

Male oysters are not only stimulated by egg suspensions but respond also to the presence of sperm in the water. In several instances ripe males attached to the kymograph were kept for two or three hours in water at 24° but failed to spawn. The discharge of sperm was, however, provoked by the addition of sperm. In that case, the latent period of the reaction, similar to the case of a spawning reaction of a female, varied from 9 to 21 minutes.

Mutual stimulation of the two sexes plays an important rôle in the propagation of oysters. The males respond more readily than the females to the increase in temperature and, under natural conditions, are apparently the first to spawn. The reaction once started by one of the males, stimulates the females and the males nearby, which in turn stimulate the others. In that way spawning spreads all over the oyster bank. The chemical stimulation is influenced in two ways by the temperature: the latter determines the lowest limit (20° for *Ostrea virginica*, 25° for *O. gigas*), below which the females fail to spawn, and supplies the initial stimulus for the spawning of the male.

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## ON THE FREE ENERGY OF GLUCOSE AND OF TRIPALMITIN

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The theoretical maximum amount of work derivable from a chemical reaction is a quantity which we may designate as the reversible work, and which is equal to the decrease in the free energy of the system plus the change in the pressure-volume product. In the form of an equation this is:  $W_R = -\Delta F + \Delta(PV)$ .

Since the magnitude of the change in the pressure-volume product is rarely significant compared to the free energy change, for practical purposes we may consider the theoretical maximum amount of work derivable from the chemical reactions discussed here as a quantity equal to the decrease in

free energy. It is possible now-a-days to compute the free energy change for most reactions involving only inorganic reactants with a high degree of precision. On the other hand, until quite recently the standard free energy data for organic compounds were too scanty to be useful in considerations of the energy changes in physiological reactions. Instead, tacitly it has been assumed that the change in the heat content, e.g., the heat of combustion, was equal to the theoretical maximum available work. This assumption is made, for instance, in the studies of the relative efficiencies of carbohydrate and of fat as fuels for muscular work; in the principle of replaceability of "isodynamic" quantities of different foodstuffs.

Recently Parks and his collaborators<sup>1</sup> have determined the entropies of a number of organic compounds among which are such elementary metabolites as glucose, palmitic acid and glycerol. From the values of the standard molal entropies and the available data on the heats of combustion the standard free energies of these compounds were computed.

This work renders it possible to compute now with some precision the energy changes incurred in the oxidation of glucose and of tripalmitin. The ratios for each of these metabolites of the reversible work as defined above to the total energy change, i.e., to the heat of combustion plus the change in the pressure-volume product, can be considered as measures of their theoretical "efficiencies" as sources or generators of energy other than heat, i.e., as fuels for work, whether mechanical, chemical, or electrical.

The conventional term "efficiency" is not used with exactly the same meaning always. In the physiological literature it is employed in the sense of the ratio of work performed by the animal to the heats of combustion of the metabolites consumed in the performance of this work. In accordance with this usage we have considered the theoretical maximum "efficiency" of a physiological fuel as the ratio of the reversible work to the total energy change. When "efficiency" is defined in this way the ratio may in some cases, as Burk has shown,<sup>2</sup> be greater than 1. Here, obviously the balance sheet is incomplete: some reactions have been omitted, or the process is an endothermic one when it proceeds under reversible conditions, drawing heat from the surroundings. "Efficiency" might also be defined in the sense of the ratio of the work performed to the calculated maximum work obtainable from the reactions involved. For clarity the term "efficiency" will be defined here explicitly in each case. The available data are sufficient also for the calculation of the free energy change involved in the conversion of tripalmitin to glucose, or vice versa.

The usefulness of these calculations is limited before all else, of course, to those systems in which the second law of thermodynamics is obeyed. In spite of the hesitancy prevalent,<sup>3,4</sup> there does not appear to be any strong *a priori* reason for rejecting the conclusions of thermodynamic calculations when the available data are as adequate as they are now, in such macro-

scopic physiological chemical changes as the oxidation of glucose or of tripalmitin to carbon dioxide and water. The accuracy of the data depends now only on the accuracy of the values for the heats of combustion, and to a lesser degree on the values employed for the concentrations of the reactants in these physiological reactions.

