IV

THE CHEMISTRY OF NARCOSIS

NARCISSUS, in Greek mythology, was the son of the river god, Cephissus, and the nymph, Leiriope. He was distinguished for his great beauty, and it was prophesied he would enjoy a long life provided he never looked upon his own features. However, he drew upon himself the vengeance of the gods by rejecting the love of the nymph, Echo; and Nemesis caused him to see his features reflected from the waters of a fountain. He fell madly in love with his own image and soon pined away. The flower that now bears his name grew up on the spot where he died. The narcissus is as interesting medically as it is mythologically because if parts of the flower are taken internally they will cause a numbness, or loss of sensation; this state is known as narcosis, and any agent that will cause it is spoken of as a narcotic. Anaesthesia and anaesthetics are more modern words that express these ideas. The use of the narcissus, as well as many other plants, for the production of narcosis, has been known for a very long time.

The history of the development of anaesthesia is an interesting record of the progress of the human race to liberate itself from Nature's lavish gift of pain. Paleopathology supplies us with an abundance of evidence that broken bones, injuries, diseases, infections, surgical operations, wounds, in fact, anything that could contribute to the production of pain was well known from the beginning of mankind. It is interesting to look back over these thousands of years and

examine the attempts of mankind to alleviate the suffering associated with these conditions. We can distinguish two periods in the development of narcotics or anaesthetics: first, the Egyptian, or ancient forms, and second, the American, or modern type.

The anaesthesia of antiquity as employed by the Egyptian surgeons was fully described by Pliny. This celebrated naturalist stated that the stone of Memphis, when powdered and mixed with vinegar, would anaesthetize the region upon which it was applied to such an extent that a minor operation could be performed without pain. Dioscorides also refers to the same fact, and describes the stone of Memphis as being about the size of a talent and greasy to the touch. Modern writers have identified this marvelous stone of Memphis as calcium carbonate, or ordinary marble, and explain the anaesthetic effect as due to the action of the carbon dioxide which is produced when the substance is treated with dilute acids such as vinegar.

The use of such soporifics as opium, Indian hemp, and the mandrake was well known to the Egyptians, Greeks, and Romans at an early date. The mandrake, which is related to the potato family, has been known from remote antiquity; it is mentioned in the Bible that Rachel sought mandrakes of Leah (Genesis XXX 14-16). The mandrake has been the subject of many legends concerning the human shape of the root of the plant and of its frightful shrieks when uprooted. In early English and German folklore it was regarded as fatal to hear these terrible shrieks, so they gathered the plant by hitching a dog to it, being very careful to plug their own ears with pitch and to blow loudly upon a horn in order to drown the cries of the plant when it was pulled up. Shakespeare, more than once, alludes to this interesting plant, as when Banquo, in Macbeth, says: "Or have

we eaten of the insane root that takes the reason prisoner?" The notion that the plant shrieked when uprooted is alluded to in Romeo and Juliet,

> And shrieks like mandrakes' torn out of the earth,
> That living mortals hearing them run mad.

The mandrake, often growing like the lower limbs of man, was supposed to have other virtues, and was highly prized for love philtres.

The second period in the development of surgical anaesthesia took place in America and was initiated by an accident that occurred in 1839 at an "ether frolic" at Anderson, South Carolina. At that time ether was a well known substance, and it was also well known that when administered in small amounts it would cause intoxication. Ether frolics were very common, particularly among the medical students, and even "ether addicts" were known. At this particular ether frolic, however, several over-enthusiastic young men forced a colored boy to inhale a considerable amount of ether; the subject did not become intoxicated, but fell over unconscious. He remained in this state for an hour or more, showing no subsequent ill effects upon his recovery. The idea at once suggested itself that this condition would be valuable in surgery. Dr. C. W. Long, of Jefferson, Georgia, was informed of the experiments, and in 1842 he administered ether to James Venable and removed a tumor from the patient's neck. It is interesting to note that the bill for this exceptional operation is still preserved, and it shows that the ether with the operation cost two dollars. Several years later ether anaesthesia was rediscovered and was thoroughly tested at the Massachusetts General Hospital, and a few years after this came into general use all over the civilized world.

The development of our knowledge concerning anaes-

thesia has been rather slow; in spite of the antiquity of the subject there is still considerable mystery surrounding the mechanism of narcosis. Several theories have been proposed to explain how narcotics cause the loss of sensation in a tissue, but they are, in general, rather restricted.

One of the theories that was advanced to explain the effect of narcotics was the theory of Verworn. Verworn studied the oxygen metabolism of various tissues while they were under the influence of narcotics, and his work showed that during anaesthesia there was a decrease in oxygen consumption. The hypothesis was then advanced that this disturbance was the cause of anaesthesia. This theory is very often referred to as the "suffocation" or "asphyxiation" theory, but it should be pointed out that the asphyxiated state does not occur by excluding oxygen from the cell but arises through the inhibition of the oxidation process by the narcotic.

