconvenient and cumbersome gas but as an asphyxiant rather than as a true anaesthetic, and to use an asphyxiant to produce anaesthesia was 'rude and unworthy of science.'[61 81-83]

Chloral and the Concept of A Pro-Drug

Nevertheless, Richardson's pre-eminence in the field of anaesthetic pharmacology, at the time of the re-introduction of nitrous oxide, was such that *The Lancet* described his authority on the matter as unquestionable.[81] Indeed, it was this very pre-eminence which led the British Association for the Advancement of Science to commission

Richardson in the next year (1869) to investigate chloral hydrate, which had recently been proposed as an anaesthetic agent by Oscar Liebreich (1839–1908) of Berlin. [84 85] At the time it was known that in vitro treatment of chloral with an alkali would liberate chloroform and formic acid, and Liebreich assumed that the narcotic effect of chloral was due to liberation of chloroform in vivo.[86]

The concept of an active metabolite, manufactured in vivo, would not have been an entirely new one to Richardson. Four years earlier, in 1865, he had speculated that somnambulists might 'through some abnormal process of digestion or respiration of the starchy elements of food, produce in their own organisms by their own organic chemistry, an agent which, like amylene, destroys remembrance, and perhaps judgement and reason, but which leaves the brain still able to act and to direct the limbs'.[58] Richardson's work appeared to confirm Liebreich's supposition that chloroform was indeed released *in vivo*.[85] However, other workers obtained conflicting results and further doubts arose. Although it was not possible to compare the degree of alkalinity of different fluids until Sørensen had proposed the pH scale in 1909,[86] Arthur Gamgee (1841–1909) doubted whether the alkalinity of body fluids was sufficiently strong to cause the decomposition of chloral hydrate into chloroform.[87] He and others also recognised that the clinical effects produced by small doses of chloral hydrate were disproportionate to those caused by an equivalent dose of chloroform and that the physiological state induced by chloral hydrate was not quite the same as that caused by chloroform.[88] However, it was not until 1948 that the true active metabolite of chloral was finally recognised as trichloroethanol.[86]

Richardson had noted that chloral reduced body temperature and thought that it might prove to be a useful alternative to opium in patients who were febrile, but he did not consider it to be a potential anaesthetic.[89] Richardson also investigated bromal hydrate and found that its narcotic action was less than that of chloral hydrate but that it caused intense bronchial irritation and oedema. He cited this as another example of how a difference in the composition and molecular weight of a compound could modify its pharmacological effects.[75]

Although Liebreich and Richardson were wrong about the active metabolite of chloral, Richardson recognised that Liebreich had 'brought out a very valuable physiological truth', namely that the body could metabolise synthetic compounds and that the metabolites could have therapeutic effects.[85]

Conclusion

Research into chemicals with anaesthetic properties played a major role in the development of experimental pharmacology in the second half of the nineteenth century. Glover, Flourens, Snow, Nunneley, Ozanam, Scoutetten and Richardson all contributed to the development of the concept of relationships between chemical structure and pharmacological action and to the methodology needed to demonstrate such relationships. Progress was hindered until the concept of valency and accurate values for atomic weights were established in the 1860s. Thereafter there was considerable progress in the field of experimental pharmacology.[90] However by the mid-1860s only a small proportion of the new knowledge had been translated into clinical practice. Two notable examples of the transition from experimental to clinical pharmacology were the introduction of physostigmine in ophthalmology and of amyl nitrite for the treatment of angina. Having isolated physostigmine from the Calabar bean in 1863 T.R. Fraser suggested its potential use in ophthalmology and, in the same year it was introduced into clinical practice by Douglas Argyll Robertson (1837–1909).[91] Four years later the experimental studies undertaken by Richardson and by Arthur Gamgee were the basis for the introduction of amyl nitrite in the treatment of angina by Lauder Brunton.[92]

As early as 1864 Richardson was both an experimental and a clinical pharmacologist. By 1864 it was recognised that the pharmacological action of anaesthetic agents might be predicted from a knowledge of chemical composition and structure but it was Richardson's systematic investigations between 1864 and 1871, combined with the new knowledge derived from valency and the periodic table, which refined and targeted such predictions. He showed that anaesthetic activity could reside in just one part of the molecule and that it could be modified by small changes in this active area. Among the hydrocarbon anaesthetic

agents he demonstrated that toxicity was related to the chlorine content and to the number of carbon atoms in a straight chain. He appreciated the importance of investigating entire families of related compounds and, by so doing, was able to introduce two new anaesthetic agents into established, albeit limited, clinical practice between 1867 and 1870. With Liebreich he was the first to recognise the concept of a pro-drug in 1869.

As Bynum has observed, the future of pharmacology now lay in the laboratory and no longer in the botanical garden.[56] Men such as Richardson, Lauder Brunton and Thomas Huxley (1825–1895) believed that the new discipline of experimental pharmacology would soon permit the synthesis of drugs which could be specifically designed to achieve specific effects in specific organs. However, the reality of such concepts was to prove much more elusive than they had hoped.[7 93]

It was not until the 1920s that experimental pharmacology was used once again in the search for new anaesthetic agents. A revival in interest in the anaesthetic properties of ethylene led to its manipulation by increasing the degree of unsaturation, as in acetylene, or by increasing the number of carbon atoms as in propylene; but these experiments were not successful.[94] However, the toxicity associated with propylene led Henderson to investigate its isomer, cyclopropane[95] and, despite its explosive properties, cyclopropane remained popular with many anaesthetists for more than twenty years. Henderson went on to show that another cycloalkane, cyclohexane, also had anaesthetic properties, but he could not investigate cyclobutane or cyclopentane because he was unable to obtain supplies.[96]

A prediction that a compound which incorporated structural aspects of both di-ethyl ether and ethylene would have anaesthetic properties led Leake and Chen to investigate vinyl ether, also known as vinyl oxide.[97] Despite concerns about stability and possible liver damage it remained in use until the 1950s.

Leake also investigated vinyl chloride[98] but it caused ventricular arrhythmias.[99] Its use did however lead to a revival of interest in the investigation of halogenated hydrocarbons from which many modern anaesthetics are derived.

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