The results of the calculations given in detail below are that the reversible work, which is practically the same as the free energy change, and which is equivalent to the theoretical maximum obtainable work in the physiological combustion of glucose, is 101 per cent of the heat of combustion; and of tripalmitin 98 per cent of the heat of combustion. This difference between glucose and a saturated fat represents, therefore, their relative theoretical "efficiencies" as fuels. In the case of the oxidation of carbohydrate the pressure-volume product change is practically zero, as the respiratory quotient for the reaction is 1. In the case of the oxidation of tripalmitin the change in the pressure-volume product is equivalent approximately to 13,000 calories. Even this quantity is negligible in comparison with the values for the heat of combustion and the free energy change which are both over 7,000,000 calories per gram mol. The computations show also that the production of fat from glucose is a process in which there is a large gain in free energy. From the assumption made here, that the second law of thermodynamics is obeyed in the body, it follows that this process is not a spontaneous one: i.e., when it does occur it is effected at the expense of the energy derived from some other reaction.

This is shown in the feeding experiments of Bleibtreu,<sup>5</sup> Rapport, Weiss and Csonka,<sup>6</sup> and Wierzuchowski and Ling.<sup>7</sup> Bleibtreu pointed out that the high respiratory quotients which are obtained when carbohydrate is converted to fat are most frequently accompanied, not by a decreased, but by an increased consumption of oxygen. In the experiments of Wierzuchowski and Ling in which a respiratory quotient as high as 1.55 was obtained, the oxygen consumption was nearly trebled, while the CO<sub>2</sub> production was quadrupled. It was calculated that, over a period of 24 hours, fat equivalent in calories to 184 per cent of the basal was manufactured from carbohydrate and stored by the animal, while the increase in metabolism over the same period was 60 per cent of the basal. Their most striking experiment was "When starch and glucose were given together on the morning of a day following a large ingestion of starch, the metabolism rose 100 per cent above the basal, and the production of fat from carbohydrate amounted to a storage of caloric energy in the form of fat equal to 260 per cent of the basal metabolism." Similarly Rapport, Weiss and Csonka observed in the hog that, when a quantity of fat whose caloric equivalent was equal to 84 per cent of the basal, was produced from carbohydrate, there was an increase in metabolism over the basal of 22 per cent. The evidence is not conclusive because it is not possible from this data to sepa-

rate the specific dynamic action due to fat production, from that due simply to the ingestion of large amounts of carbohydrate, i.e., to the effect which Lusk has designated as the specific dynamic action due to plethora. The latter effect, however, subsides within 4 or 5 hours after the ingestion of the carbohydrate and has never been found to provoke an increase in metabolism of the order of magnitude of 100 per cent of the basal. In one experiment Wierzuchowski and Ling observed, 20 hours after the ingestion of 700 gm. of corn starch, a respiratory quotient of 1.4 and an increase in the metabolism of 45 per cent over the basal. At this time the fat production from carbohydrate was 4.1 grams per hour. The power of the dog to transform carbohydrate to fat is apparently much less than that of the hog, and the increase in metabolism following the administration of large amounts of carbohydrate apparently is less, and is over sooner than in the case of the hog. Here also the evidence is not conclusive because there are no experiments on record in which as large amounts of sugar were given to dogs as were provided in the diets of the hogs in the experiments of Wierzuchowski and Ling. The experiments of Boyd, Hines and Leese, quoted by Lusk<sup>8</sup> suggest, however, that the specific dynamic action of carbohydrate in dogs would not under any circumstances approach the high figures observed in hogs. In these experiments glucose was administered continuously intravenously to a dog in such amounts that the blood sugar rose from 0.1 per cent to 0.7 per cent. Under these conditions "the maximal increase in metabolism ever recorded in a dog after glucose administration was obtained." During the injection the increase over the basal was 48 per cent. One hour after the cessation of injection the blood sugar had returned to a normal level, and the metabolic rate was now only 16 per cent above the basal. Three hours after the injection the increase over the basal was only 5 per cent. The mere deposition of carbohydrate in the tissues, therefore, cannot, it seems, account for the very high values for the specific dynamic action of carbohydrate observed in the hog many hours after ingestion of the carbohydrate.

The difference between these two animals appears to be that in the hog much more carbohydrate is converted to fat. The source of the energy for this conversion under the conditions of these experiments is derived largely from the oxidation of carbohydrate. The very large values for the specific dynamic action indicate that only a fraction of the energy released by this oxidation is actually used in the conversion; the remainder escapes unused as heat.

