THEORIES OF ANAESTHETIC ACTION

BY

J. H. BURN AND H. G. EPSTEIN

(From the Department of Pharmacology and the Nuffield Department of Anaesthetics, Oxford)

This vast subject has been studied by so many that it is impossible to do more than indicate briefly a few of the most important observations and the theories based upon them. But it is always safe to begin with Claude Bernard (1875), who defined narcosis as a depression of the activity of lower forms of life which disappeared when the substance causing the depression was removed; he thus distinguished a narcotic from a substance producing an irreversible change. The depression might be a depression of motility, a loss of irritability, a cessation of mitosis, or a slowing of metabolic processes. Anaesthesia is a term first proposed by Oliver Wendell Holmes in a letter to Morton in 1846; it is used when narcotics are given to a more highly developed organism such as man. The essential feature remains that the depression, the loss of consciousness, and other effects must be reversible.

The stages of anaesthesia are marks of a progressive depression beginning in the cortex and proceeding lower. The cortex itself is affected at certain points more than at others, for the sensory area is depressed when the motor cortex is still active; when finally the depression has travelled to the spinal cord there is muscular relaxation. The fortunate exception to this progressive paralysis is the medulla, in which the respiratory and vasomotor centres still function when the musculature is relaxed, so far as most anaesthetics are concerned. But this is not true of all. If attempts are made to obtain muscular relaxation with nitrous oxide the respiratory centre fails owing to oxygen lack first. With cyclopropane, again, the margin between muscular relaxation and respiratory failure is narrow. The differences in the sensitiveness of various parts of the brain are, however, small compared with the difference between the sensitiveness of the brain and that of other tissues.

Sensitivity of the Brain to Anaesthetics

During the time taken by operations, anaesthetics accumulate in the brain more than in other tissues such as muscle, and the greater sensitiveness of the brain is thus accompanied by a greater affinity for anaesthetics. It was at one time thought that the accumulation of an anaesthetic in the brain was due to the greater blood supply of that organ; after long-continued anaesthesia, however, some accumulation is observed at a time when the differences due to blood supply must have disappeared (Nicloux and Yovanovitch, 1924). The greater affinity of brain tissue for anaesthetics may have its explanation in the tissue composition. So long ago as 1847 von Bibra and Harless based their theory of narcosis on the high lipoid content of the brain, which they suggested was dissolved out of that organ by the anaesthetic and deposited in the liver! Fifty years later the well-known theory of Meyer (1899) and Overton (1899, 1901) was also based on the high lipoid content of the brain.

A third difference between the brain and other tissues is its great susceptibility to the effects of oxygen lack; there are indeed very great differences between brain and other nervous tissue. Thus the small pyramidal cell area of the cerebrum and the Purkinje cell area of the cerebellum, when deprived of oxygen, die in about 10 minutes. On the other hand, the spinal cord survives for 50 minutes and the sympathetic ganglia for 200 minutes. An explanation for the great sensitiveness of the brain to anaesthetics would therefore be provided if it could be shown that anaesthetics interfere with processes of oxidation, as some have suggested. Such evidence would also account for the steps in which the different portions of the central nervous system are influenced by the narcotic agent. Owing to the differences in the sensitiveness of the different parts of the central nervous system, workers since Claude Bernard have in the main studied the action of narcotics in lower organisms. Even among these Meyer and Overton found that a small increase in the extent ot organization and functional differentiation was accompanied by an increased sensitiveness to narcotics.

Primary Action of Narcotics

Two very obvious features of narcotics are the great variation in their chemical structure and that most of them enter and leave the tissues unchanged; these facts suggest that the primary action of narcotics cannot be chemical, but must rather be due to the production of physical changes such as in solubility, adsorption, etc. Among the many changes which narcotics have been said to produce, those about which there is a balance of agreement are a decrease in the permeability of the cell to water and water-soluble substances, and also a diminution in the state of hydration. Lucké (1932), for example, observed that in the unfertilized egg of the sea-urchin water exchange through the surface is reduced by narcotics. Anselmino (1928), too, has confirmed earlier observations that narcotics delay the haemolysis of red cells by hypotonic solutions, and that the length of the delay is in linear proportion to the concentration of the narcotic. Gerstner (1940) has shown that the permeability of the skin covering the frog's abdomen for ions is diminished in the presence of various alcohols. Turning to evidence for a diminution in the state of hydration, we find that Lapicque (1930) observed in nervous tissue that, in a concentration which reduces conduction, narcotics cause dehydration. Kochmann (1923a) observed a similar effect in frog muscle immersed in 0.75% saline: when the narcotic was applied the weight of the muscle diminished; when the narcotic was removed the weight returned to its former value.

