CHEMOTHERAPY AND THE CENTRAL NERVOUS SYSTEM

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By

HENRY McILWAIN

Ph.D., D.Sc.

Professor of Biochemistry in the University of London at the Institute of Psychiatry (British Postgraduate Medical Federation); Honorary Biochemist, the Bethlem Royal Hospital and the Maudsley Hospital

Formerly member of scientific staff, Medical Research Council, and of the Council's Department of Bacterial Chemistry, and Unit for Cell Metabolism

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PREFACE

THE preparation of this book was prompted by the great practical problems presented today by nervous, mental and emotional disorders. It has two major themes: firstly the development of methods and principles in chemotherapy as a whole, and secondly the application of chemotherapy to produce drugs for use in the treatment of mental disorders.

Chemotherapeutic approach to such problems has a much greater background of previous investigation than is generally realised: for the first groups of synthetic medicaments acted at the central nervous system. One object of the present writing is to see current endeavours in this wider setting. To this end, the aims and guiding principles of workers during a century of investigation have been examined, together with the practical outcome of their work. The mode of action of successful agents has been appraised together with its dependence on chemical, biochemical and biological factors.

There is thus recounted a subject to which chemistry, biochemistry, pharmacology, physiology and clinical medicine have contributed, and in its presentation the interests of workers and students in each of these subjects has been borne in mind. The book derives from lecturing and research experience in faculties both of science and medicine, in London and elsewhere. Certain parts feature in lectures for the Academic Postgraduate Diploma in Psychological Medicine at the Institute of Psychiatry; others have been given as specialist lectures in London, Sheffield and at the National Institutes of Health of the United States Public Health Service.

I am greatly indebted to many who have helped the production of this book. My especial thanks are due to Professor A. J. Lewis, R. B. Rodnight and my wife who commented on or corrected the manuscript or proof; and to Drs. J. B. Brierley, D. L. Davies, A. McCoubrey and D. A. Pond who helped similarly with the parts of the book related to their own specialties.

H. MCILWAIN.

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The chemist . . . derives innumerable useful truths that are applicable to the improvement of manufactures and arts and to the preparation of remedies. . . . Hitherto scarcely any demand has been made upon the science of chemistry by arts, manufactures or physiology, which has not been responded to. Every question, clearly and definitely put, has been satisfactorily answered. Only when the inquirer has no precise idea of the problem to be solved has he remained unsatisfied.

The philosopher's stone, for which the ancients sought with a dim and ill-defined impulse, was, in its perfection, nothing else than the science of chemistry . . ., which promises to disclose to us the laws of life, and which must finally yield to us the means of curing disease and prolonging life.

Justus von Liebig. Familiar Letters on Chemistry.
Edited by W. Gregory, 1851.
London: Taylor, Walton & Maberly.

CONTENTS

CHAPTER 1

CHEMICAL SYNTHESIS OF THERAPEUTIC AGENTS

This chapter contains little chemical data but is concerned with the discovery of how best to apply synthetic organic chemistry to the treatment of disease and discomfort. A major stage in this discovery concerned surgical anaesthesia and was therefore directly related to the central nervous system. Before describing this stage, mention will be made of other attempts during the last century to apply the new subject of organic chemistry, to diseases which involved the brain.

Medical applications of organic chemistry

The way to synthesize quite new classes of organic medicaments was learned only gradually during the nineteenth century. Its development was roughly contemporaneous with that of organic chemistry itself. Chemical synthesis of therapeutic agents represented then as now only one way in which organic chemistry could be applied in medicine, and it was not the first or most obvious of these applications.

One early approach consisted of the isolation of the active principles of existing drugs, prepared from plants or animals. Another early approach, which had specific reference to the nervous system and mental illness, was that of Couerbe (1833). Couerbe sought chemical differences between materials isolated from the brain of normal people, and the insane or idiot. After much chemical fractionation of cerebral constituents, he concluded that differences existed in phosphorus content. Couerbe sought therapeutic application of this finding, which contributed to the idea of phosphorus-containing brain-foods; this idea was condemned as false by Liebig (1851), but survived this and other condemnations. It may be regarded as a precursor of nutritional therapies. Iodine was discovered as valuable in cretinism and myxedema in the 1840s, but its status remained tentative until the end of the century, when thyroid extracts were also applied. The major development of nutritional and hormonal therapies concerns the present century.