There are two rather serious objections that have been raised against this theory; the first is that the decrease in oxygen consumption does not, in every case, run parallel to the various stages of narcosis, and furthermore it varies from narcotic to narcotic. The second objection is more fundamental, if the decrease in oxygen consumption is the cause of anaesthesia then it should be impossible to anaesthetize an organism that does not normally use oxygen to maintain its life functions. This experiment was tried on the intestinal worm, Ascaris, which does not require oxygen, and it was found that this organism could be easily anaesthetized. As a matter of fact it is now known that the anaerobic forms of life can be narcotized with the same ease as the aerobic; this shows that the decrease in oxidation is not essential for the production of narcosis.

The Meyer and Overton theory of narcosis is based upon

the fact that narcotics are soluble in lipoids or fats, and that the strength of their action is related to the partition ratio as measured between fat and water. Meyer formulated the theory in the following way:

(a) All chemically indifferent substances which are solvents for fats and similar bodies, must exert a narcotic action upon living protoplasm, in so far as they can diffuse therein.

(b) The effect must manifest itself first, and most strongly, in those cells in whose chemical structures these fatty or lipoid substances predominate and presumably are the essential carriers of the cell function, namely, in the nerve cells.

(c) The relative efficiency of such narcotic agents must be dependent upon their mechanical affinity for lipoid substances, on the one hand, and for the remaining body constituents, i. e., principally water, on the other hand. It is dependent, therefore, upon the partition coefficient which determines their distribution in a mixture of water and lipoid substance.

There are a number of serious objections to this theory. Experiments indicate that when a nervous tissue takes up a drug it does not do so by simple solution but by colloidal adsorption. Furthermore, the distribution of the narcotic within the body does not run parallel to the lipoid content of the various tissues, thus the grey substance of the brain contains 8.5% lipoid and the white matter 16%, yet narcosis starts sooner in the grey matter and is stronger than in the white matter. It is well known that the distribution coefficient will vary with the temperature, and experiments have been made to see if there is any parallelism with the change in strength of the narcotic at various temperatures; the results indicate that there is no definite relationship between the partition coefficient and degree of narcosis. Op-

tically isomeric drugs offer a very interesting test of this theory. The optical antipodes have the same chemical structure and identical solubilities and distribution coefficients, consequently the Meyer and Overton theory would predict that they would be of equal physiological activity. However, actual experience shows that in numerous cases one isomer is many times more active than the other. The Meyer and Overton theory thus, is clearly not in agreement with the facts and consequently can no longer be seriously considered.

The theory of narcosis proposed by Traube is in many respects similar to that proposed by Meyer and Overton. The theory merely points out the parallelism between the depression of the surface tension of water by a narcotic and its strength as a narcotic. This theory has the same inherent weakness as the Meyer-Overton theory in that it only associates the physiological activity of a substance with some physical property and does not offer an adequate explanation of the mechanism by which the drug exerts its effect. Moreover, all narcotic substances do not necessarily depress the surface tension of water; magnesium sulfate behaves as a mild narcotic, yet causes an increase in surface tension. Chloroform has a negligible effect on surface tension, nevertheless it is a good narcotic. The same situation is true also of hydrocarbons and many of their halogen derivatives. One must conclude therefore, that Traube's relationship is not fundamental.

Narcosis, in its broader aspects, offers several problems that are entirely out of the scope of the theories mentioned above. For example, one can narcotize a tissue by heating or cooling it sufficiently; this would be quite unexpected on the basis of the theories already discussed. Furthermore, narcosis can be produced mechanically, as by a sharp blow,

by means of an electrical current, and finally by the mere injection of distilled water.

The only theory proposed up to the present time that has any possibility of covering the many phases of narcosis was suggested in 1860 by Binz and developed later by Claude Bernard into many of its logical conclusions. This theory postulates that narcosis is caused by the mild agglomeration of the protoplasm of the nerves or tissue, and furthermore, that upon removal of the narcotic the agglomerated material will break up and be redispersed to the normal state. If the material is so strongly coagulated that the redispersion will not take place, then death occurs, and the effect of the narcotic is spoken of as "toxic". Two objections have been raised against this theory, the first is that the narcotizing concentration is much lower than the agglomerating concentration, and secondly, if the agglomeration took place it would not be reversible; both objections are based upon medical philosophy and are not the results of experiments.