TABLE I.—(*Kochmann*, 1923a)

	Chloroform	Chloral Hydrate	Ether	Ethyl Alcohol
Molar concentration	0·004	0·006	0·19	1·0
Weight loss % ..	2	10	2·5	5·0

The figures in Table I show the wide variation between the concentrations of different narcotics necessary to produce a certain degree of anaesthesia. They also show that, in narcosis, dehydration occurs and the percentage loss of weight in the tissue is not correlated with the concentration of the narcotic in the surrounding fluid; the weight loss therefore cannot be due to osmosis, which is in any case unlikely, since the narcotic enters the cell. Actual water loss is observed when medium concentrations of chloral hydrate act on fibrin flakes (Jurisič, 1937). Heilbrunn (1920) observed that the cytoplasm of sea-urchin eggs becomes more fluid under the influence of narcotics, indicating that water is set free.

Narcotics not only produce dehydration in living cells but exert effects on colloidal solutions which can also be interpreted as dehydration. Labes (1921) observed that alcohols affected albumin solutions so that they were more easily precipitated by other agents, and the effect increased with the number of carbon atoms in the alcohol used. Now since the stability of hydrophilic (water-attracting) protein colloids depends on the degree of hydration, it seems very likely that the effect of the alcohols was to produce dehydration. It is worth noting that Claude Bernard, and later Bancroft and Richter (1931), have based their "coagulation" theory of narcosis on the reduction of the stability of colloids and their precipitation. Unfortunately for their theory there are substances which reduce this stability but have no narcotic action; the experimental evidence supporting this theory is still meagre.

In all these experiments it is important to note that the changes were reversible provided that the concentrations of the narcotics used were not excessive. Moreover, the effect of any one narcotic was in linear relation to its concentration in all experiments in which different concentrations were studied.

While narcotics produce narcosis when applied in most concentrations, in very low concentrations they appear to cause excitation. Even in anaesthesia of human subjects there may be an element of actual excitation, though the usual explanation which is given of the stage of excitement is that it is due to the release of lower centres from the control of higher centres, the real effect of the anaesthetic being to depress these higher centres. If narcosis is actually due to diminished permeability, and if the early stage of excitation is considered to be the opposite, it should be accompanied by increased

permeability. Gerstner found such an increase in the frog's skin, and then, after the application of higher concentrations, the permeability was diminished. Lapicque also observed that with low concentrations of narcotics there was an increase in nerve conduction and also an increase in hydration. Beecher (1938) quotes several observations showing that very low concentrations of narcotics always increase the normal functions of small organisms. These effects of low concentrations, however, have not been very extensively studied, and relatively little is known about them. Nevertheless, since they occur, any theory of narcosis which is to be satisfactory must explain them.

Before discussing a theory which considers dehydration as the primary effect of a narcotic, it should be pointed out that the process is not merely a withdrawal of water such as occurs in osmosis. The withdrawal of water by osmosis causes no change in the force of attraction between a "hydrophilic" colloid and water, whereas the dehydration we are now considering involves a diminution of this attraction (Seelich, 1941). It is therefore evident that only certain kinds of water withdrawal will have a narcotic effect. A further point is that the dehydration and the decreased permeability due to narcotics are not independent. In experiments with artificial membranes it has been found that dehydration leads to diminished permeability (Gurewitsch, 1934).

The Dehydration Theory

Traube (1904, 1935) introduced a theory of narcosis which was later greatly extended by Lillie (1909) and Warburg (1920). This theory depended on the parallelism between the potency of a narcotic and the degree to which the narcotic reduced the "surface energy" of a water–air boundary.

