THE PRODUCTION OF UNCONSCIOUSNESS

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Why the body should become unconscious as a result of drugs has led to many theories about the action of anaesthetic agents and narcotics on the brain. Over 100 years ago von Bibra and Harless (1847) established a correlation between anaesthetic action and the relative solubilities of certain substances in the lipoid and non-lipoid constituents of the brain cell. This theme was elaborated by Meyer (1901) and Overton (1901) independently, who both showed that there was a connexion between anaesthetic activity and the distribution coefficient of certain drugs in a lipoid water system. At about the same time Lillie (1916) demonstrated that anaesthetic action was related to viscosity and surface tension, and later Gellhorn and Weidling (1925) described an alteration in the permeability of the plasma membrane of the cell under anaesthesia. All these theories indicated how the anaesthetic agent gained access to the cells, but they did not afford any explanation of the drug's action and it was not until 1932 that a reasonable theory of anaesthetic action was propounded. By measuring changes in oxygen consumption of isolated slices of brain tissue, Quastel and Wheatley (1932) showed that brain tissue respiration was depressed by nearly all anaesthetic drugs. Furthermore, this effect was rapid and reversible and the sensitivity of the brain was in marked contrast to that of other organs. The suggestion was put forward that all narcotics achieve their action by interfering with some part of the tissue enzyme chain responsible for the oxidation of glucose, in short a state of controlled histotoxic anoxia. Although this theory was acceptable on general principles, there was no direct evidence to show that anaesthetic agents had a specific action on any particular enzyme, and the antagonists to the theory pointed out that the concentration of drugs necessary to depress cellular respiration *in vitro* was many times greater than that which was necessary to achieve anaesthesia *in vivo*. Moreover, depression of oxygen utilization was not a unique characteristic of anaesthetic agents and many other drugs of variable pharmacological action, having no anaesthetic properties, have been

shown to depress oxygen uptake. McElroy in 1947, however, postulated a theory which overcame most of these objections while retaining the basic principles and this theory is the most acceptable today (Butler, 1950). He suggested that the central nervous system has two parallel systems for metabolism. The first, or basal, system keeps the cell alive and is dependent upon the breakdown of carbohydrate, which in turn depends upon the presence of tissue enzyme activity. The second, or energy, system is responsible for the production and breakdown of adenosinetriphosphate (ATP), high energy phosphate which enables the cell to function and emit energy. ATP is known to be the basic source of utilizable energy inside the cell and McElroy concluded that anaesthetic agents act at the site of ATP synthesis or breakdown, so inhibiting energy production and resulting in unconsciousness. The amount of ATP in the cell is minute and so the rate of production and breakdown must be rapid if the cell is to produce energy continuously. With such a rapid turnover, it follows that the change from the conscious to the unconscious state is extremely critical, immeasurable in fact with present day biochemical techniques. If the amount of narcotic is great the basal system is also affected and tissue respiration becomes measurably depressed.

The practical production of unconsciousness has undergone many changes since the early days. Originally, the depth of anaesthesia considered sufficient for all surgical procedures was that at which the patient failed to move on the incision. As abdominal surgery advanced, however, such light anaesthesia resulted in many troublesome reflexes and shock became the limiting factor. Crile (1899) thought that surgical shock was due to noxious stimuli reaching the brain from the operation site via the somatic nerves and he evolved a technique consisting of light general anaesthesia supplemented by infiltration of the operative area with a local anaesthetic solution, or by means of spinal analgesia. With either method the surgical time was limited to the duration of action of the local anaesthetic agent. Another school favoured

the use of very deep aether or chloroform to prevent shock, but the dosages of drugs used were so large that they exerted a toxic effect and operating time was again limited. Such methods remained in vogue for many years and there were no major changes in anaesthetic techniques until the introduction of the intravenous barbiturates and cyclopropane in the 'thirties.' These agents induced anaesthesia rapidly and their action was short, but by the administration of frequent small doses the depth of anaesthesia could be controlled easily and the tendency was to use lighter levels than previously. During the second world war blood transfusions began to be used extensively in the treatment of battle casualties and it was soon realized that fluid loss was a more important factor than anaesthesia in the production of shock. Accordingly, still lighter levels were employed, albeit at the expense of muscular relaxation. The advent of the curarizing drugs in 1946 provided a solution to the problem. At first these compounds were used merely to supplement relaxation; later better operating conditions were obtained when the curarizing drugs were used to provide all the relaxation and very light anaesthesia with nitrous oxide or the barbiturates to render the patient amnesic. At the same time controlled or assisted respiration became necessary because the large doses of relaxants caused partial or complete respiratory paralysis. This striving for very light anaesthesia re-introduced some of the problems that occurred in the 19th century. For example, hiccough, which was hardly ever seen with deep aether, was now a troublesome complication, so although surgery could be more extensive, operating conditions were not necessarily ideal. Supplementary drugs were therefore added to the anaesthesia with the idea of subduing autonomic activity.