The most convincing manner in which this question can be investigated would be to examine the colloids of a living cell in its normal environment under the ultra-microscope and observe what takes place when the organism is exposed to a narcotic. This experiment was carried out with yeast cells; a young vigorous culture was exposed to chloroform and placed under the ultramicroscope. At first nothing happens, after about ten minutes the Brownian movement is noticed to be decreased, and a few minutes later small aggregates of the colloids are seen. The coagulation now goes much faster, and in a few minutes, a light, but very pronounced flocculation occurs. If the material is now washed free of the narcotic and again examined under the ultramicroscope it is observed that the larger agglomerates break up, and after a short time the colloidal material is dispersed

again to its original state. When the cells are treated with some toxic agent, as bichloride of mercury, the agglomeration is rapid and quite irreversible, thus illustrating the colloidal aspect of toxic action. The experimental facts, therefore, are in agreement with the theory.

It is a far fetched analogy between the narcosis of yeast cells and that of the higher organisms, and an analysis of the relation of coagulation to narcosis is more difficult in the higher forms of life, yet the evidence is clear cut, and indicates that coagulation and narcosis proceed hand in hand. The material in nerves that is undergoing the agglomeration is believed to be proteins. Now some of the colloid reactions of proteins are rather characteristic; thus if a protein sol is exposed to solutions of different hydrogen ion concentration there will be found to be a rather narrow band of concentrations in which it will precipitate. This region is called the "iso-electric" point of the protein. The iso-electric points of the protein of nerves and muscles have been measured and are fairly well known. Hence, it is not improbable that if nervous tissues were exposed to solutions of various hydrogen ion concentrations it would be found that regions which correspond to the iso-electric points of the proteins would also be regions of narcosis. This experiment was carried out by measuring quantitatively the irritability of a nerve when exposed to buffer solutions of different hydrogen ion concentrations. It was found that at the iso-electric points there were minima in the irritability curve which indicates that whenever coagulation of the protein occurs, there is a loss of irritability, or narcosis results.

The researches of Professor F. Marinesco, which involved the direct observation of the colloids of a living nerve cell under the ultramicroscope, also give direct evidence of the coagulating effect of narcotics. He showed that agents

such as alcohol and magnesium sulfate coagulated the material within the nerve cell. Even more interesting, from the colloidal point of view, was the observation of mechanical coagulation, which was brought about by gently tapping the material. He also studied the effect of water on the nerve cells and found that it produced coagulation; it will be remembered that anaesthesia can be produced by injection of water into the tissue. Thus the idea of Binz and Claude Bernard that narcotics bring about a coagulation of the colloids of the tissue is not a vague dream but an observed reality that includes cases peculiarly difficult to account for on any other theory.

The chain of evidence that shows the relationship between narcosis and coagulation is strengthened by studies of the viscosity of cell protoplasm. When a tissue or group of cells is centrifuged and periodically examined under a microscope, one can observe and measure within the protoplasm the rate of sedimentation of the visible particles, such as fat and pigment. If the material is treated with a narcotizing agent and examined by this method it will be found that the viscosity of the protoplasm has undergone a marked change. These changes that occur in the protoplasm clearly indicate that the colloids are undergoing a coagulation. The narcotic decreases the viscosity of the material within the cell during narcosis, higher concentrations of the drug will cause the viscosity to pass through a minimum value and then rise rapidly above normal. Both changes in the viscosity are different phases of the same thing, namely, coagulation. It is well known that bio-colloids are highly hydrated; such colloids have a layer of water around the micellae that is commonly called the water sheath. The water that constitutes this sheath is not free, but is bound to the surface of the particles. In the first phase of the

coagulation the narcotic is adsorbed upon the colloidal substrates and displaces the material that was previously adsorbed there. This increase in the amount of free, or unbound water will have the same effect on the viscosity of the sol as dilution, that is, a decrease. Also, according to Einstein's treatment of viscosity, the decreased volume of the particles will tend to lower the viscosity. As soon as the electrical charge on the micellae is lowered to such a value that flocculation occurs, the particles come together to form agglomerates, or chain structures, as in jellies, thus bringing about the increase in viscosity.

The investigation by this method of those peculiar cases of physical narcosis that find no explanation in other theories, such as by heat, cold, distilled water, a mechanical blow, and by electrical means, shows in every case the typical coagulation curves. Thus it seems that coagulation of the nervous protoplasm by chemical agents is only a special case of coagulation. The generalization can then be formulated that coagulating agents, irrespective of their nature, can behave as narcotics under suitable conditions.

In conclusion we can say that the chemistry of anaesthesia is the chemistry of sols, gels, displacement adsorption, coagulation, viscosity changes, peptization, adsorption, swelling, and catalysis; briefly, colloid chemistry applied to the muscles, nerves, glands, and cells of the affected tissues. The ultimate effect of a narcotic is the reversible coagulation of the cell colloids. This is preceded by a state of stimulation which depends upon the decreasing stability of the colloids before coagulation.

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