The surface energy of pure water is measured by the work which must be done to enlarge the surface by 1 sq. cm. The molecules inside are held there by the attraction of other molecules, and in order to move molecules to the surface this attraction must be overcome. The surface energy of water is much greater than that of organic fluids like oil. Small amounts of certain substances dissolved in water (or other liquids) diminish its surface energy, and their activity is measured by the reduction in surface energy which a given concentration produces. Owing to the force of attraction which they exert being less than the force exerted by water molecules, these substances are less attracted to the interior, and therefore displace water from the surface. These substances are termed "surface-active." If an attempt is made to increase the surface the molecules of the substance will require less work to put them there, so that the surface energy is reduced. Accumulation of a substance in a surface, or adsorption, is inseparable from a reduction in surface energy. If we consider a water–oil boundary, the interface energy is less than that of a water–air boundary, because the oil molecules exert an attraction on water molecules in the interface which the air does not, and thereby reduce the pull from the bulk of the water. Certain substances which dissolve in oil lower this interface energy still further; they do this by a similar process to that just described for a water–air boundary, and they accumulate in the interface. When we come to an interface between protein colloids or lipoids and water, their attraction for water is usually so strong that the interface energy is very small. These colloids are said to be "strongly hydrated." If we add to such a system a third substance which would cause great reduction of surface energy at a water–air boundary it will have very little effect, because the surface energy is already so low. The slight reduction which might be caused by adding a "surface-active" substance would, however, lead to increase in hydration of the protein or lipoid.

If now we consider narcotics, some of which are strongly surface-active at a water–air boundary, we know from the experimental observations discussed that at medium concentrations they do not cause hydration, but on the contrary dehydration. This fact excludes any hypothesis of their action which involves adsorption on the cell membrane surface as the primary mechanism. Simple models of cell membranes can be made, however, in which surface-active narcotics cause dehydration and an increase in surface energy. The basis for these models is the idea that the lipoid content of a cell membrane is a mixture, some components being strongly surface-active or hydrophilic, and accumulating (that is to say, being adsorbed) on the surface. Other components, being the greater part of cell-membrane lipoids, are less hydrophilic. Seelich (1940) suggests that the narcotics dissolve in the lipoids of the cell membrane and thereby alter the distribution of the surface-active lipoids between the surface and the interior of the cell membrane; the surface-active lipoids come inside, and their place is taken on the surface by less hydrophilic lipoids. Dehydration therefore occurs, the interface energy rises, and permeability diminishes.

One of the models chosen by Seelich consists of a layer of liquid paraffin in contact with water. This system has an interface energy of 51. The surface-active lipoid component is represented by 0.05% ergosterol in the liquid paraffin. This reduces the water/paraffin interface energy to 4—a value of the same order as that of the interface energy between lipoid and water. When a strong surface-active narcotic, *n*-propyl alcohol, is added in a concentration of 0.3 mol/litre, the interface energy does not decrease, but rises from 4 to 8. We know that the narcotic effect of homologous alcohols rises with the number of carbon atoms in the chain, and when the above experiment is done with butyl alcohol the same rise of interface energy is obtained with only 0.05 mol/litre. If so much ergosterol is put in the paraffin that some of it is undissolved and present as visible droplets, it can be observed that the addition of narcotics to the water results in the solution of these droplets in the paraffin. It is of further interest that for very low narcotic concentrations—e.g., 0.01 mol/litre propyl alcohol—a decrease of interface energy, indicating increased hydration and permeability, occurs in the model; this bears out what has been observed in actual cells.

Other Theories of Narcosis

We can now consider how far other theories of narcosis can be harmonized with this. Traube correlated narcotic activity with lowering of the surface energy of a water–air boundary; such a boundary constitutes a bad model for the cell membrane–plasma boundary, and, as already pointed out, lowering of surface energy is accompanied by hydration, not by the dehydration which actually occurs.

Warburg has extended Traube's rules to form a comprehensive theory. Like Traube, he assumes an accumulation of narcotics on the surface of cell membranes; this is supposed to lead to a displacement of enzymes from positions on the surface in which they catalyse oxidations; at the same time this adsorption of narcotics is supposed to "block the pores" of the membrane, leading to a decrease of permeability. Some of the evidence for this theory is that amino-acids, adsorbed on activated charcoal, are displaced when narcotics are added. It is unlikely that the water-repellent surface of charcoal is a good model for the water-attracting colloids of the cell membrane. Moreover, the arguments valid against Traube's theory apply here also.

The earlier theory of Meyer and Overton is really a rule and not a theory, since it does not explain narcotic action. It points out that there is a close relation between narcotic activity and the distribution coefficient of narcotics in a lipoid/water system. (If oil is in contact with water and a narcotic is added, the narcotic distributes itself in a fixed ratio between the oil and the water. This ratio is the distribution coefficient.) The coefficient rises as the narcotic increasingly prefers the oil. The son of Hans Horst Meyer—namely, K. H. Meyer (1937)—has recently re-examined the distribution coefficients and has used oleic alcohol instead of the classical olive oil to represent the lipoid phase. He compared the distribution coefficients with the concentrations of narcotics in water necessary to paralyse tadpoles. The figures he got are given in the first two columns of Table II, and it can be seen that the narcotizing concentration for tadpoles diminishes as the distribution coefficient rises. In the last column is given the concentration which would have been present in oleic alcohol in contact with water containing the narcotizing concentrations in the first column. The figures in the last column are very close together, and Meyer concludes that to obtain narcosis the same concentration of any narcotic in certain lipoids is required.