In the equation of Bleibtreu which was employed by Rapport, Weiss and Csonka, and by Wierzuchowski and Ling for the comparison of the values obtained from indirect with those from direct calorimetry, the specific dynamic effect of the process of fat-production from carbohydrate is tacitly implied. Bleibtreu considered that in the formation of 100 grams

of pork fat with an elementary composition of C, 76.54%, H, 11.94%, and O, 11.52%, 191.35 grams of glucose would be required in order to provide the carbon. The hydrogen of the glucose, not used to form fat, combines with some of the unused oxygen to form water; and the remaining oxygen is consumed in the combustion of more glucose, over and above the basal requirement. If the process of fat formation did not exert a specific dynamic action, this unused oxygen presumably would be available for purposes of the basal metabolism, so that, under these conditions, the consumption of inspired oxygen would be reduced. But, as Bleibtreu pointed out, the oxygen consumption is increased, in spite of the release of a large quantity of oxygen from the carbohydrate. The observations on plants of Terroine and Bonnet and their collaborators<sup>20,21,22</sup> show similarly that the formation of fat from carbohydrate involves an expenditure of energy which manifests itself in an addition to the basal metabolism. Their results are discussed in detail below.

It seems improbable that the production of fat from carbohydrate is carried on with the same expenditure of energy in all animals. The specific dynamic action of this process in any animal can be considered as the reciprocal of the ability of that animal to transform carbohydrate into fat. The final equation of Bleibtreu is

$$270.06 \text{ gm. glucose} = 100 \text{ gm. fat} + 115.45 \text{ gm. CO}_2 + 54.6 \text{ gm. H}_2\text{O}$$

In animals such as the hog or goose, that transform carbohydrate into fat very readily, the amount of glucose used and CO<sub>2</sub> and water formed to produce 100 grams of fat will be less than in a dog. The procedure of Lusk and his pupils, of first deducting the specific dynamic action, as indicated by the increased oxygen consumption, and then estimating the calories equivalent to the CO<sub>2</sub> production over and above that required for an R. Q. of 1, tends to obscure the differences between animals, and by an apparent more or less satisfactory agreement between direct and indirect calorimetry endows the empirical equation of Bleibtreu with an unwarranted generality.

The converse reaction, the hypothetical conversion of tripalmitin to glucose, is accompanied by a work content decrease which amounts to 21 per cent of the theoretical maximum amount of work available, and to 20 per cent of the total energy change in the combustion of tripalmitin. If fat is converted into carbohydrate before its energy can be used in muscular work, the energy equivalent to the decrease in work content must be wholly dissipated as heat instead of used for work. Under these conditions fat must necessarily be less efficient as a source of energy for work than carbohydrate.

There are described in the literature a number of attempts to determine experimentally the relative efficiencies of carbohydrate and of fat as fuels for

muscular work in the animal body. The careful study by Krogh and Lindhard of about ten years ago<sup>9</sup> led to a general acceptance of a figure for the efficiency of fat as a fuel for muscular work 11 per cent less than that of carbohydrate. Unfortunately the reliability of this estimate has been impaired by the subsequent work of Hill, Long and Lupton<sup>10</sup> on the oxygen debt, and by the studies of Rapport and Ralli,<sup>11</sup> and particularly of Best, Furusawa and Ridout<sup>12</sup> on the respiratory quotient of the excess metabolism during the performance of and recovery from muscular work. The serious deficiency in the data of Krogh and Lindhard is their omission of the metabolism during recovery. Their estimate of 11 per cent difference in efficiency between the two fuels is based upon observations on the "excess" metabolism only during the performance of the work.

The later observations of Rapport and Ralli on the "excess" metabolism of mild exercise by dogs are in accordance with those of Krogh and Lindhard in so far as they found that according to whether the diet is preponderantly carbohydrate or fat, respectively more carbohydrate or fat is burned. It is possible, therefore, that in the experiments of Krogh and Lindhard, the respiratory quotient during recovery was the same as that during the exercise. If this was the case, and if the recovery period is of the same length on the two diets, then the same relative differences that were observed on the carbohydrate and fat diets might have been found for the total excess metabolism.

