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*CLAUDE BERNARD'S THEORY OF NARCOSIS**

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The predominant theory of narcosis at the present time is that of Overton and Meyer, which postulates that lipoid solubility is the important factor. It is quite evident that a substance which is soluble both in lipoids and in water will pass into the cell readily; but that does not give us a theory of narcosis, unless we postulate that all substances which pass into the cells produce anesthesia—which is obviously absurd.

It is true that Meyer did make this assumption explicitly. "All chemically indifferent substances, which are soluble in fats and similar substances, must exert a narcotic action upon living protoplasm, in so far as they diffuse therein." It is not to be believed that anybody would now admit the truth of this assumption, an assumption which ignores the known differences between sensory nerves, sympathetic nerves, and motor nerves. Consequently the theory of Overton and Meyer is at best a theory of permeability and not a theory of narcosis at all.

Over sixty years ago, Claude Bernard[1] put forward the theory that anesthesia always occurred when we have reversible coagulation of the colloids of the sensory nerves. This was rejected for two reasons: that the concentrations necessary to coagulate nerve colloids (meaning proteins) were much higher than those occurring in anesthesia; and that coagulation by anesthetics was irreversible. Claude Bernard did not know enough colloid chemistry to overthrow these two criticisms and consequently his theory went into the discard temporarily.

It is true that relatively high concentrations of alcohol, for instance, are necessary to coagulate a moderately pure, negatively charged sol—forty per cent by volume in the case of copper ferrocyanide.[2] If we add nearly enough electrolyte to precipitate the copper ferrocyanide sol, we can make the amount of alcohol necessary to coagulate it as small as we please. Under these conditions, the coagulation is reversible. The two apparently serious objections to Claude Bernard's theory have therefore been eliminated.

When an acidified albumin sol is treated with sodium sulphate until it is on the verge of precipitating, one drop of the common alcohols or a small crystal of chloral hydrate is sufficient to coagulate the albumin. With a negatively charged albumin, calcium chloride can be used. Edestin acts similarly but is not sensitized so much as albumin, which we can perhaps take as typical of the colloids of the sensory nerves.

Claude Bernard merely said reversible coagulation of the nerve colloids, without committing himself whether these are proteins or lipoids. Since we know relatively little about reversible coagulation of lipoids and since some of the proteins seem to behave like the nerve colloids, it will be wise to discuss proteins only, until such time as it becomes necessary to consider the behavior of the lipoids in addition. Proteins are admittedly the important factor in the case of anaphylactic shock. For the time being, therefore, Claude Bernard's theory is that reversible coagulation of the proteins of the sensory nerves is always accompanied by anesthesia. We are making the additional explicit assumption that there is increased irritability as the nerve colloids approach the point of instability and the beginning of reversible coagulation. One would normally expect with increasing amounts of anesthetic to observe increasing irritability, anesthesia, and death in case the coagulation becomes irreversible. It is well known that there is a period of irritability before anesthesia begins and after anesthesia passes off. Since strychnine has a stimulating effect in small doses and causes death when administered in larger doses, it seemed probable that there might be a range of concentrations, perhaps very narrow, within which strychnine would act as an anesthetic. The matter is complicated by the facts that strychnine apparently affects the sympathetic nerves as well as the sensory nerves, and that it also interferes with the oxygen metabolism. In spite of this, the prediction in regard to strychnine was verified. It is a simple matter to anesthetize a frog with strychnine so that he will stay in a deep narcosis for several days. It is also possible to anesthetize a dog with strychnine provided he is given oxygen to minimize the unwanted effects of the drug.

Professor Otto Rahn of the College of Agriculture reported at a meeting of the Research Club on the action of mercuric chloride on bacteria. If the corrosive sublimate was administered in small doses or for short times,

