MISLEADING STATISTICS

Present statistics, resting on far too slight a basis, indicate the risk to life and limb in California to be small—ridiculously small, less than the risk from common trivial diseases. But this is not a true picture. It is due to the past occurrence of the small number of greater shocks at fortunate times of day. Had the Long Beach earthquake, or that at Santa Barbara, for example, to say nothing of the San Francisco shock, occurred at unfavorable hours the statistical story would be a very different one. Energetic shocks will not always continue to occur at most favorable times of day. Some time one will happen when people are in the streets, or in theaters, churches, schools, etc. Once again the answer is the same. If all buildings are well built the risk will be small. Even panic will be reduced. If bad or unsuitable construction is general disaster or catastrophe will result. The moral is—design and build well on good ground, and in case of doubt insure. There is no other way to security.

To conclude—necessarily the greater part of this article deals with the risk that there is, its geographic spread over the region, and what can be done to lessen it. It is very desirable to fix the attention of residents upon the actual situation and to persuade them to courses of procedure which will ensure greater and greater safety. On the other hand, as stated in the beginning, the risk from earthquake occurrence in the California region, though more general and widespread than most residents realize, is nevertheless much smaller than most non-residents and some local people commonly think—far less than the risk in many other parts of the country from hurricanes, floods, tornadoes and other natural causes of disaster. In justice to California and neighboring territory emphasis must be placed upon these facts. It would be unfair to the region if efforts to secure in it safe building and constructional procedure should be construed as a warning of danger of great magnitude constantly impending at all places. While no one can foretell the future of earthquake occurrence in any practical way, the historical record since its beginning in 1769 gives no warrant for such alarm or serious apprehension. All that is warranted is recognition that earthquakes will continue to occur in the future as they have occurred in the past and that safety from the shaking requires good judgment in the selection of sites and the adoption of suitable resistant methods of construction.

THE ROLE OF AEROBIC PHOSPHORYLATION IN THE PASTEUR EFFECT

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A DECREASE in rate of carbohydrate utilization upon admission of oxygen is characteristic of many tissues. The various mechanisms which have been proposed for this Pasteur effect have been adequately reviewed by Burk.[1] It is the purpose of this note to call attention to a possible mechanism which does not appear to have been specifically mentioned elsewhere.

This mechanism is, in short, the following: If both aerobic and anaerobic carbohydrate breakdown are necessarily phosphorylative processes, inorganic phosphate and a phosphate acceptor are essential reactants; in their absence neither glycolysis nor oxidation could proceed. The Pasteur effect could then be regarded as the cessation or reversal of glycolysis which takes place when concentrations of inorganic phosphate and phosphate acceptors become low because of the phosphorylative oxidations which occur in the presence of oxygen. The necessary conditions for the operation of this mechanism are:

(1) The glycolysis reactions must be readily reversible.

(2) Phosphorylation (esterification of inorganic phosphate) must be an essential step in both the glycolytic and the oxidative processes.

(3) The oxidative phosphorylation reactions must be capable of reducing the inorganic phosphate (and phosphate acceptor) concentration to a level lower than that attained at glycolytic equilibrium. That is, oxidative phosphorylation must be possible at inorganic phosphate concentrations too low to permit glycolytic phosphorylation.

(4) The number of molecules of phosphoric acid esterified when one molecule of carbohydrate is oxidized must be greater than the number esterified when one carbohydrate molecule is glycolized.

(5) The same reservoirs of phosphate ester, inorganic phosphate and phosphate acceptor must be available to both the glycolytic and the oxidative enzyme systems.

An adequate discussion of the likelihood that these conditions are actually fulfilled in isolated muscle can not be given here. Each point can be given only the briefest consideration.

(1) The glycolysis reaction may be summarized by the following equation:

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[1] D. Burk, *Cold Spring Harbor Symposia on Quantitative Biology,* 7: 420, 1939.

$$\text{Glycogen} + 3\ H_3PO_4 + 3\ \text{creatine} \rightleftarrows 2\ \text{lactic acid} + 3\ \text{phosphocreatine}^{*}$$

(The participation of hydrogen ions is neglected for simplicity, although their inclusion would strengthen the argument.) The reactions summarized by the above equation, like any series of enzymatically catalized reactions, must necessarily be reversible. Whether appreciable reversal can take place under physiological conditions depends upon the position of the equilibrium point. That the equilibrium falls, in muscle glycolysis, well within the physiological range of reactant concentrations is elegantly illustrated by such data as those of Lundsgaard,[2] which show that after muscular work, glycolysis proceeds only to a definite equilibrium point. High concentrations of lactate occur only in the presence of high concentrations of creatine and inorganic phosphate (and low concentrations of phosphocreatine). High phosphocreatine concentrations and low phosphate concentrations permit the formation of only a limited amount of lactic acid. Experimental demonstrations of the ready reversibility of a number of component reactions of the glycolytic process have been given by Cori and Cori,[3] Ohlmeyer,[4] Meyerhof *et al.*,[5] and others.