Leathes and Raper<sup>13</sup> calculated that a quantity of heat equivalent to 20 per cent of the heat of combustion of fat is evolved in the conversion of fat to carbohydrate. They consider that this figure is at variance with the figure of 11 per cent lower efficiency of fat obtained by Krogh and Lindhard, if it is considered that fat is converted to carbohydrate before it is burned. This difference between 20 per cent and 11 per cent constitutes a discrepancy only if it is assumed that before fat can provide energy for any kind of work in any tissue of the body it must first be converted to carbohydrate. If the energy available for work released by the combustion of fat can be utilized by the viscera, without its previous conversion to carbohydrate, then even if such a conversion is obligatory in skeletal muscle, it would still be possible to reconcile the difference between the calculated 20 per cent and the observed 11 per cent lower efficiency of fat, by postulating a selective utilization of fat by the viscera and of carbohydrates by the muscles when muscular work is carried out on a high fat diet; or by some such mechanism as that suggested by Rapport and Ralli, that the energy of combustion of fuels other than a fraction of the free lactic acid may serve in the re-synthesis of glycogen in the recovery phase of muscular contraction.

But until the observations of Best, Furusawa and Ridout on the excess metabolism during muscular exercise have been explained, any conclusions

regarding the nature of the fuel used in muscular exercise can only be tentative so long as they are based, as they are above, upon inferences drawn from respiratory quotients. Best, Furusawa and Ridout found that "The respiratory quotient of the excess metabolism of muscular exercise is not invariably unity, but increases with the severity of the exercise from a value approximately the same as the basal quotient for very mild exercise, through unity for moderate exercise, to one considerably above unity for very severe exertion." These observations in so far as they pertain to excess metabolism during mild exercise confirm the similar earlier findings of Rapport and Ralli.

If eventually it is found that muscular work is performed on a fat diet with an efficiency considerably less (more than a few per cent less) than on a carbohydrate diet, this inefficiency cannot be ascribed to differences between the free energy and heat energy of these two metabolites; but rather to differences in their intermediary metabolism, whereby more energy escapes as heat in the case of fat than in the case of carbohydrate.

These conclusions regarding the losses of energy incurred both in the conversion of fat to carbohydrate and vice versa are supported by the observations of Terroine and Bonnet and their collaborators on germinating seeds and moulds. The problem is simplified with these forms on account of the absence of any specific dynamic action due to plethora.<sup>20</sup> In the mould *Sterigmatocystis nigra* Terroine and Bonnet<sup>21</sup> found that for every 100 calories of potential energy contained in the glucose used in the process of conversion to fat, 11 per cent was lost as heat when the fatty acid content of the mycelium rose from 3.1 per cent to 9.0 per cent; 13 per cent was lost when the fatty acid content was 10.5 per cent; and 17 per cent was lost when the fatty acid content was 12.3 per cent. If in the feeding experiments on the hog one ascribes the whole of the specific dynamic action of the carbohydrate to the work of converting carbohydrate to fat, the ratio of energy lost to the total employed is 18 per cent in the experiment of Rapport, Weiss and Csonka, and 23 per cent in the experiment of Wierzuchowski and Ling. The latter estimates are certainly too high, as only a fraction of the total specific dynamic action of carbohydrate in these feeding experiments could have arisen from the production of fat. There must have been another fraction due simply to the plethora effect. The "specific dynamic action" of formation of fat from carbohydrate will therefore be apparently the same in plants as in the hog.

The problem of the energy losses incurred in the utilization of fat in animals also is elucidated by the observations made on plants, where the production of carbohydrate from fat is unequivocal and easily demonstrated. In germinating grains Terroine, Trautmann and Bonnet<sup>22</sup> observed that when fat is converted into cellulose, 23 per cent of the energy of the fat used is lost. Similarly in the mould *Sterigmatocystis nigra* the

amount of energy lost in the conversion to carbohydrate varied, depending upon the fat used between 18.8 per cent and 25.8 per cent. These values are in accord with that calculated, and substantiate the criticism, based upon calculated energy changes, of the view that fat must first be converted to carbohydrate before it can be utilized in muscular work.

