THE GROUP PHARMACOLOGY OF ANAESTHETIC AGENTS

I: THE ABSORPTION—ELIMINATION OF INHALED DRUGS

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PROBABLY no other drugs lend themselves so well to pharmacological considerations on a group basis as do the inhalation anaesthetics. Before, however, the details of their actions are discussed it is necessary to consider the processes which make it possible for them to produce their effects. First they must be transferred by a process of mechanical mixing from the atmosphere in which they are presented, into the patient's alveolar air. Then they find their way by diffusion at a speed governed by physico-chemical considerations across the alveolar membrane into the blood circulating through the pulmonary capillaries. They are carried thence in the first instance mainly to the brain, where they exert their specific action, but ultimately they find their way into all the tissues of the body in greater or lesser quantity. Finally, when the administration of the anaesthetic is stopped, the inhaled drug is eliminated by a reversal of all these processes.

THE ENTRY INTO THE LUNGS

The first process in the absorption of a volatile anaesthetic into the body is its entry into the lung alveoli. This is essentially a mechanical procedure in which there occurs mixing of a known volume of air in the chest with an atmosphere of known concentration. It is brought about by a reciprocating flow of gases. The variables involved are the tidal air, the dead space air, and the capacity of the chest, and it is a simple matter to calculate how long is required to attain concentrations approximating to equilibrium. The mathematical statement of what happens is a geometric progression, i.e. an algebraic expression of a situation in which there is added to the gas in the lungs at each breath an amount of anaesthetic which is a constant fraction of its predecessor. This fraction is determined essentially by the ratio of the effective ventilation at each breath to the functional residual capacity of the lungs.

Neither the physical constants of the anaesthetic agent nor its concentration appear in the expression and the times required to attain concentrations in the lung of 90, 95, and 99 per cent of equilibrium are, in fact independent of these. In other words, if one excludes consideration of the gas which passes from the lung across the alveolar membrane, the time required for this phase of the induction of anaesthesia can be regarded as constant irrespective of the agent used. It is, for all practical purposes, complete in those with healthy lungs in about two minutes. Where disease interferes with mixing of the entering gases this part of induction may be prolonged to seven minutes but it is never any longer (Comroe et al., 1955). The duration can be sharply reduced by hyperventilation and prolonged by respiratory depression, but because it is so short relative to the duration of the next stage, the administration of carbon dioxide solely for this purpose is barely worth while except when agents irritant to the tracheo-bronchial tree are being given.

THE ENTRY OF ANAESTHETIC DRUGS INTO THE BLOOD STREAM

The essential factors controlling the entry of anaesthetics into the blood stream, are twofold. First, they must cross the alveolar membrane which from the physicochemical point of view can be regarded as a watery solution of protein. Secondly, they must enter into solution in the blood stream. The factors governing the first process are the partial pressure of the anaesthetic drug in the alveolar gases, and the solubility of its vapour in water, the factors influencing
the second process are its solubility in blood and again the partial pressure of its vapour. The rate of diffusion of gases and vapours in any situation is inversely proportional to the square root of their vapour densities. It can, however, readily be calculated that the amount of variation introduced by this factor into the absorption of anaesthetic agents is small in comparison with the other variables involved and for practical purposes it can largely be neglected.

For the consideration of their absorption across the alveolar membrane, anaesthetic agents have been divided by Harris (1951) into three classes. The first group includes substances like diethyl and divinyl ether which have a high solubility in water and in blood. They pass rapidly across the alveolar membrane. Indeed, they pass into the blood at a rate which is in excess of the speed at which comparable amounts of the vapour are taken in in the inspired air. There is thus a tendency to the development of a deficit between the partial pressure of the ether in the inhaled mixture and that in the alveoli (fig. 1). Further, because the solubility of ether vapour in blood is very high the tension rises slowly (fig. 2). In consequence of these two factors the entry of ether into the blood during the induction of anaesthesia is always very slow. These effects have been amply demonstrated by Haggard (1924) in his classical studies of the rise in the concentration of ether in the arterial blood of the anaesthetized dog. He then found that for two hours or more after beginning the inhalation of an ether-air mixture of fixed strength there was a steadily increasing concentration of the drug in the blood stream. Indeed, Henderson and Haggard (quoted by Robbins, 1935) found that only 50 per cent saturation of the body tissues was attained after this interval.