Modern techniques aim at dividing anaesthesia into its component parts (Gray, 1954). Firstly small amounts of hypnotic agents are used to produce light unconsciousness and amnesia, then other drugs to subdue autonomic activity, either by their analgesic action or by a specific inhibition of the autonomic systems, and thirdly satisfactory operating conditions are obtained with relaxants. If desired, control of blood pressure and haemorrhage can be achieved either by total sympathetic blockage with spinal analgesia or by chemical autonomic block with drugs such as the methonium compounds.

Few new anaesthetic drugs have been introduced in recent years but modern methods have altered the way in which the standard agents are administered. Nitrous oxide, which in former days was used more as a vehicle for carrying the volatile anaesthetic agents, is now employed to maintain a

light unconscious state. Aether is rarely chosen as the sole agent except in paediatric practice, and even as a supplement to nitrous oxide is rapidly losing favour because of the increased use of diathermy for most surgery. For the same reason cyclopropane is less popular than formerly although still favoured in certain special units. As well as being explosive, the increased bleeding and cardiac irregularities produced by this agent have all contributed to its diminished employment. Of the non-inflammable agents, trichlorethylene is commonly used. Although relatively non-volatile, trilene is markedly analgesic at low concentrations and with nitrous oxide will produce satisfactory anaesthesia for most operations. The other non-explosive agent, chloroform, is now used only occasionally because it is considered dangerous from a medical-legal point of view. However, this drug is extremely potent, producing ideal operating conditions in skilled hands, and still has a place in anaesthesia, especially for some E.N.T. surgery where diathermy and deep anaesthesia are necessary. The intravenous barbiturates, notably thiopentone, are the most popular of all the agents used to produce unconsciousness. They are more hypnotic than analgesic and so are ideal for induction, but they can also be given intermittently throughout the operation to supplement nitrous oxide.

Among the newer drugs, pethidine is now firmly established as the drug of choice for analgesia. It is given intermittently and has the advantage of lasting longer than the barbiturates and, at the same time, has marked antispasmodic properties so less disturbing reflexes are likely to occur. Recently the antihistamines have been added to the anaesthetists' armamentarium. All these compounds are hypnotic when given in large doses and are thought by some to have autonomic ganglion blocking properties as well. Promethazine ('Phenergan') is the most widely used, either as a premedication or in divided doses during anaesthesia. Chlorpromazine ('Largactil') will produce a state of unconsciousness unaided, but is usually employed to enhance the action of other agents.

There are certain techniques for improving operating conditions which themselves modify the amount of anaesthetic agents needed to produce a given depth of unconsciousness. When controlled hypotension is employed the dosage of drugs is reduced considerably and if the pressure is raised the anaesthesia lightens suggesting that with these methods there is a diminution in cerebral blood flow to levels at which part of the unconsciousness is due to cerebral ischaemia. Controlled respiration is another technique which alters dosage. This is performed vigorously the over-ventilation

produces a respiratory alkalosis which enhances the action of anaesthetic agents; conversely, large doses are needed in the presence of a respiratory acidosis. The reason why anaesthetic agents are potentiated by a rise in blood pH is not understood, possibly they are broken down more slowly under alkalotic conditions. Alternatively, changes in acid-base balance may alter the susceptibility of the brain to narcotic agents. Finally, the dosage of all anaesthetic agents varies with body temperature. In hypothermia, where there is a fall in oxygen consumption due to the decreased rate of metabolism, light nitrous oxide oxygen is sufficient to keep the patient unconscious. Not only is deep anaesthesia unnecessary, but it is actually harmful because drugs are not detoxicated at low temperature and so exert their effect for too long a period.

By using a combination of drugs to achieve unconsciousness, modern anaesthesia is less toxic and more easily controlled than that of 50 years ago. However, the splitting-up of anaesthesia into different components has resulted in the use of a multiplicity of drugs and there is a real danger of

'balanced anaesthesia' becoming 'polypharmacy.' The tendency to use a number of different drugs for their own individual pharmacological action ignores the possible accumulation of side-effects. Also the pharmacological effects of a particular drug in an animal are not necessarily the same in man. The state of anaesthesia is still not properly understood and possibly in the future there will be less emphasis on pharmacology and more on the physiology of unconsciousness.

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