ANESTHESIA IN RELATION TO CARDIAC DISEASE *

L. Corsan Reid, M.D.†

Anesthesia in relation to cardiac disease is a subject which covers such a wide field of investigation that it is necessary to restrict one's remarks to those particular phases in which recent contributions have been singularly interesting as well as highly informative. These might be grouped under the following heads:

1. Anesthesia and the Cellular Respiration Mechanism in Cardiac Disease.
2. Anesthesia and the Role of Vitamin B in Cardiac Disease.
3. Anesthesia and Vago-vagal Reflexes in Cardiac Disease.
4. Anesthesia and the Climacteric in Cardiac Disease.

I. Anesthesia and the Cellular Respiration Mechanism in Cardiac Disease

Cellular respiration may be defined as those biological processes and chemical mechanisms by which the cell converts the bound, radiant energy of the sun stored in food stuff molecules to free, utilizable, biotic energy, thereby making possible cellular activity and even cellular existence.

All energy comes ultimately from the sun, and in this, the cell does not differ from that of any other energy-converting mechanism such as the stove, the furnace, the steam engine, the dynamo, or even the water-fall. The energy present in coal, for instance, is transformed into heat by the use of a stove, or a furnace, and is converted into mechanical energy by the steam engine. This mechanical energy may then be converted to electrical power by means of the dynamo. These various contrivances are capable of liberating the bound, radiant energy of the sun for a particular purpose. The cell itself has a comparable mechanism to convert the radiant energy present in food to biotic energy. This mechanism is very different, of course, from that of a furnace or a steam engine, but it is, nevertheless, such a contrivance. In the furnace, the carbon atoms are oxidized, and in the cell, hydrogen atoms are oxidized.

The various parts of this mechanism are the enzymes, dehydrogenases, 4 carbon dicarboxylic acids, a cell pigment called cytochrome, and certain respiratory carriers such as flavoprotein or the yellow

* Read before the Section on Anesthesia of the Connecticut State Medical Society, and the American Society of Anesthetists, Inc. Hartford, Connecticut, May 22nd, 1940.

† New York Medical College and Flower Fifth Avenue Hospitals, New York City.

enzyme of Warburg, coenzyme I, coenzyme II, and the enzymes, oxidases. In order to give these different components an objective, integrated, interrelationship which can be readily visualized, one might compare them to a heat production mechanism.

In the heat production mechanism as shown in Figure 1, there is a fuel bin containing coal, a loading chute, and an endless chain on which are buckets which convey the coal to a chute leading into the furnace where it is burned with the production of heat, giving off smoke and ashes in the process.

In the cell, every one of these various components of the heat production mechanism has a counterpart. For instance, the fuel bin is

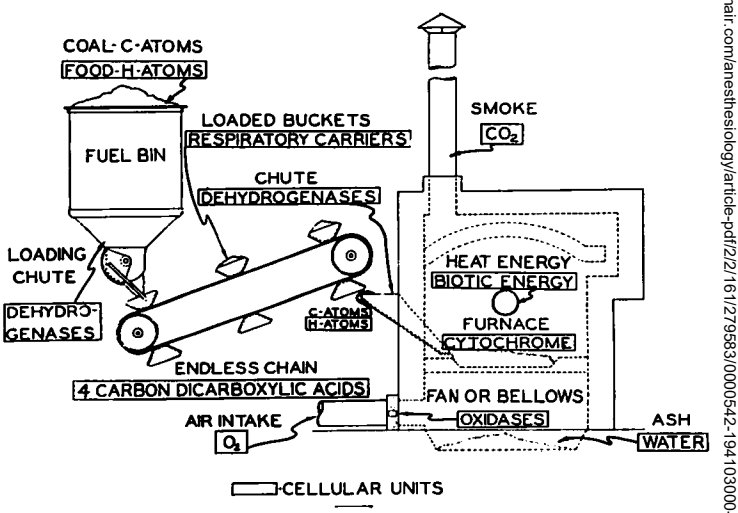

Fig. 1. A Biotic Energy Production Mechanism as Compared to a Heat Energy Production Mechanism.