A further chemical approach to mental disorders sought to understand and control the results of infectious disease. The obvious involvement of the brain in the deliria and coma of fevers led J. L. W. Thudichum between 1865 and 1882 to study the organic constituents of the brain, arguing (1884): "When the normal composition of the

brain shall be known to the uttermost item, then pathology can begin its search for abnormal compounds or derangements of quantities. . . . I believe that the great diseases of the brain and spine, such as general paralysis, acute and chronic mania, melancholy, and others, will all be shown to be connected with specific chemical changes in neuroplasm. . . . The knowledge of the composition and properties of neuroplasm and of its constituents will also aid us in devising modes of radical treatment in cases in which at present only tentative symptomatic measures are taken. In short, it is probable that by the aid of chemistry many derangements of the brain and mind, which are at present obscure, will become accurately definable and amenable to precise treatment, and what is now an object of anxious empiricism will be one for the proud exercise of exact science."

Chemical means of treatment in fact have had many successes, but did not develop by the route envisaged by Thudichum. With suitable orientation and inspiration, as can be judged from this and the succeeding chapters, there were produced during Thudichum's lifetime agents which acted on the brain and were of great therapeutic importance. With 80 years more experience of the application of chemistry to pathology than had Thudichum, we would now no longer demand such complete chemical knowledge before seeking its application. Chemotherapeutic research in fact was largely independent of this type of chemical information.

Inhalation anaesthetics

The real power of synthetic organic chemistry in its practical application to medicine was first displayed by the spectacular way in which relatively simple substances modified the activity of the brain. This first found application in general anaesthesia. Though the desire to relieve apprehension and suffering in surgical operations must long have been present and met only inadequately by mandragora, morphine or alcohol, the discovery of effective agents was largely the work of the mid-1800s. It then proceeded hand in hand with the rudimentary but growing organic chemistry of the day, and contributed to the realization that this new science had great potentialities in medicine. Liebig's expression of this feeling is quoted on p. viii. The early investigations of anaesthesia also had commendably close support from the physiology of the day.

The introduction of volatile anaesthetics has been interestingly recounted (Snow, 1858; Symposium, 1946; Duncum, 1947) and only a few points relevant to the present subject can be included here. Though earlier attempts were made, the first clear and experimentally based suggestion for the use of an artificially prepared compound to

relieve the pain of surgery was made by Humphry Davy. Davy's suggestion was made with respect to nitrous oxide, and during his employment as an investigator at an institution founded to study the medicinal properties of gases and vapours: the short-lived Pneumatic Institute founded by Thomas Beddoes in 1798. Beddoes had himself experimented in the administration of various gases and volatile liquids in disorders especially of the lungs. Davy's previous apprenticeship to a surgeon makes understandable his interest in anaesthesia; this appears however to have been superseded by his interest in chemical research as such and he neither emphasized nor pursued the study of the agent whose properties he had discovered. Though he wrote "As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations . . ." he later regarded these studies as unscientific and misguided, writing in 1800 "Whenever we attempt to combine our scattered physiological facts we are stopped by want of numerous intermediate analogies, and so loosely connected or so independent of each other are the different series of phenomena that we are rarely able to make probable conjectures, much less certain predictions concerning the results of new experiments. An immense mass of pneumatological, chemical, and medical information must be collected, before we shall be able to operate with any certainty on the human constitution."

Davy thus deliberately chose other spheres of work; the probable conjectures and reasonably certain predictions were shortly to be made by others. Nitrous oxide achieved popular fame as laughing gas, partly as a result of Davy's demonstrations of its properties to scientific audiences, and knowledge of these properties was spread by itinerant lecturers in the United States to those who later rediscovered its anaesthetic powers and applied them in dentistry and surgery.

Organic compounds as anaesthetics

Ether as an anaesthetic appears like nitrous oxide to have been introduced through popular interest in the more spectacular of its physiological properties. In retrospect, Snow (1858) suggested that its soporific properties may have been observed in the sixteenth century when it was first prepared. Its attempted use in 1795 in consumption formed part of the background in which Beddoes' Institute was founded. Ether was reputed to be similar to nitrous oxide in its exhilarating effects, was used when nitrous oxide was not available, and its ability to deaden pain noticed and applied in minor surgery by C. N. Long in Georgia. A similar and independent sequence of events a few years later, with W. T. G. Morton playing a major role, established in 1846 the potentialities of ether as an inhalation anaesthetic in surgery.