*Calculations:* The symbols employed are those of Lewis and Randall.<sup>14</sup> Throughout, the activity of the reactants will be considered as equal to their molar concentrations. This is permissible because even the allowances for the free energy of solution and dilution, and for temperature, are very small compared with the free energy changes when the reactions are considered as occurring with the metabolites and end products in their standard states. In the re-calculation of the standard free energies at 37°C. instead of at 25°C., the values of the heats of formation and of combustion will be taken to be the same at the two temperatures. The free energy values employed in the calculations which follow are taken from the table of revised values of Parks, Kelley and Huffman.

*Glucose:*

$$\Delta F_{298}(\text{solid}) = -219,000 \text{ calories.}$$

From the second-law free energy equation  $\frac{-\Delta F_2}{T_2} - \frac{-\Delta F_1}{T_1} = \int_{T_1}^{T_2} \frac{\Delta H}{T^2} dT$ ; and  $\Delta H_{298} = -303,000$  calories,  $\Delta F_{310} = -215,600$  calories. Interpolating from the data in the International Critical Tables, the solubility of glucose at 37°C. is 146 gm.  $C_6H_{12}O_6 \cdot H_2O$  in 100 gm. water. The mol fraction

of the saturated solution at 37°C. is  $\frac{132.7}{\frac{132.7}{180} + \frac{113.3}{18}} = .11$ . Considering

the concentration of glucose at the site of oxidation to be nearly the same as it is in the blood, normally approximately 0.1 gm. in 100 cc., the mol

fraction is  $\frac{0.1}{\frac{180}{90}} = .00011$ , and the free energy of the dilution per mol is

therefore  $-\Delta F = RT \ln \frac{.11}{.00011} = 4250 \text{ cal.} \therefore \Delta F \text{ glucose (mol fraction} = .00011) = -219,900 \text{ calories.}$

The concentrations of oxygen, carbon dioxide and water in the blood and tissues are not those of their standard states, and accordingly slight corrections are introduced in the free energy computations for these deviations, in addition to the modification of the standard free energy values for the change in temperature from 25°C. to 37°C.

*Oxygen:* Krogh<sup>15</sup> gives the following values for the difference in oxygen tension between the blood in the capillaries and the muscles under the following physiological conditions: rest, 6.5 – 3.5 per cent of an atmosphere; massage, 2.5 per cent; work, 0.4 per cent; maximum circulation, 0.25 per cent. Considering, therefore, the oxygen tension in the muscles during work to be 100 mm. mercury, the free energy decrease per mol of oxygen due to "dilution" is  $-\Delta F = RT \ln \frac{760}{100} = 1250$  calories.

*H<sub>2</sub>O:*

$$\Delta F_{298} = -56560.$$

$$\Delta H = -68270.$$

$$\therefore \Delta F_{310} = -56100.$$

In plasma the mol fraction of water is .995.<sup>16</sup> The correction for dilution is therefore negligible.

*CO<sub>2</sub>:*

$$\Delta F_{298} \text{ CO}_2 \text{ (g)} = -94,260 \text{ calories.}$$

$$\Delta H = -94,300 \text{ calories.}$$

$$\therefore \Delta F_{310} \text{ CO}_2 \text{ (g)} = -94,260 \text{ calories.}$$

Considering the pressure of CO<sub>2</sub> in the tissues to correspond to 40 mm. of mercury, the correction for the free energy decrease due to the dilution of the CO<sub>2</sub> is

$$-\Delta F = RT \ln \frac{760}{40} \text{ calories} = 1800 \text{ calories.}$$

$$\Delta F_{310} \text{ CO}_2 \text{ (g) (40 mm. Hg)} = -96,100 \text{ calories.}$$

*Oxidation of Glucose:* C<sub>6</sub>H<sub>12</sub>O<sub>6</sub> (mol fraction .00011) + 6O<sub>2</sub> (g) (100 mm. Hg) = 6CO<sub>2</sub> (g) (40 mm. Hg) + 6H<sub>2</sub>O (l);  $-\Delta F_{310} = (-219,900) + (-6 \times 1250) - (-6 \times 96,100) - (-6 \times 56,100) = 685,800$  calories. The heat of combustion of glucose in solution is 676,080 calories.<sup>17</sup>

$$\therefore \frac{\text{Free Energy of Combustion}}{\text{Heat of Combustion}} = \frac{685,800}{676,080} = 1.01.$$

The change in the pressure-volume product is negligible here.