the food supply containing hydrogen atoms which are loaded into the buckets by the enzymes, the dehydrogenases; the buckets are represented by the respiratory carriers, coenzyme I, coenzyme II, and flavoprotein or the yellow enzyme of Warburg. The endless chain is formed by the four carbon dicarboxylic acids. The respiratory carriers (buckets) carry the H atoms to the dehydrogenases (chute) which transfer them to the cytochrome (furnace) where they are oxidized (burned) under the influence of oxygen (draught) which is activated by the enzymes, oxidases (fans) with the production of biotic energy, giving off CO_2 (smoke) and water (ash).

In this scheme, the dehydrogenases activate the hydrogen of the

triose, and these H atoms are carried along the chain by certain respiratory carriers which are both hydrogen acceptors and hydrogen donators. Eventually, the hydrogen is transferred to cytochrome from which it is removed by the enzyme, oxidase, in the presence of oxygen to form water (Fig. 2). The pharmacological action of anesthetic agents and alkaloids on this cellular mechanism appears to be restricted to the enzymes, dehydrogenases. Cyanides, sulphides, and carbon monoxide act on the enzymes, oxidases, at the other end of the cycle (1, 2).

What are the practical applications of these conceptions? It is obvious, of course, that any cardiac lesion which involves either the

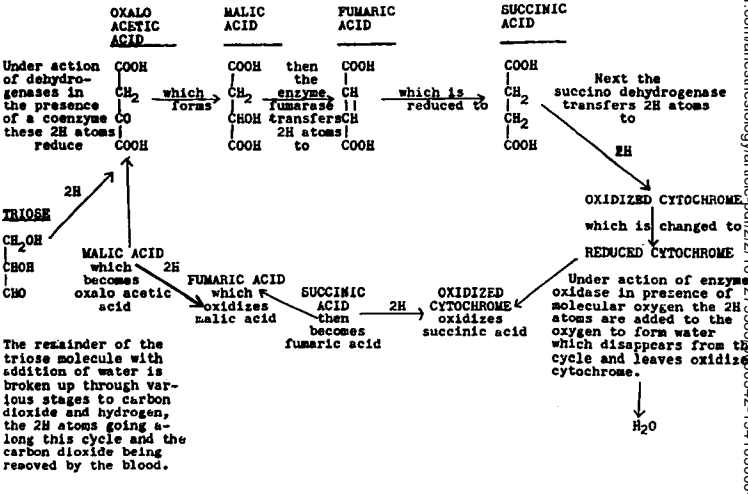

FIG. 2. Scheme of Cellular Oxidation in Muscle Cell from St. Gyorgyi (2) and Keilin (1) with Modifications, Reid (4).

vascular tree, the myocardium, or the specific tissue will lead to a profound disturbance in the production of energy, the actual diminution of which will depend on the particular tissue involved and its extent. In any event, this energy production is still further interfered with by anesthetic agents which, by inhibiting the dehydrogenases, prevent, so to speak, the proper loading of the buckets with fuel, and hence, decreased efficiency in the cellular liberation of the radiant energy in the food stuff molecules.

This action probably is the principal cause of the hyperglycemia which so often accompanies anesthesia. As a result of the inhibition of the dehydrogenases, the fuel is not removed and glucose accumulates

in the blood. The enzymes responsible for the transition of glycogen to glucose remain unaffected by anesthetic agents. This interference with carbohydrate metabolism is very interesting because Long (3) has recently suggested that sometimes myocardial failure may be due to an alteration or interference with the carbohydrate metabolism in cardiac muscle.