TABLE II

	Narcotic Conc. for Tadpoles (mol/litre H_2O)	Distribution Coefficient Oleic Alcohol–Water	Narcotic Conc. mol/litre of Lipoid Model
Ethyl alcohol	0·33	0·10	0·033
Propyl alcohol	0·11	0·35	0·038
n-butyl alcohol	0·03	0·65	0·020
Ether	0·024	2·10	0·050
Luminal	0·008	5·90	0·048
Chloroform	0·00008	325·00	0·026

The Meyer–Overton theory appears to fit easily into the framework of the dehydration theories of Kochmann (1923b) and Seelich (1940). A high distribution coefficient means that even when there is a low concentration of the narcotic in the water there is enough narcotic in the lipoid to alter the distribution of the surface-active lipoid components, with consequent dehydration and decreased permeability. Warburg's conception of the displacement of enzymes may also be useful, even if the adsorption of the narcotics on membrane surfaces is rejected. The surface-active lipoids which are displaced may indeed be enzymes, and their removal may be responsible for the diminished oxidation which is observed (Quastel and Wheatley, 1934). The decrease in permeability may hamper the transport of carbohydrate to the enzymes, and so reduce metabolism in another way. Since, too, the transmission of stimuli is accompanied by the passage of ions through the cell membrane, the reduction of permeability (Winterstein, 1926; Hoeber, 1926) will interfere with this transmission, and cells will become unresponsive.

In conclusion, certain modern electrical theories of narcosis should also be mentioned which are based on the idea that the transient state of negativity arising when a nerve is stimulated is interfered with by narcotics. It is thought that a narcotic first produces a state of negativity on the cell surface as does a normal stimulus; the subsequent paralysing effect is seen in the persistence of the negative state, which would have disappeared immediately after a normal stimulus. No further stimuli which normally cause a state of negativity to travel along a nerve can now be transmitted, since the cell membranes are maintained in maximum negativity by the action of the narcotic (Beutner, 1931). These theories infer the stages of excitement and paralysis to be of the same kind, while the experimental evidence discussed above seems to point to a difference between the two; moreover they do not attempt to provide evidence that the electrical state of the narcotized cell is correlated with the potency of narcotics in a homologous series. Until this has been done their value is uncertain.

REFERENCES

Anselmino, K. J. (1928). *Pflügers Arch.*, **220**, 633.
Bancroft, W. D., and Richter, G. H. (1931). *J. Phys. Chem.*, **35**, 215.
Beecher, H. K. (1938). *The Physiology of Anaesthesia*, p. 36, London.
Bernard, C. (1875). *Leçons sur les Anesthésiques et sur l'Asphyxie*, Paris.
Beutner, R. (1931). *J. Pharmacol.*, **42**, 258.
Bibra, E. von, and Harless, E. (1847). *Die Wirkung des Schwefeläthers in chemischer und physiologischer Beziehung*, Erlangen.
Gerstner, H. (1940). *Pflügers Arch.*, **244**, 68.
Goodman, L., and Gilman, A. (1941). *The Pharmacological Basis of Therapeutics*, p. 30. New York.
Gurewitsch, A. (1934). *Protoplasma*, **20**, 561.
Heilbrunn, L. V. (1920). *Biol. Bull. Wood's Hole*, **39**, 317.
Hoeber, R. (1926). *Physikalische Chemie der Zelle*, Leipzig.
Jurisič, P. J. (1937). *Kolloid Z.*, **78**, 95.
Kochmann, M. (1923a). *Biochem. Z.*, **136**, 49.
—— (1923b). Heffter's *Handbuch der experimentellen Pharmakologie*, **1**, 466. Berlin.
Labes, R. (1921). *Pflügers Arch.*, **186**, 98.
Lapicque, L. (1930). *Arch. int. Pharmacodyn.*, **38**, 209.
Lillie, R. S. (1909). *Amer. J. Physiol.*, **24**, 14.
Lucké, B. (1932). *Biol. Bull. Wood's Hole*, **60**, 72.
MacLeod, J. J. R. (1930). *Physiology and Biochemistry in Modern Medicine*, 6th ed., p. 170. St. Louis.
Meyer, H. H. (1899). *Arch. exper. Path. Pharmak.*, **42**, 109.
Meyer, K. H. (1937). *Trans. Faraday Soc.*, **33**, 1062.
Nicloux, M., and Yovanovitch, A. (1924). *C. R. Soc. Biol.*, Paris, **91**, 1285.
Overton, E. (1899). *Vjschr. naturf. Ges. Zürich*, **44**, 88.
—— (1901). *Studien über die Narkose*, Jena.
Quastel, J. H., and Wheatley, A. H. M. (1934). *Biochem. J.*, **28**, 1521.
Seelich, F. (1940). *Pflügers Arch.*, **243**, 283.
—— (1941). *Ergebn. Physiol. Biol. exp. Pharm.*, **44**, 446.
Traube, J. (1904). *Pflügers Arch.*, **105**, 541.
—— (1935). *Biochem. Z.*, **279**, 166.
Warburg, O. (1920). *Jber. ges. Physiol.*, **1**, 136.
Winterstein, H. (1926). *Die Narkose*, Berlin.