The fact that the free energy of combustion is greater than the heat of combustion means only that if it were possible to convert into work all the free energy released by the oxidation of glucose, approximately 9000 calories would be absorbed per gram mol of glucose oxidized. Actually in the body, of course, only a small fraction, between 15 and 30 per cent of the free energy, is utilized, the remainder being dissipated as heat.

The experimentally determined values for the standard molal free energies of palmitic acid and of glycerol permit a fairly good approximate computation of the free energy of tripalmitin. In the hydrolysis and formation of a great variety of esters Berthelot and Saint-Gilles<sup>18</sup> found that the equilibrium constant for the reaction, acid + alcohol = ester + water, was always in the neighborhood of 4; and that the value of the equilibrium constant seemed to be independent of temperature in the range from 100°C. to 220°C. One may assume from these observations that for this type of reaction  $\Delta F$  and  $\Delta H$  are equal, or nearly so. The value of  $\Delta F$  at 25°C. then becomes about -800 calories per linkage mol of ester. The value for the heats of combustion in the International Critical Tables, however, yield values for the heats of formation of esters with the higher acids as high as 15,000 calories. No heat data are available in regard to glycerol esters. Since it is insignificant in the final result here whichever value is chosen for  $\Delta H$  we have preferred the alternative of assuming that the heat of ester formation in the case of tripalmitin is approximately 1000 calories per linkage. The free energy of formation of tripalmitin from glycerol and palmitic acid is accordingly taken as +2400 calories.

The reaction may be represented as follows: 1 glycerol + 3 palmitic acid  $\rightarrow$  tripalmitin + 3 water;  $-\Delta F = +2400$  calories.

Parks, Kelley and Huffman give -115,700, and -94,000 as the free energy values at 25°C. of glycerol and palmitic acid respectively. The free energy of water at 25°C. is -56,560. The value for the free energy of palmitic acid is based upon a value for the heat of combustion of 2,379,000 calories. The value given in the International Critical Tables is slightly higher, 2,380,000 calories. With this value, the free energy of palmitic acid is -93,000 calories. From these figures an approximate value for the free energy of tripalmitin is -227,000 calories.

Assuming that the heat of ester formation of tripalmitin is +3000 calories,  $\Delta H$ , the heat of formation of tripalmitin, is simply the sum of the heats of formation of 1 gram mol of glycerol and three of palmitic acid plus 3000 calories, minus the heat of formation of three gram mols of water, and is equal to -610,500 calories. The free energy,  $\Delta F$ , at 37°C. then is -211,000 calories.

Because fat in the tissues probably exists as a saturated solution in equilibrium with the solid phase there is no free energy of solution to be taken into account for tripalmitin.

*Oxidation of Tripalmitin:*  $2C_{61}H_{98}O_6$  (solid) +  $145O_2$  (100 mm. Hg)  $\rightarrow$   $102CO_2$  (40 mm. Hg) +  $98H_2O$ ;  $-\Delta F = (2 \times -211,000) + (145 \times -1250) - (102 \times -96,100) - (98 \times -56,100) = 14,696,750$  calories; = 7,348,000 calories per gram mol of tripalmitin. The diminution in the pressure-volume product is equivalent to 13,000 cal. per gram mol of tripalmitin oxidized.

There are no data available on the direct measurement of the heat of combustion of tripalmitin; but little error will be involved in assuming it to be equal to the sum of the heats of combustion of 1 mol of glycerol and 3 mols of palmitic acid. The value then is 7,537,000 calories, minus 3000 calories, the heat of esterification.

$$\therefore \frac{\text{Free energy of combustion}}{\text{Heat of combustion}} = \frac{7,348,000}{7,534,000} = .98; \quad \frac{\text{Reversible work}}{\text{Total energy change}} = \frac{7,335,000}{7,521,000} = .98.$$

The theoretical maximum work obtainable from the oxidation of tripalmitin is therefore relative to their respective heats of combustion, only 3 per cent less than that of glucose.

The free energy changes in the conversion of tripalmitin to glucose under physiological conditions may be considered in three stages: (1) the hydrolysis of tripalmitin, (2) the conversion of glycerol to glucose, (3) the conversion of tripalmitin to glucose.

The hydrolysis may be taken to incur a free energy change of - 2400 calories.