The discovery was thus largely empirical, but in a space of time which was remarkably short for the period, much was learned of the types of substances which caused anaesthesia, and of their mode of action and practical use. By 1847 J. Y. Simpson in Edinburgh had examined a variety of volatile substances (Table 1) including acetone, dichloroethane,

Table 1

Substances from which the first anaesthetics were selected

Beddoes [1] and Davy [2]	Simpson [3] and Flourens	Nunnerley [4]	Snow [5]
O_2	Et_2O	EtBr, EtCl	Et_2O, $CHCl_3$
CO_2	$(CH_2Cl)_2$	$CHCl_3$, $(CH_2Cl)_2$	$EtNO_3$, EtBr
CO	Me_2CO	Me_2CO	CS_2, $MeNO_3$
H_2	$EtNO_3$	$EtNO_3$	C_6H_6, $CHBr_3$
N_2O	C_6H_6	C_6H_6	$(CH_2Cl)_2$, Me_2CO
	$CHCl_3$	$CHCl_3$	$MeCHCl_2$
	CHI_3	CHI_3	MeOH, EtOH
			EtOCOMe
			amylene

[1] Beddoes & Watt (1796).
[2] Davy (1800); Hickman in 1824 made extensive trial of CO_2.
[3] Simpson (1847).
[4] Nunnerly, T. of Leeds (cf. Duncum, 1947) investigated in all some 30 preparations in 1849.
[5] Snow (1858).

ethyl nitrate, benzene, iodoform and chloroform and from them made his famous selection of chloroform as substitute for diethyl ether. In the same year Snow (1847) described a practical apparatus which enabled him to administer and observe the effects of defined quantities of ether. Snow later investigated a wide range of compounds and from them selected amylene (Table 1) for extensive trial. Many of these materials, including those of Nunnerly, were newly prepared or investigated specifically for use as potential anaesthetics. Groups of simple organic compounds were between 1830 and 1850 drawing theoretical as well as practical interest: forming as they did the basis for conceptions of organic radicals, substitution, and the theory of types (Schorlemmer, 1879). Chloroform, ethyl chloride, ethers and esters were prominent in both types of study.

Dosage and progress of anaesthesia

Snow carried out experiments with ether and chloroform which clearly demonstrated that the factor which conditioned the intensity of their action, was the concentration of substance concerned in the air breathed. This was shown when small animals were confined in vessels of different sizes into which different quantities of the anaesthetics were released. The total quantity of anaesthetic to which the animal was exposed, or

which it could be calculated to have breathed, was found to be less important than the concentration in the air inhaled. Increasing concentrations of ether, chloroform and also of other agents were associated with a regular series of changes in the animal's behaviour (Table 2).

Table 2

Action of chloroform and ether on mice and guinea pigs (*Snow*, 1858)

Effect	Quantities required of			
	Chloroform		Ether	
	mg./l	ml. vapour /l.	mg./l	ml. vapour /l.
Minimal effects: slightly less brisk in movement	19·7	3·7	39·5	12
Staggering, unable to stand or walk	29·5	5·5	59	18
Lying, drowsy or sleeping, but reacts to pinching	47 to 69	8·8 to 12·9	79	24
Lying breathing naturally; little or no reaction to pricking	79 to 89	14·8 to 16·6	99	30
Lying, breathing stertorous or feeble; no response to prick: full recovery on removal	134	25	119 to 158	36 to 48
Breathing ceases, but recovers on removal from vapour	147	27·5	—	—

Measured quantities of the liquids were added to vessels of known volume in which the animals were observed. At intervals they were removed and their response to pinching or pricking was noted. Experiments on ether were mainly with mice, and on chloroform with guinea pigs. Snow's data, in apothecaries' measure, have been converted to the values quoted as mg/1. and further, assuming 1 mmole occupies 22·4 ml., to those for ml. of vapour/l. The maximum effect of a given concentration of vapour was usually obtained within 1 to 3 min. For a recent use of this technique, see Courvoisier, Fournel, Ducrot, Kolsky & Koetschet (1953).