JOHN SNOW—ANAESTHETIST AND EPIDEMIOLOGIST

In the senior common room of a college mention of the name Poincaré would ring a bell, or rather it would ring bells. The modern historians would suppose the French Premier and President in question: the mathematicians that his cousin was intended. In medical circles the name Snow excites memories not of two men but of the different activities of one man. Probably in a mixed company more would remember Raymond Poincaré the statesman than Henri Poincaré the mathematician; certainly in a medical company more would recollect Snow as the English pioneer of scientific anaesthesia than as an epidemiologist. But Snow's classical papers on the epidemiology of cholera have been reprinted in America with an excellent introduction.[1]

John Snow (1813–58), the son of a Yorkshire farmer, was educated for general medical practice and, as an apprentice, had experience of the 1831–2 epidemic of cholera in Newcastle. He "walked" the Westminster Hospital in 1837–8, qualified in 1838, and graduated M.B.Lond. in 1843, M.D. 1844. His first paper, "Asphyxia and the Resuscitation of New-born Children," was published in 1841. In 1846 the first inhalations of ether in this country did not greatly impress surgeons. "The distrust arose," wrote Benjamin Ward Richardson, "from the manner in which the agent was administered." Snow remedied the mistakes and soon became known as an anaesthetist. He published a short treatise on ether anaesthesia in 1847. After the introduction into medical practice of chloroform by Simpson, Snow carried out a number of researches and satisfied himself of the practical advantages of the drug. He soon became one of the most successful and respected anaesthetists in London.

The cholera epidemic of 1848 perhaps recalled memories of his experience in general practice, and he published a brochure of 31 pages "On the Mode of Communication of Cholera" in 1849. The second edition (139 pages) published in 1854 is a classic of epidemiology. Snow's incrimination of a pump in Broad Street, Golden Square, is as dramatic as any detective story, but the statistical evidence by means of which he established a high correlation between the consumption of dirty water and mortality from cholera in South London is a model of research. Private enterprise and free competition in the sale of water had the result that in one and the same street families might buy water from different companies. Snow was supplied by the General Register Office with the names and addresses of persons dying of cholera in the epidemic of 1854; he and another medical man made a house-to-house visitation, and from the data the collection of which "was necessarily attended with a good deal of trouble," he was able to draw up an unanswerable case against dirty water. William Farr, who gave him every encouragement, was able to produce in the epidemic of 1866 equally cogent statistical evidence. Where Snow was in advance even of Farr and Simon was in his firm conviction that the ingestion of water polluted with a presumably living contagium was the *only* method of epidemic dissemination. Farr to some extent, and Simon to a greater extent, still hankered after that variant of miasmatic epidemiology which found a possible cause of epidemics in air contaminated by the products of putrefaction.

English science has owed much to amateurs, and it may be that Snow will be longer remembered by his researches in epidemiology—undertaken because the subject interested him—than by his professional work, valuable as that was.

[1] *Snow on Cholera . . . with an Introduction by Wade Hampton Frost.* New York: The Commonwealth Fund. 1936.

The Bristol Council for Rehabilitation was inaugurated on Oct. 4, 1945, at a meeting attended by members of the Bristol and District Divisional Hospitals Council, and representatives of the Ministries of Health, Labour and National Service, hospitals, medical institutions, and industry. Its constitution is modelled on that of the British Council for Rehabilitation, with which it is affiliated. A report of the first year's work has been issued from Royal London House, Queen Charlotte Street, Bristol, 1.