(2) Phosphorylation has long been recognized as a necessary component part of the glycolysis process. It has also been known that aerobic muscle recovery involves phosphorylation. Thus, Meyerhof and Nachmannsohn[6] showed in 1930 that the oxygen uptake which resulted when oxygen was admitted to fatigued muscle brought about an amount of phosphocreatine resynthesis which was proportional to the amount of oxygen used. The mechanism of this phosphorylation is stil unknown. Kalckar[7] and Colowick, Welch, and Cori[8, 9] have shown phosphorylations to be involved in biological oxidative processes. While it has not been shown that phosphorylation is an absolutely essential step in these oxidations, such an assumption at least does not appear too difficult.

(3) The fact that aerobic phosphorylations are able[6] to restore muscle phosphocreatine concentration to the resting level (with corresponding depletion of inorganic phosphate and creatine), while glycolytic phosphorylation stops far short of this achievement, seems sufficient evidence that oxidative phosphorylation is capable of operating at lower inorganic phosphate levels than is glycolytic phosphorylation.

(4) The number of molecules of inorganic phosphate esterified when one molecule of carbohydrate is completely oxidized has not as yet been accurately determined. Meyerhof and Nachmannsohn[6] concluded that the number is at least 24 (4 to 5 molecules of phosphocreatine synthesized for each O_2 molecule used). There are, however, a number of reasons for believing that this figure may be too high. Colowick, Welch, and Cori[9] recently obtained roughly two molecules of phosphate ester per molecule of O_2 used in pyruvate oxidation. Whatever the true figure may be, there seems to be little doubt that the number of aerobic phosphorylations per sugar molecule far exceeds the number of anaerobic phosphorylations (3 for glycogen, 2 for glucose).

(5) The availability of the same phosphate reservoir in muscle to both aerobic and anaerobic systems seems to be clearly demonstrated by the fact that either aerobic or anaerobic phosphocreatine resynthesis is possible.

On the basis of the above assumptions, the reactions taking place in isolated muscle could be expressed by the diagram below.

$$\begin{tikzcd}
\text{(1)} & 3\ H_3PO_4 + 3\ \text{creatine} + \text{glycogen} \arrow[r, shift left] \arrow[d, shift left] & 2\ \text{lactic acid} + 3\ \text{phosphocreatine} \arrow[l, shift left] \arrow[d, shift left] \\
\text{(2)} & H_3PO_4 + \text{creatine} \arrow[u, shift left] \arrow[d, shift left] & \text{phosphocreatine} \arrow[l, "\text{(muscular or other metabolic work)}"'] \arrow[u, shift left] \arrow[d, shift left] \\
\text{(3)} & x\ H_3PO_4 + x\ \text{creatine} + \text{glycogen} + 6\ O_2 \arrow[u, shift left] \arrow[r, shift left] & 6\ CO_2 + 5\ H_2O + x\ \text{phosphocreatine} \arrow[l, shift left] \arrow[u, shift left]
\end{tikzcd}$$

When a resting isolated muscle is stimulated, work is done at the expense of energy of phosphorylation (reaction 2). Anaerobic restitution (reaction 1) immediately sets in, and proceeds rapidly toward the right until equilibrium is reached. At equilibrium, very considerable concentrations of inorganic phosphate and creatine still remain. If oxygen is now admitted, aerobic restitution (reaction 3) begins.

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* In the present note the simplifying assumption will be made that phosphocreatine, the chief esterified phosphorus reservoir of muscle, is the only reservoir; the intermediation of such compounds as adenosinetriphosphate will be neglected. Since the various phosphate esters are in equilibrium with one another, this assumption is permissible.

[2] E. Lundsgaard, *Biochem. Z.*, 233: 322, 1931.

[3] G. T. Cori and C. F. Cori, *Jour. Biol. Chem.*, 135: 733, 1940.

[4] P. Ohlmeyer, *Biochem. Z.*, 283: 114, 1935.

[5] O. Meyerhof, P. Ohlmeyer und W. Möhle, *Biochem. Z.*, 297: 113, 1938.

[6] O. Meyerhof and D. Nachmannsohn, *Biochem. Z.*, 222: 1, 1930.