Another interesting reaction which might be mentioned, on the same basis, is the use of morphine in the presence of cyanosis and dyspnea. Every clinician is aware of the fact that morphine is highly beneficial when the cyanosis and dyspnea are due to cardiac disease, but most pernicious when due to pulmonary lesions such as bronchitis, asthma, emphysema, etc. The depression of the respiratory center as an explanation is not altogether satisfactory because an accumulation of CO_2 should stimulate even a depressed center. Accordingly, the suggestion has been made (4) that as morphine inhibits the dehydrogenases, the cellular oxidation-reduction cycle becomes inefficient and a decreased amount of CO_2 is formed. This decreased formation of CO_2 is not adequate to stimulate a depressed respiratory center and respiration then becomes inefficient. The only stimulation left to the respiratory center is that of oxygen lack on the carotid sinus mechanism, and if respiration sometimes abruptly fails it is not surprising. Undoubtedly, many of the failures of CO_2 build-up, previously explained on the basis of deficient oxygen intake, etc., are more readily intelligible on the basis of an inhibition of the dehydrogenases.

One might well hesitate, or even apologize for speaking to a group of anesthetists about a postoperative, supplemental oxygen supply, but in the light of this scheme it becomes an even more imperative and logical procedure, and is deserving of a much wider application than that now in vogue. If, for example, on a high mountain there is too little oxygen or a decreased oxygen tension, the body compensates by increasing the blood volume, the number of red cells, the percentage of hemoglobin and respiratory activity. Therefore, it is logical to compensate for a decreased efficiency of the cellular oxidation-reduction systems, as a result of the action of anesthetic agents, by an increased oxygen tension through a supplemental oxygen supply. Other applications of these principles might well be pointed out, but in the case of anemia, the lesson seems very obvious. Here, there is insufficient draught in the furnace due to the failure of arrival of adequate oxygen supplies for the cell; so if one also cuts down the fuel supply by inhibiting the enzymes, dehydrogenases, with an anesthetic agent, cellular activity becomes further restricted. Since little can be done for the inhibited enzyme action, a supplemental oxygen supply will compensate for the insufficient oxygen (draught) available to the cell. In any event, after the necessity for anesthesia has passed, the earlier the cells are returned to their optimal, functional capacity, the better for all concerned.

ANESTHESIA AND THE ROLE OF VITAMIN B IN CARDIAC DISEASE

Vitamin B is of the utmost importance and in some ways unique; it is necessary for growth and well-being earlier in the evolutionary scale than any other vitamin. Besides being essential for mammals and birds, it is also necessary in the frog, insects, and even the lowly flour beetle (5). Therefore, it is not surprising that it plays a singularly important role in cellular activity.

As you will recall, the metabolism of the myocardium is, in many ways, unusual (6); even the utilization of carbohydrates is different from that of other tissues. For instance, adrenaline has no effect on cardiac glycogen, nor has insulin. It is not reduced by exercise, and increases in starvation, but is greatly diminished during anoxia and hypoglycemia. While much of the heart's energy comes from carbohydrate sources, it, nevertheless, has the capacity to function well under aglycemic conditions, thereby utilizing fat and proteins.

Vitamin B_1, or thiamin, functions, according to Peters (7) (8), by acting as the prosthetic group to the enzyme concerned in the oxidation of pyruvic acid. It manifests its absence, clinically, by cardiac dilatation, tachycardia, and flattening of the T wave, these changes being reversible with an adequate B_1 diet. These findings were probably first described by Wenckebach, and a recent article by Dustin, Weyler and Roberts (9) shows very well, indeed, by means of x-ray studies, the decreasing size of the heart and the changes in the electrocardiogram under vitamin B_1 therapy, all of which give abundant testimony for the necessity of an adequate amount of this substance in the diet, particularly if anesthesia is contemplated.

In the cellular respiration mechanism shown in figure 1, the respiratory carriers, coenzyme I, coenzyme II, and flavoprotein, are synthesized from the constituents of vitamin B_2. The active functioning part of coenzyme I and coenzyme II is nicotinic acid amide which, of course, is formed from nicotinic acid, which is the pellagra preventing portion of vitamin B_2. Flavoprotein or the yellow enzyme of Warburg has for its active group, riboflavin which forms the other part of the vitamin B_2 complex.