The second group of anaesthetics is exemplified by nitrous oxide and ethylene. These agents have a moderate solubility in water and moderate solubility in blood. They therefore pass across the alveolar membrane at a slower rate than ether; but their water solubility is such that they can cross in quantity sufficient to ensure early equilibrium between the tension of the anaesthetic in the blood leaving the lungs and its partial pressure in the alveolar air (fig. 3). Further, because the actual amount of anaesthetic taken up by the circulating blood is considerably less than that which finds its way into the lungs at a single breath, there is little tendency to the development of a deficit in the lungs as compared with the concentration in the inspired mixture.

There is experimental support for these views. Thus Gray (1954) in a study of the nitrous oxide content of the blood in patients anaesthetized for the operation of the abdomen found that five minutes after the beginning of the inhalation of an ether-air mixture of fixed strength the concentration of ether in the pulmonary arterial blood of the patient was between 0·1 and 1·0 per cent. This, however, did not remain at that concentrated but fell during the first two minutes of the inhalation of the mixture and then rose more slowly (fig. 2). During this period the concentration of ether in the blood of the patient is seen to be correlated with the tension of the drug in the inspired air (fig. 3). The latter factor is seen to have a marked influence on the concentration of ether in the blood of the patient (fig. 4) and this is attributable to the fact that the tension of the drug in the inspired air is inversely proportional to the square root of the amount of oxygen present (fig. 5).
with this agent was able to show that there was little more than five minutes delay in the development of equilibrium between the inhaled gases and their concentration in the blood. These figures contrast sharply with the two hours or more required to attain equilibrium with ether during the experiments of Haggard (1924). The picture for ethylene is not so clear cut, but Nicloux and Yovanovitch (1925) showed that the blood concentration of ethylene in dogs did not increase seriously after twenty minutes' inhalation of the gas (fig. 2).

The last group of inhalation anaesthetics are those which have low water solubility and a low blood solubility. The classic example is chloroform, but the same properties are shared by trichlorethylene, and, to a lesser extent, by cyclopropane. In the case of these agents, the inhaled anaesthetic finds great difficulty in escaping from the alveoli into the blood. The blood tension tends to remain, therefore, considerably below the partial pressure of the drug in the alveoli (fig. 4). There is no rapid loss of inhaled anaesthetic and the alveolar mixture very soon attains equilibrium with the inhaled gases. On the other hand, the barrier opposed by the alveolar membrane to the passage of these agents slows their entry into the blood and equilibrium is attained only a little more quickly than with ether (fig. 2).

Robbins (1935) studied the absorption of anaesthetic drugs on a different basis which neglected the influence of the film of watery solution of protein which comprises the alveolar membrane. He determined the solubility of the agents in blood in vitro, and, expressing this in terms of milligrammes per 100 ml, he related it to the anaesthetic content of the inhaled mixture in the same units. He called this the "distribution ratio". As would be expected, the findings were somewhat at variance with those of other workers,
but they are none the less interesting to refer to, particularly as the actual concentrations of ether in the blood of animals seem to correspond more closely with those found in clinical anaesthesia than do those of many other workers. On the other hand, the distribution ratio he obtained for ether in vivo was 1:10, while that in vitro was almost 1:14. It is, therefore, apparent that full equilibrium was not attained in the animals to whom he gave this agent. The essential significance of his results with cyclopropane is, however, not quite so clear (Robbins, 1936).