These could clearly be recognized in the progress of action of the same agents in man, and comparable concentrations of ether or of chloroform vapour were found to be needed for equivalent effect in the different species examined. The concentration of anaesthetics in the air breathed by subjects undergoing surgery Snow determined by measuring the quantity of agent placed in his inhaler, and present in it after different intervals when the subjects were observed to be anaesthetized to different degrees.

Considering the novelty of the situation of testing synthetic organic

compounds as centrally-acting drugs, these investigations by Snow and by some of his contemporaries constitute a remarkably perspicacious combination of clinical trial with animal experiment. Their quantitative aspect is noteworthy. Snow's description of the levels or stages of anaesthesia encountered in man has been generally adopted and will be familiar to many readers. Nevertheless, as these stages represent the means used in practice in controlling the first centrally-acting synthetic drugs they are given more fully in the following paragraphs, largely in Snow's terms (1847, 1858; see Goodman & Gilman, 1955).

The first stage extends from the beginning of inhalation to include all that of which the subject is conscious and can later recollect. His feelings during this time are usually agreeable though local irritation and a feeling of suffocation may occur with ether; his face is flushed and he may experience hallucinations and illusions, of warmth, noises or lights. The pain of neuralgia or of labour may be relieved by sufficient anaesthetic to reach this stage, but not the pain of surgical operation or even of dentistry. If an average man breathes smoothly a mixture of 45% of ether vapour with 55% of air, he usually consumes about 8 g. of ether per minute (some of this is again expired). He then reaches the first stage of anaesthesia at the end of the first minute, and the second stage at the end of the second.

After anaesthesia has been established, and then terminated by stopping the inhalation of anaesthetic, a condition akin to the first stage of anaesthesia is again encountered. Consciousness is regained before full awareness of pain and this condition induced by ether has received limited trial for special surgical procedures (Artusio, 1954).

The second stage lasts from loss of consciousness until surgical anaesthesia is established. During it mental functions may be exercised, and voluntary actions performed, but in a disordered manner. Transition through it from the first to the third stage may occur smoothly especially in children but often involves excitement or delirium, and laughing, screaming or gesticulation. A distinct second stage may not be observed during recovery from the third stage of anaesthesia.

The third stage is that most generally desired in surgery and is indicated by regular breathing and by loss of control over the head and limbs, so that these can be moved by an observer without resistance. The eyelid also if moved gently will remain as placed. The pain of surgery is now no longer felt and though at the beginning of this stage it may evoke signs, as of groaning, none of this is recollected. This stage Snow at first divided into two degrees, reached after 3 and 4 minutes of inhalation of ether under the conditions just described, and later writers divide into four planes of increasing effect which are most suitable for different types of surgery. If, after ether anaesthesia has reached

this stage, the ether is discontinued and the subject breathes air, he remains in the third stage for only 2 or 3 minutes; after chloroform, the corresponding time is only about 1 minute.

The fourth stage. At this point the gradual loss of activity and reflexes which has proceeded through the preceding stages, begins to extend to other functions which cannot be halted briefly without danger; this stage is thus avoided in practice. During it the muscles of respiration begin to suffer the loss of power which previously involved the voluntary muscles; respiratory movements become difficult, feeble or irregular. The pupils dilate, vasomotor tone is lost, blood pressure low, and the heart irregular.

Material interaction of anaesthetics with the body

Ether and chloroform were shown during the 1840s to be transferred from the lungs to the blood and so to the body as a whole. After their