Therefore, an adequate amount of vitamin B_2 is essential to assure the necessary supplies of respiratory carriers which form such a highly important link in the cell respiratory mechanism. This brief review of vitamin B deficiency shows rather clearly that an adequate preoperative vitamin diet becomes of the greatest importance to the anesthetist, particularly where the cell respiratory mechanisms are already under strain or restricted from lesions in the heart or other parenchymatous organs.

ANESTHESIA AND VAGO-VAGAL REFLEXES IN CARDIAC DISEASE

The frequency with which vago-vagal reflexes disturb cardiac activity have recently been shown rather clearly (10). These changes were

most pronounced during light anesthesia, especially during the introduction of intratracheal tubes, or inflation of cuffs, etc. The derangement to cardiac activity was most pronounced under cyclopropane, and the explanation for this appears to be a potentiation of vagal action by this agent (11).

They are undoubtedly more easily elicited following morphine, avertin, and digitalis as has been shown in the case of the carotid sinus reflex (12). Some of these effects may be illustrated by a few slides showing some electrocardiographic tracings during the insertion of tubes and other forms of respiratory irritation which form the trigger mechanism for the initiation of these reflexes. In a few instances, there were irradiation effects within the autonomic nervous system when impulses spread from the vagus to the sympathetic giving rise to tachycardia and auricular extrasystoles.

Vago-vagal reflexes might very well give rise to constriction of the coronary arteries with decreased blood supply to the myocardium (13), but in these studies (10) their effects were apparently limited to the specific tissue. Figures 3, 4, 5, 6.

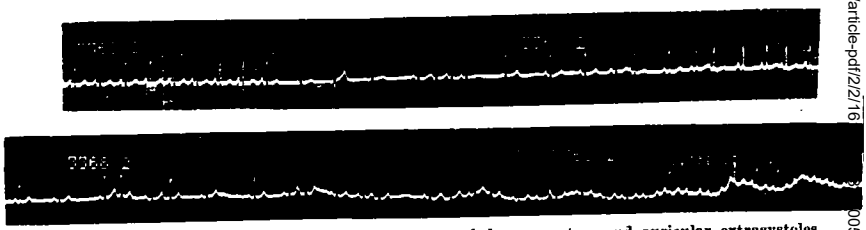

FIG. 3. 3368 Vagus inhibition with escape of deeper centers and auricular extrasystoles during insertion of tube and reappearance of normal rhythm immediately after tube removal (cyclopropane). Reproduced by courtesy of Surgery, Gynecology and Obstetrics. Surg., Gynec. & Obst. 70: 157–162 (Feb. 1) 1940.

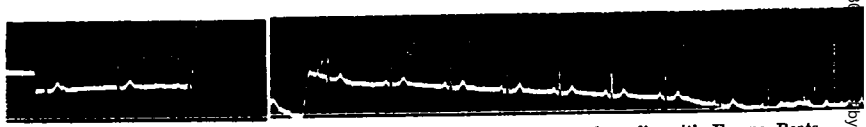

FIG. 4. 3425 Auricular Ventricular Block and Marked Bradycardia with Escape Beats During Insertion of Tube (N_2O and O_2). Reproduced by courtesy of Surgery, Gynecology and Obstetrics. Surg., Gynec. & Obst. 70: 157–162 (Feb. 1) 1940.

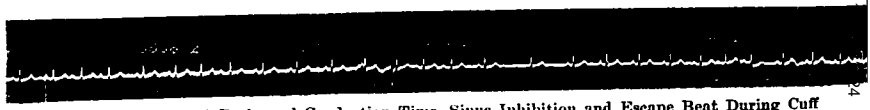

FIG. 5. 3558 Prolonged Conduction Time, Sinus Inhibition and Escape Beat During Cuff Inflation (Cyclopropane). Reproduced by courtesy of Surgery, Gynecology and Obstetrics. Surg., Gynec. & Obst. 70: 157–162 (Feb. 1) 1940.