*Conversion of Glycerol to Glucose under Physiological Conditions:*

$$\Delta F_{298} \text{ glycerol} = -115,700 \text{ calories.}$$

$$\Delta H_{298} \text{ glycerol} = -159,300 \text{ calories.}$$

$$\therefore \Delta F_{310} \text{ glycerol} = -113,700 \text{ calories.}$$

Glycerol exists in the blood in a minute concentration. In order to assign some figure for the free energy of dilution we shall assume that in the liver, where the conversion may be said to occur, its concentration is of the order of magnitude of a mol fraction of  $10^{-4}$ , so that the free energy of dilution is approximately 5000 calories.

$$\therefore -\Delta F_{310} (\text{mol fraction } 10^{-4}) = -118,700 \text{ calories.}$$

$\therefore 2C_3H_8O_3$  (mol fraction  $10^{-4}$ ) +  $O_2$  (100 mm. Hg)  $\longrightarrow$   $C_6H_{12}O_6$  (mol fraction .00011) +  $2H_2O$ ;  $-\Delta F = 103,400$  calories = 51,700 calories per mol of glycerol.

The pressure-volume product change is approximately 600 calories, and is negligible.

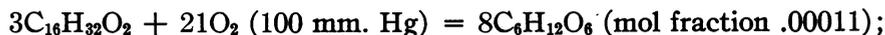
*Conversion of Palmitic Acid to Glucose under Physiological Conditions:*

$$\Delta F_{298} \text{ palmitic acid} = -93,000 \text{ calories.}$$

$$\Delta H_{298} \text{ palmitic acid} = -221,000 \text{ calories.}$$

$$\therefore \Delta F_{310} \text{ palmitic acid} = -88,000 \text{ calories.}$$

Therefore, under physiological conditions, for the reaction:



$-\Delta F = 1,469,000$  calories; pressure-volume product change,  $\Delta(PV) = -13,000$  calories. The total change in work content in the conversion under physiological conditions of tripalmitin to the maximum possible amount of glucose is 1,505,000 calories. Therefore for tripalmitin,

$$\frac{\Delta W_R \text{ conversion}}{W_R \text{ oxidation}} = \frac{1,505,000}{7,335,000} = .21;$$

and

$$\frac{\Delta W_R \text{ conversion}}{\text{Total energy change in oxidation}} = \frac{1,505,000}{7,521,000} = .20$$

The conversion of tripalmitin to glucose involves the liberation of a large fraction of the energy of the fat. The reverse reaction, the formation of one gram mol of tripalmitin from  $8\frac{1}{2}$  gram mols of glucose, would incur a gain in the quantity of that energy which we have designated as reversible work, equivalent to the total energy of oxidation of approximately 2 gram mols of glucose. The reaction almost certainly does not take place in a reversible manner, and a better guess, it seems, would be that at least 4 gram mols of glucose would be required. The unused energy would escape as heat and in direct calorimetry would represent the specific dynamic action of this process.

A concise statement of the free energy relationship between carbohydrate and fat is obtained from the comparison of the free energy content per gram mol of carbon in glucose and in tripalmitin. Per gram mol of carbon the free energy content of glucose is  $-36,500$  calories; and of tripalmitin  $-2060$  calories. It is clear that any process by which carbohydrate is converted into fat in such a manner that all of the carbon of the one compound is re-constituted into the other involves a large gain in free energy which must be supplied by other processes. If the mechanism by which this energy is supplied is not a perfectly reversible one, a larger amount of energy will be produced than is used in the conversion of carbohydrate into fat; and the excess, lost as heat, will appear as specific dynamic action. Similarly the converse production of carbohydrate from fat is accompanied by a large decrease, i.e., liberation of free energy, which will appear, wholly or in part, as heat or work.

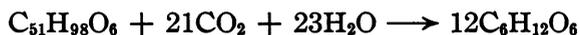
In plants, as the observations discussed above show, this released energy is not used for any other purpose, and escapes, presumably, as heat.