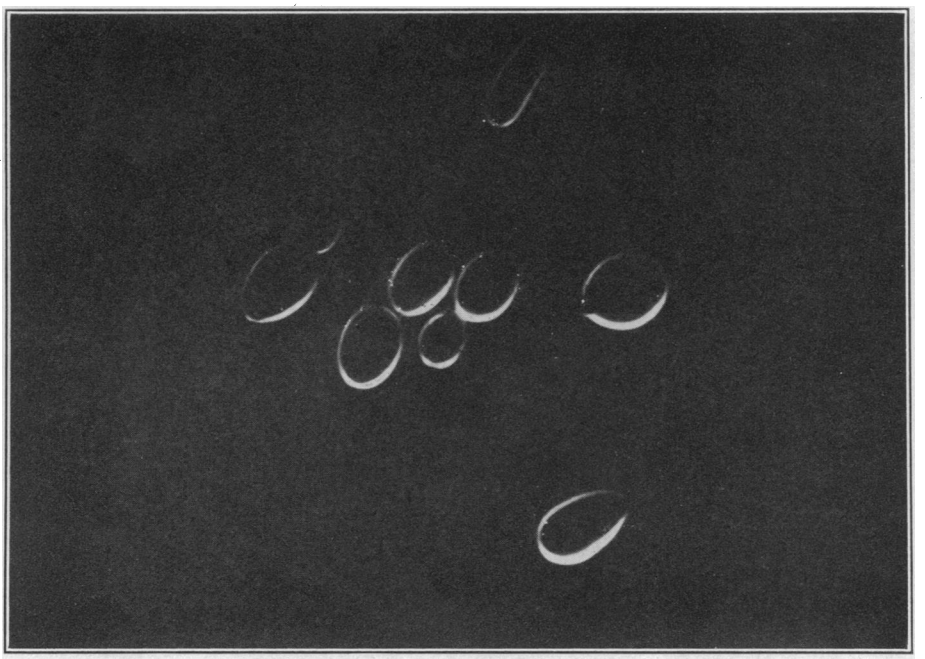

FIGURE 1

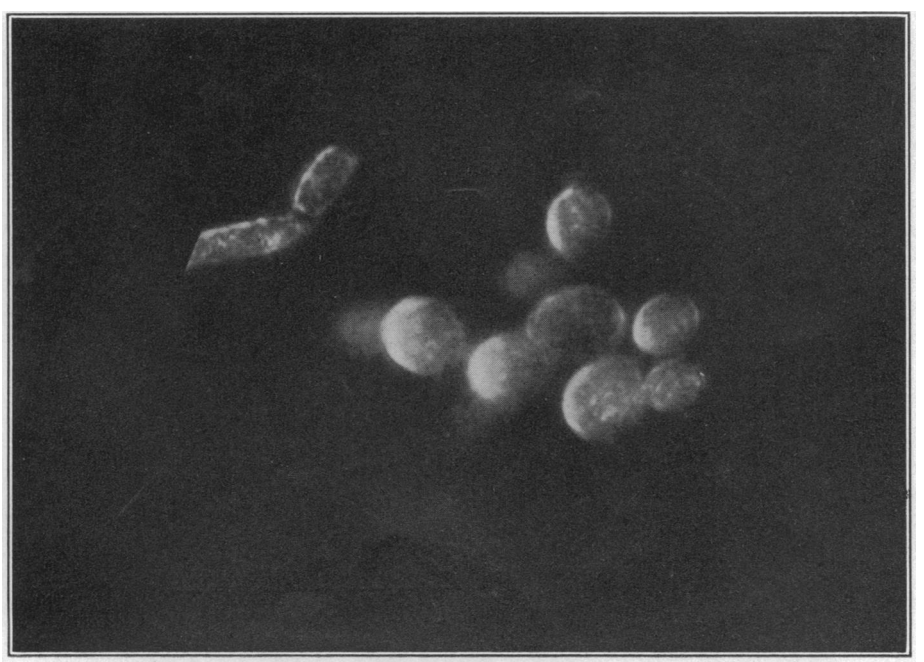

FIGURE 2

there was no apparent deleterious action. If larger doses were given or if a small dose were allowed to act for a longer time, a range of dormancy was observed. The bacteria could be aroused from dormancy by elimination of the mercuric chloride. If the dose were still larger, a range of death was observed. This meant that no treatment would cause the bacteria to function again. Following out the analogy with ordinary anesthetics, it was predicted that the very small doses should have produced irritability and a consequent increase in the rate of growth of the colonies. This was actually observed.

Dr. M. J. Brown of the Roessler and Hasslacher Chemical Company has called our attention[3] to the effect of hydrocyanic acid on the eggs of some scale insect found on citrus trees. A relatively high concentration of hydrocyanic acid gas killed the eggs of the scale; but a low concentration stimulated the eggs so much that a larger percentage hatched than in the control groups. This is analogous to the action of corrosive sublimate on bacteria and doubtless a range of dormancy could have been found if anybody had been interested in looking for it. These are merely special illustrations of the general phenomenon that all depressor substances exert a stimulating affect when used at appropriate dilution.

Marinesco[4] has shown that dilute alcohol coagulates the colloids in living cells; but he did not show that the colloids went back when the narcotic was removed. In order to establish this for a simple case, we prepared young, vigorous cultures of ordinary baker's yeast by inoculating yeast into Laurent's medium made up with 1.5% dextrose. Subcultures were made every twenty-four hours, the third subculture being used in the experiments. The yeast cells were examined under the ultramicroscope and photographed. The culture was then treated with the narcotizing concentration of amyl alcohol, about two per cent, and again placed under the ultramicroscope. After about ten minutes the Brownian movement is perceptibly slower. A few minutes later coagulation becomes visible and then a light but very pronounced flocculation occurs. The complete change requires twenty-five minutes, although the time depends upon the concentration of the narcotic, the temperature and the individual culture. A similar coagulation was obtained by treating the yeast cells with such other narcotics as chloroform, paraldehyde, ether and chloral hydrate. Figures 1 and 2 show the yeast cell before and after flocculation.