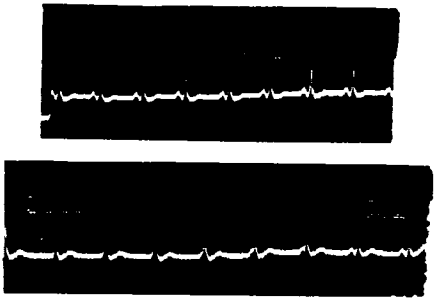

FIG. 6. 3362 Auricular Ventricular Rhythm During Insertion of Tube (N_2O, O_2, Ether) Reproduced by courtesy of Surgery, Gynecology and Obstetrics. Surg., Gynec. & Obst. 70 157–162 (Feb. 1) 1940.

It cannot be insisted upon too frequently that these reflexes are important at any time, but particularly so in structurally altered hearts or during light anesthesia. It is important to realize that all hearts under anesthesia are functionally deranged; that is, a normal heart under anesthesia is as vulnerable to derangement from vagal stimulation as an organically diseased heart would be without anesthesia. The injurious effects on cardiac activity, potentially present in vago-vagal reflexes, are preventable, or at least minimized, by atropine therapy.

ANESTHESIA AND THE CLIMACTERIC IN CARDIAC DISEASE

It has been known for a long time that the climacteric, in the vast majority of cases, proves very disturbing and gives rise to innumerable complaints. Hot flashes and palpitation are almost regular occurrences during the menopause, and a high percentage of women have palpitation, cardiac pain, and dyspnea during this time, a triad also found in organic heart lesions with unsual frequency.

These symptoms, however, received little attention until Scherf (14) showed very clearly that the circulatory and respiratory systems, during ovarian dysfunction, were profoundly altered as shown by electrocardiograms and respiratory tracings, and what is most important, they were reversible with estrin therapy. These cardiac reactions with which one is principally concerned here, as shown in the electrocardiograms, are sinus tachycardias, depression of the S.T. segment, and flattening of the T wave, all of which disappear under estrin therapy. Therefore, all patients during the climacteric who have symptoms referable to the heart suggesting myocardial disease, particularly if they have fibroids and are about to be operated upon, should have the benefit of a course of estrin therapy to exclude its possible deficiency

being an etiological factor. This is true in young women as well showing evidences of hypogonadism (Fig. 7).

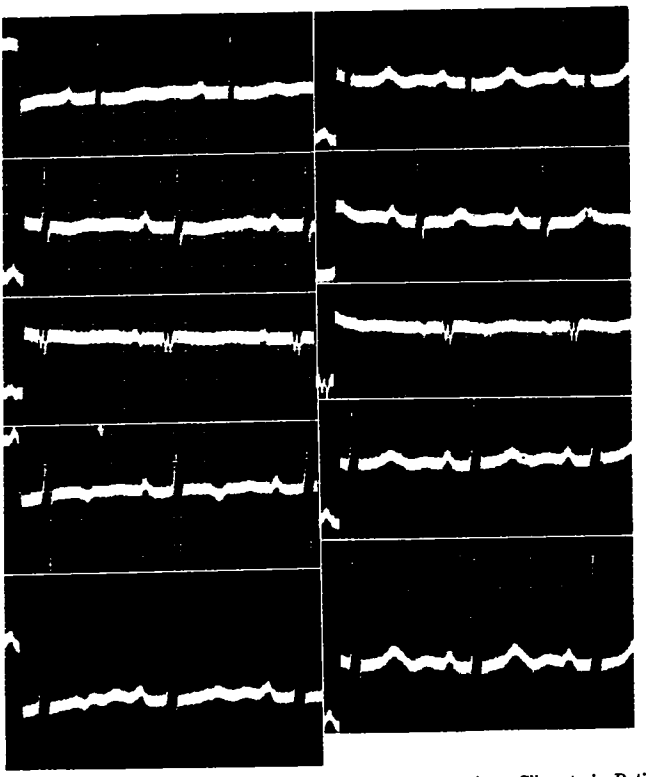

FIG. 7. Prolonged Conduction Time and Abnormal T-waves in a Climacteric Patient, Normal Electrocardiogram Appearing after 3 Weeks' Treatment. *Figure 7.* Reproduced by courtesy of Annals of Internal Medicine. Ann. Int. Med. 13: 1419, 1940.