It follows from the small difference in the ratios of the reversible work obtainable to the total released in the combustion of glucose and of tripalmitin, that the explanation for any large differences observed experimentally in their respective efficiencies as fuels must be sought in their intermediary metabolism. If fat must be converted to glucose before it can serve as a fuel for muscular work, the large free energy change involved

in the conversion of fat into glucose renders it probable on theoretical grounds (i.e., the process probably is not perfectly reversible) that fat will be less efficient as a fuel. On the other hand, if the oxidation of fat *per se* can serve, as suggested by Rapport and Ralli, in the re-synthesis of lactic acid to glycogen, then there is no *a priori* reason for considering that fat will be less efficient than lactic acid. The plausibility of the suggestion of Rapport and Ralli is enhanced by the observations of Himwich, Koskoff and Nahum<sup>14</sup> that the liver possesses a great avidity for the lactic acid liberated in the blood-stream during exercise; and by the observation of Rapport and Ralli on dogs, confirmed by Best, Furusawa and Ridout on men, that the excess metabolism of mild exercise is that of the basal metabolism at that time.

If fat is first converted to glucose, as Best, Furusawa and Ridout maintain, then the free energy of conversion must be considered as lost for purposes of muscular work. It is interesting to compute from the calculations carried out above the minimum theoretical difference in efficiency of fat and carbohydrate under these circumstances. If the efficiency of the process of muscular contraction is taken first at 30 per cent, then 30 per cent of the energy of glucose derived from tripalmitin would be used, which corresponds to 23.1 per cent of the heat of combustion of the tripalmitin. If the muscular work is carried out at a 10 per cent efficiency then 7.7 per cent of the heat of combustion of tripalmitin is used. In each case fat is 77 per cent as efficient a fuel as carbohydrate. The experimental investigations into the difference in efficiency of fat and carbohydrate have in no case yielded figures as high as this, showing, if subsequent investigations do not yield a very different result, that fat is burned during muscular work as such; and that the efficiency of the processes by which this energy is used is not much less than is the case with glucose.

Krogh and Lindhard criticize the estimations of the energy changes in the conversion of fat to carbohydrate as follows: "We are not convinced of the validity of any of these summary methods of calculating the waste of energy incidental to the conversion of fat into sugar or any other substance. As a reason for suspicion against summary methods of calculating the loss of energy in question we would suggest the making up of 1 molecule of fat (tripalmitin) into 12 molecules of sugar by the addition of 21 molecules of CO<sub>2</sub> and 23 of H<sub>2</sub>O, which would result in a *gain* of energy amounting to about 18 per cent." It is interesting to compute the free energy change for this proposed hypothetical reaction.



From the data given above the free energy change,  $-\Delta F$  is  $-881,000$  calories. In other words, this reaction could not occur except at the cost of other reactions. As it is improbable that a reaction such as this would

proceed under ideal, reversible conditions, we may expect instead of a gain in energy of 18 per cent, a wastage as heat of approximately 1,000,000 calories for each molecule of tripalmitin converted to glucose.

The computations carried out above show that the cycle of storage of carbohydrate by conversion to fat and its later reconversion to carbohydrate preliminary to its ultimate oxidation, is one which is carried out at the cost of a considerable amount of energy to the organism. From studies of the degree of reversibility of reactions *in vivo* it may be possible to estimate how much of this expended energy, i.e., not contained in the newly formed molecules as chemical potential energy, is, from the nature of the reactions and substances involved, inevitably wasted as heat, and how much under suitable conditions can be converted into work.

*Summary*—1. The theoretical maximum amount of work obtainable from the oxidation under physiological conditions of glucose, and of tripalmitin has been computed from the standard free energies and heats of combustion of these compounds.

2. It has been shown that the theoretical difference in efficiency, i.e., the ratio of the theoretical maximum work obtainable to the total energy change, is little different for glucose and for tripalmitin.

3. The process of conversion of glucose into tripalmitin probably exerts a considerable "specific dynamic action" on metabolism.

4. From the fact that the conversion of tripalmitin to glucose involves a release of energy approximately equivalent to 20 per cent of the theoretical maximum work available from the oxidation of tripalmitin, and the observation that the difference in efficiency of fat as a fuel for muscular work, as compared with carbohydrate, is much less than 20 per cent, it follows either that fat is burned as such in the provision of energy for muscular work, or that the energy released in the hypothetical conversion of fat to carbohydrate is not dissipated as heat, but is used for work; and the efficiency of utilization of this energy is little different from that in the consumption of carbohydrate.

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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<sup>1</sup> 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.