PRACTICAL APPLICATIONS

These theoretical considerations concerning the absorption of inhaled drugs have a practical application in clinical anaesthesia. Thus during the induction of ether anaesthesia the essential problem is to obtain the entry of large quantities of ether rapidly into the lungs whence it will find its way without difficulty into the blood stream. This can be accomplished, either by hyperventilation with carbon dioxide, or by giving the patient an anaesthetic mixture to inhale containing an amount of ether considerably in excess of that which, at equilibrium, would produce an anaesthetic concentration of the drug in the blood stream. The latter technique has been employed for many years. Its quantitative aspects were studied in neurosurgical cases by Boothby (1914), who, using the Connell "anesthesiometer," gave his patients 13 per cent ether to inhale for the first twenty minutes of the procedure, and then maintained anaesthesia thereafter with something like half this amount; but even this, as Robbins (1935) points out, still represents something like twice the true equilibrium concentration in the inspired air even with a distribution coefficient of 1:10.

Practising anaesthetists have long been aware of a need steadily to reduce the percentage concentration of lipoid soluble anaesthetic agents given to patients as the administration proceeds. Indeed this fact was given the title of the "law of diminishing resistance" by Gill (1906). During ether anaesthesia the apparently diminishing resistance of the patient is the result of two factors. First, it indicates the gradual disappearance of the deficit between the tension of the drug in the blood and its partial pressure in the inhaled mixture. Secondly, it reflects the gradually increasing saturation of the tissues with ether, with the result that the administration of the same amount of the drug now produces a much greater rise in blood concentration. It is common knowledge that this law is not applicable to patients under nitrous oxide. This is yet another pointer to the fact that equilibrium between the inhaled gases and the blood is rapidly attained when this agent is used.

The law of diminishing resistance is applicable to anaesthesia with chloroform, trichlor-
ethylene and cyclopropane, but for a different reason. Here the cause of the apparent diminution in resistance to anaesthesia is the slowly rising blood concentration of the drug. Raising the initial alveolar partial pressure of these drugs will tend to hasten the attaining of anaesthetic concentrations in the blood stream; but these high concentrations can relatively quickly become dangerous and overdose phenomena appear. Chloroform and cyclopropane very readily produce respiratory arrest if their administration is pushed. In the case of trichlorethylene, however, the increasing tachypnoea reduces the effective ventilation of the lungs, and the patient is thus preserved from the worst effects of too high a concentration of the drug, though at the cost of some hypoxia.

THE DISTRIBUTION OF ABSORBED ANAESTHETIC DRUGS

After their absorption into the blood stream anaesthetic drugs are distributed to the tissues of the body. The rate of uptake by any individual structure depends on its blood supply and the solubility of the anaesthetic drug in it. Tissues in which the agent is relatively insoluble achieve equilibrium with the blood concentration fairly quickly, because the uptake of a small amount leads to a large increase in the tension of the drug. Tissues in which the drug is very soluble, with the exception of those with a profuse blood supply, take a long period of exposure to reach equilibrium. For example, the subcutaneous fat, which has a high avidity for anaesthetic drugs and a poor blood supply, seems virtually never to be fully saturated with lipoid soluble agents. Even the brain which has an exceedingly good blood supply requires at least three-quarters of an hour before all the lipoid in its structure becomes virtually saturated.

Apart from some very early studies made about the turn of the century with inaccurate methods, there are comparatively few quantitative investigations of the uptake of anaesthetic drugs by the tissues. There is also a fallacy in this connection which has arisen from an oversimplification. Haggard (1924) stated that the venous blood concentration of an experimental animal exposed to an ether vapour of fixed strength, was a measure of the total amount which the animal had taken up. It was, however, some time before it was appreciated that while this statement is approximately true of the animal as a whole, it took no account of the distribution of the absorbed drugs in the individual tissues of the body.

The details of this aspect of the problem were studied by Dybing and Dybing (1945) in rats. They showed that the brain took up anaesthetic drugs relatively very rapidly; indeed because of the high solubility of ether in the lipoid of the brain, the concentration of this agent, though not its tension, was higher than that in the arterial blood. In the less well vascularized muscles, the rate of uptake was found to be slower, and no doubt the amount of ether in the subcutaneous fat must have been even less.