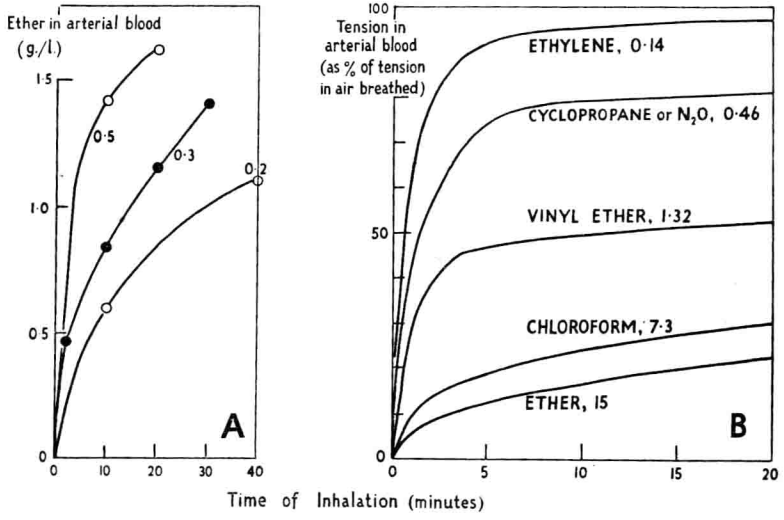

FIG. 1. Transfer of anaesthetics from air to blood. *A.* Ether in the arterial blood of dogs breathing the substance at different levels in air. The levels, in g./l. air, are given beside the curves. *B.* Approximate course of uptake of different anaesthetics by arterial blood. (Haggard, 1924; Kety, 1950, 1951). Values accompanying the different compounds give their partition coefficients between blood and air.

administration ceased they were found to be exhaled unchanged in the breath. Snow found little in urine, and pictured the substances arriving at the brain by the bloodstream. Later investigations have confirmed all these points; the concentration of ether in the urine is actually almost exactly that of the blood, but the quantity so excreted is small.

In this series of transfers the physical properties of the anaesthetics condition their uptake by the body. The mechanics of breathing results in only a gradual increase in the concentration of gaseous anaesthetics in the lung. Exchange at the lungs is normally very effective, so that the tension of anaesthetic in arterial blood is generally close to that in the alveoli. Air with ether at increasing levels leads to increased arterial concentrations and more rapid anaesthesia (Fig. 1*A*). Both the alveolar and arterial levels are conditioned not only by the rate of arrival of anaesthetic in the lungs, but also by its rate of removal by the blood; and here a dominant factor is the solubility of anaesthetic in the blood.

Of the common volatile anaesthetics, ether has greatest solubility in blood: air containing 1 mg./100 ml. of ether is in equilibrium with blood or saline containing 15 mg./100 ml., this being expressed as a partition coefficient, λ, of 15. The corresponding value for chloroform between blood and air is 7·3 and for cyclopropane, 0·46. Considering diethyl ether, the partition coefficient of 15 implies that each breath brings only a very small proportion of the ether which could be dissolved in the body and its arterial level builds up more slowly than does that of the other anaesthetics, as indicated in Fig 1*B*. Speed of attainment of equilibrium by the different gases in this figure is seen to increase with decreasing partition coefficient; with rapid attainment of equilibrium comes rapid induction of anaesthesia. Kety's (1951) review gives a detailed theoretical and practical treatment of this subject.

Frequently, to accelerate initial uptake, inhalation of anaesthetics is commenced with them at high concentration in the air breathed, and the concentrations are lowered as anaesthesia is induced. These and other factors concerning their administration are detailed in texts on anaesthesiology.

Uptake by the brain

Interaction of an anaesthetic with the brain has, understandably, been studied in greatest detail in the case of diethyl ether, the first compound extensively employed as an anaesthetic, and still much used (Haggard, 1924). It must first be noted that anaesthesia can be caused without necessarily exposing any part of the body, other than the brain, to the compound. This was achieved by injecting a 5% solution of ether in saline, directly to the carotid artery of dogs. When 0·5 g. of ether was added per minute, immediate signs of general anaesthesia ensued although the general arterial blood contained only 0·03 g. ether/l; the cerebral venous blood contained 0·9 g./l. indicating the removal of at least 80% of the substance by the brain. As the brain constituted only 5% of the body weight, this procedure succeeded in highly localising the administered ether.

During normal inhalation anaesthesia, the substance enters the brain much more gradually than in this experiment and concomitantly with its entry to other organs of the body. This is illustrated in the dog by the data of Fig. 2. Ether coming from the lungs leaves the heart by the arterial blood and is supplied uniformly to the body as a whole. The arterial level rises gradually as respiration adds increasing quantities to those already in the body. Venous blood throughout 30 minutes' etherization remained at levels appreciably below the arterial: during this period, which extends beyond those typical of the early use of ether, equilibrium is not achieved and ether is still actively entering the body.