SUMMARY

1. All anesthetic agents and most alkaloids inhibit the enzymes, dehydrogenases, which form such an important link in the chain of events which gives rise to the production of energy by the cell. This accounts, in part at least, for the hyperglycemia during anesthesia as well as decreased CO_2 build-up and various degrees of failure of cellular function.

2. A high vitamin B content in the diet is necessary to assure an adequate supply of respiratory carriers such as flavoprotein, and nicotinic acid amide, as well as thiamin. Accordingly, the diet, preoperatively, becomes of the greatest importance to the anesthetist.

3. Irritation of the respiratory tract or esophagus may set up vago-vagal reflexes with resulting derangement of cardiac and respiratory activity, and all such contemplated procedures, as the introduction of tubes, catheters, etc., should be covered by adequate preoperative therapy to minimize or actually prevent the undesirable reactions potentially present in autonomic reflexes.

4. Every operative case during the menopause which shows any cardiac symptoms or signs, or electrocardiographic findings suggestive of cardiac lesions, should have the benefit of an adequate course of estrin substitution therapy.

The author wishes to express his thanks to Boyd Sleith and Joseph Mooney for their assistance with Fig. 1, and to Miss Ethel Muller for assistance in preparation of the manuscript.

REFERENCES

1. Keilin, D.: Ergebnisse Enzymforschung II: 254, 1933.
2. Von Szent Gyorgyi, Albert: Perspectives in Biochemistry, Cambridge University Press, 1937, p. 172.
3. Long, C. N. H., and White, A.: Intermediary Carbohydrate Metabolism, Ergebnisse d. Physiol. 40: 164, 1938.
4. Reid, L. Corsan: Cellular Respiration, Brit. J. Anesth. 17: 41 (July) 1940.
5. Vitamins, A Survey of Present Knowledge, Medical Research Council Reports, p. 129, 1932. London, England.
6. Reid, L. Corsan: Carbohydrate Metabolism, Bulletin New York Medical College and Flower Fifth Avenue Hospitals, April 1939, p. 59.
7. Peters, R. A.: Pyruvic Acid Oxidation in the Brain—Vitamin B, and the Pyruvate, Oxidase, in the Pigeon's Brain, Jour. of Biochem. 30: 2206, 1936.
8. Peters, R. A., and O'Brien, J. R.: The Vitamin B Group, Annual Review of Biochem. 7: 305, 1938.
9. Dustin, C. C.; Weyler, Henry, and Roberts, C. P.: Electrocardiographic Changes in Vitamin B, Deficiency, New England J. Med. 220: 15–21, No. 1.
10. Reid, L. Corsan, and Brace, Donald E.: Irritation of the Respiratory Tract and its Reflex Effect upon the Heart, Surg. Gynec. & Obst. 70: 157 (Feb. 1) 1940
11. Adriani, John, and Rovenstine, E. A.: Proceedings Amer. Phys. Society, New Orleans, 1940, p. 3.
12. Rovenstine, E. A., and Cullen, S. C.: The Anesthetic Management of a Patient with a Hyperactive Carotid Sinus Reflex, Surgery 6: 167 (Aug.) 1939.
13. Scherf, David, and Schonbrunner, E.: Ueber den pulmocoronaren Reflex bei Lungenembolien, Klin. Wchnschr. 10S: 340, 1937.
14. Scherf, David: The Respiratory and the Circulatory System in Females with Ovarian Dysfunction, Annals Int. Med 13: 1414, 1940.

The Annual Dinner for Diplomates of the American Board of Anesthesiology, Inc., will be held on June 4, 1941, in Cleveland, Ohio. Further details will be announced at a later date.