Direct studies of the uptake of anaesthetic drugs by the tissues were also made by Seevers and his colleagues (1935). They created pockets of air in the subcutaneous tissues and in the peritoneal cavities of experimental animals. They determined the rate at which ethylene and cyclopropane found their way into these pockets, and showed that the passage of cyclopropane inwards was more rapid than was that of ethylene. They ascribe this difference to a slow entry of ethylene into the blood from the lungs, an explanation which is rather surprising in view of the relatively good water solubility and moderate blood solubility of the gas. There are, however, so many factors involved in studies of this kind that it is very difficult fully to reconcile all that is known about the uptake of anaesthetic agents with the various theoretical considerations which seem to govern them. It is, however, interesting that the passage of nitrous oxide into air-containing cavities in the human subject has recently been reported during anaesthesia in tuberculous patients with a pneumothorax or pneumoperitoneum (Hunter, 1955).

THE ARTERIOVENOUS DIFFERENCE

The reflection of the passage of any substance from the blood into the tissues is an arteriovenous difference in its concentration. Thus the normal individual metabolizing glucose has a higher blood sugar level in his arterial than in
his venous blood. A diabetic patient on the other hand, who is unable to metabolize glucose, shows no such difference. A patient in whom ether is passing from the blood into the tissues shows a similar difference in concentration which diminishes progressively to the point of complete saturation. The capacity of the tissues for absorbing ether is so great that it requires many hours administration before the arteriovenous difference disappears. It is also interesting that the arteriovenous difference in the vessels supplying the brain becomes smaller more rapidly than does the corresponding difference in ether concentration in the mixed venous blood. This once again reflects the more rapid uptake of anaesthetics by the brain because of its better blood supply.

The arteriovenous difference in concentration has also been worked out in some detail by Robbins (1936) for cyclopropane, and he has found that with this agent it is gone after thirty-five to forty-five minutes administration to experimental animals. Presumably the interpretation of this rapid absorption lies in the relatively smaller solubility of cyclopropane in the tissues than that of ether.

RECOVERY FROM ANAESTHESIA

The laws governing the elimination of anaesthetic agents after their administration are exactly similar to those governing their uptake. The only part of this process which is of interest is the elimination of the anaesthetic substances from the tissues. For within the first few minutes after the withdrawal of any agent its blood concentration and its concentration in the pulmonary alveoli fall to relatively low levels. The elimination of anaesthetic drugs from the tissues is a much slower matter. It has been studied in detail for chloroform by Buckmaster and Gardner (1907), by Haggard for ether (1924), by Robbins (1935) for cyclopropane. With all these agents the process is, as would be expected, exponential in its rate, occurring more rapidly to begin with and tailing off subsequently. The essential problem is the elimination of the drug which has reached the tissues, and once again the governing factors are the solubility of the drug in the blood stream and the effectiveness of the blood supply to the various organs. There is one important difference between absorption and elimination. During absorption the drug finds its way to the brain more quickly than it does to other organs, and the onset of unconsciousness is relatively rapid. During recovery, on the other hand, the tension of the anaesthetic in the brain must of necessity remain always just a little higher than the concentration of the general venous blood (fig. 5). Therefore, as long as the less vascular tissues are pouring anaesthetic into the blood stream, it is impossible for a complete recovery of the central

![Diagram of elimination process](https://academic.oup.com/bja/article-abstract/28/6/244/261968)
nervous system to occur, even though its blood supply is such that, were it isolated from the rest of the body, all the anaesthetic could be removed from it in a comparatively short time.

Because a high partial pressure of nitrous oxide is required to produce anaesthesia, and because its solubility in the tissues is low, this agent is much more rapidly and completely eliminated on stopping its administration. There is, therefore, not the same tendency to prolongation of the recovery period with this agent. Its rapid elimination has, however, one disadvantage, Fink and others (1954) have shown that as much as twenty-five litres of the gas may be eliminated from the body in the first ten minutes of the recovery period. By its bulk this may displace oxygen from the alveoli and give rise to temporary hypoxia which they think might be severe enough to precipitate the collapse of a critically ill patient.

REFERENCES

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