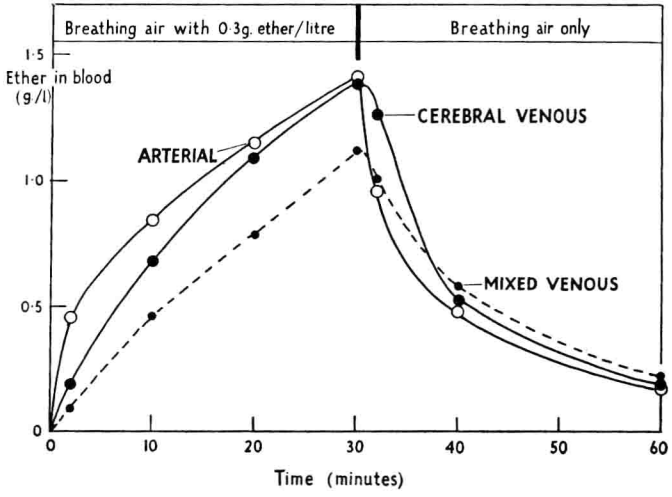

FIG. 2. Entry of ether to the brain of a dog (14 kg.), breathing air containing 0·3 g. ether/l. at 38° C (Haggard, 1924); and its subsequent loss on breathing air only. Arterial blood was sampled at the femoral artery, cerebral venous at the jugular, and mixed venous at the right heart.

Equilibrium is however being approached in the brain; throughout, the brain depletes the blood of ether to a lesser extent than do most other organs of the body. This is almost certainly due to the rapid blood supply to the brain, which explains also its more rapid approach to equilibrium.

The quantities of ether entering the brain are given by the area between the curves quoting the composition of arterial and cerebral venous blood. This supposes the sampling of the cerebral venous blood to have been adequate; the sampling is not easy but it and the analysis of such curves have been examined carefully (Kety, 1948; see McIlwain, 1955) in relation to the exchange of nitrous oxide and oxygen; it may

be noted that the entry of ether to the brain is slower than that of nitrous oxide.

Events when administration of ether is stopped also emphasize the rapidity of exchange between the brain and blood. The level of ether in the arterial blood immediately falls, at first quickly but later more slowly as the blood receives ether from the organs of the body. This transfer is indicated by the initially higher levels in venous blood, gradually approaching those of the arterial blood during the 30 min. of measurement. Here again it is noteworthy that the greater arterio-venous difference is first at the brain, but after 5 min. when much ether has been lost, this difference falls below those of other organs of the body with more sluggish blood supply; these can at this stage be regarded as contributing to maintaining the cerebral level of ether.

The quantities of ether in the brain during anaesthesia in experimental animals are also open to direct study (Henderson, 1930; Dybing & Dybing, 1945; 1948). In rats and rabbits at various stages of depression, the level in the brain was found to be rather higher than in the blood itself. This reflects the greater solubility of the substance in cerebral lipids than in aqueous fluids, which can be demonstrated in the separated tissue. After 5 min. inhalation when the blood level of ether was 0·77 mg./g., that of the brain was 1·08 and of the leg muscle 0·46. After 25 min. values were blood, 1·3, brain, 1·4 and muscle 0·9 mg./g., indicating more uniform distribution. The distribution of ether in different parts of the brain has been examined and approximate uniformity found.

Distribution of chloroform between the blood and brain *in vivo* has also been found to be slightly in favour of the brain (see Henderson, 1930). Blood levels of chloroform at the various levels of surgical anaesthesia have recently been re-examined (Morris, Frederickson & Orthy, 1951). Mean levels at the first and fourth planes were 7·5 and 14 mg./100 ml. in the general venous blood of patients. Dogs appeared to require three times these levels for a comparable degree of depression.

Action at the brain

Both Flourens and Snow carefully and experimentally differentiated between the effects of ether or chloroform, and those of anoxia or asphyxia with which analogies had been drawn by other workers: "In ordinary asphyxia the nervous system becomes paralysed through the action of . . . blood deprived of oxygen; during etherization the nervous system becomes paralysed primarily through the direct action upon it of this singular agent. . . ." Snow's (1847) experiments with mice also showed that they were anaesthetized as readily with ether in oxygen as with ether in air. However, effects on bodily oxidation could