The narcotized culture was centrifuged, the supernatant liquid poured off from the cells, and fresh, sterile medium added. The cells were washed twice in this way and examined again under the ultramicroscope. The material in the cells soon develops a slight Brownian movement, then the aggregates break up into smaller particles and the motion becomes more pronounced. At the end of twenty-five or thirty minutes, the material is peptized completely and the cell is normal in every respect. The yeast

will ferment the medium and will reproduce just like normal cells. If too much narcotic is added or if it is allowed to act for too long a time, the coagulation becomes more marked and cannot be reversed. The cell is dead. This set of experiments is a great triumph for the theory of Claude Bernard.

In terms of the theory, a local anesthetic must be a substance which is not transported rapidly by the blood and which consequently acts where it is injected. Administering adrenalin along with novocaine closes the capillaries to some extent and thereby helps localize the action of the latter.

Claude Bernard points out that both morphine and ether act first on the brain; but that morphine acts less rapidly on the sensory nerves than do the true anesthetics. Consequently, administering morphine will displace ether or chloroform to the sensory nerves and will cause anesthesia with less chloroform or ether than would be needed without the morphine.

In terms of the theory, the difference between an anesthetic like ether and a habit-forming drug like morphine must be that the ether is eliminated relatively rapidly, while the morphine or some of its reaction products are retained, keeping the system in the irritable stage. Experimentally, this has been found to be true. An obvious corollary is that a compound which would peptize the colloids of the sensory nerves and which had no deleterious effect on other parts of the organism should furnish relief to drug addicts. We are working on this problem now.

Nitrous oxide does not coagulate yeast and does not narcotize it. Nitrous oxide does not coagulate albumin and yet it is an anesthetic for man, being much used in dentistry. Nitrous oxide apparently interferes with the oxygen metabolism, giving rise to acid products which cause the flocculation. H. Wieland,[5] whose critical study on nitrous oxide led to the discovery of acetylene as an anesthetic, was the first to emphasize the necessity of separating nitrous oxide and acetylene from the narcotics of the ether and chloroform type. He points out that these gases produce an effect similar to mountain sickness. He is led to the view that there is an inhibition of oxidation especially in the brain.

The general conclusions to be drawn from our investigations are as follows:

1. Claude Bernard was right in postulating that reversible coagulation of the colloids of the sensory nerves produces or accompanies anesthesia.

2. Decreasing stability of the nerve colloids mean increasing irritability up to the point of incipient coagulation.

3. Claude Bernard's theory affords an apparently adequate explanation of the difference between a general and local anesthetic.

4. Claude Bernard's theory accounts for the effects observed when morphine is used together with chloroform or ether.

5. Claude Bernard's theory offers an apparently adequate explanation for the difference between a true anesthetic and a habit-forming drug.

6. Claude Bernard's theory accounts for the phenomena observed in the action of mercuric chloride on bacteria, of strychnine on frogs and dogs and of hydrocyanic acid on the eggs of citrus scale.

7. Decreasing stability of a suitable colloid or group of colloids—accompanied by increasing irritability up to a certain point and then reversible coagulation—will apparently account for the law, accepted as universal by biologists, physiologists, and bacteriologists that all depressor substances exert a stimulating effect when used at an appropriate dilution.

8. Claude Bernard's theory offers a clue to a scientific method of countering habit-forming drugs.

9. Nitrous oxide and acetylene are not true anesthetics in the sense that ether and chloroform are. These two gases cause reversible coagulations of the colloids of the sensory nerves indirectly, and not directly as ether and chloroform do.

10. Claude Bernard's theory dealt with the colloids of sensory nerves. There is, therefore, nothing to prevent reversible coagulation of other materials besides proteins from being important in connection with anesthesia. It seems wise, however, to see how much can be explained solely by reversible coagulation of the proteins. We then have the behavior of the other colloids in reserve to be called into play when and as needed.

11. The Overton-Meyer theory accounts satisfactorily for many, though not for all, cases of cell permeability; but it is not true that all substances which enter the cells produce narcosis, and consequently the Overton-Meyer theory is a theory of permeability and not in any proper sense a theory of narcosis at all.

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[1] Cf. *Leçons de l' anesthesie*, **1875.**

[2] Gurchot, *J. Phys. Chem.*, **30**, 83 (1926).

[3] Bancroft, *The Rice Institute Pamphlet*, **15**, 275 (1928).

[4] *Kolloid-Z.*, **11**, 209 (1912); *Troisième Congrès internationale de Neurologie et de Psychiatrie* (1913).

[5] *Archiv. exp. Path. Pharm.*, **92**, 96 (1922).