[7] H. Kalckar, *Enzymologia*, 6: 209, 1939.

[8] S. P. Colowick, M. S. Welch and C. F. Cori, *Jour. Biol. Chem.*, 133: 359, 1940.

[9] S. P. Colowick, M. S. Welch and C. F. Cori, *Jour. Biol. Chem.*, 133: 641, 1940.

The resulting reduction in inorganic phosphate and creatine and increase in phosphocreatine displaces the equilibrium of reaction 1 toward the left. Glycogen resynthesis then begins, the inorganic phosphate thus produced being continuously reesterified by reaction 3. The mechanism of energy coupling is clear. A part of the energy of carbohydrate oxidation is converted to energy of phosphorylation by the aerobic phosphorylation mechanism. This energy of phosphorylation is then expended in resynthesizing glycogen from lactic acid.

In a steady state of rest or low work output, under aerobic conditions, glycolysis would be regulated by the fact that the aerobic phosphorylations can proceed at a lower concentration of inorganic phosphate than is compatible with an appreciable glycolysis rate. Furthermore, the rate of carbohydrate oxidation will be limited by the available concentration of inorganic phosphate. It would thus necessarily follow that oxidation is slow in the resting state because of the lack of the inorganic phosphate which is essential to the phosphorylative oxidation process. Only the liberation of inorganic phosphate concomitant with metabolic work would permit acceleration of carbohydrate oxidation. When the rate of inorganic phosphate liberation exceeds the rate of oxidative phosphorylation, the resulting accumulation of phosphate will accelerate glycolysis.

In view of the foregoing, the mechanism of the Pasteur effect in muscle and other tissues is readily outlined. Since oxidative phosphorylation is more energetic (*i.e.*, capable of attaining a higher phosphocreatine-creatine ratio) than glycolytic phosphorylation, the admission of oxygen to muscle rapidly reduces the level of inorganic phosphate and raises the phosphocreatine-creatine ratio until a point is reached where glycolysis must begin to reverse. Since the number of molecules of phosphoric acid esterified per molecule of carbohydrate consumed is much larger in oxidation than in glycolysis, a much lower rate of carbohydrate disappearance suffices to maintain a high phosphorylation level in the face of the energy demands for muscular work or other energy-consuming reactions. One measure of the Pasteur effect is the number of carbohydrate molecules protected from glycolysis per carbohydrate molecule oxidized. This quotient should be equal to the ratio of the number of molecules of phosphoric acid esterified when a carbohydrate molecule is oxidized to the number esterified when a carbohydrate molecule is glycolized.

When yeast grows anaerobically its sole source of energy is, as far as present knowledge goes, the two molecules of phosphate ester which are produced when one molecule of glucose is converted into ethyl alcohol and carbon dioxide. In other words, the yeast cell seems able to utilize energy of phosphorylation for every energy requirement of its metabolism. It is only reasonable to suppose that aerobically, the energy of phosphorylation used by the cell is supplied by the phosphorylations accompanying aerobic oxidation. If the respiratory mechanism of yeast is similar to that of animal tissue, it may be assumed that the number of aerobic phosphorylations is sufficiently large to account for the decreased fermentation observed[10] for yeast under aerobic conditions.

The Pasteur effect in yeast, as in muscle, would thus be interpreted as following from the fact that, aerobically, a relatively low rate of sugar utilization suffices to reesterify phosphate as rapidly as it is liberated by energy-consuming metabolic reactions.

Since the foregoing was submitted, the paper of Colowick *et al.* (*Jour. Biol. Chem.*, 137, 343, 1941) has appeared, in which it is concluded that at least 10 atoms of phosphate are esterified per glucose molecule oxidized. This is supporting evidence for point (4) above. Moreover, Cori (Biological Federation Annual Meeting, Chicago, April, 1941) has announced the experimental reversal of the conversion of glucose-1-phosphate into glucose-6-phosphate (point (1) above), and has independently reached the conclusion that energy of aerobic phosphorylation is utilized for carbohydrate resynthesis. Once this conclusion is reached, it becomes difficult to escape consideration of the interpretation of the Pasteur effect outlined above.

OBITUARY

GEORGE ELLETT COGHILL

GEORGE ELLETT COGHILL belonged to that small and select group of scientific workers who at the beginning of a fruitful career formulate a specific program of research with a clearly defined objective and thereafter devote themselves consistently and unfalteringly to intensive investigation of the chosen theme. In his case the problem has so wide implications and the results of the inquiry are of so great interest in fields as far apart as comparative embryology and human motivation that it may safely be said that his work is one of the major American contributions to fundamental biology.

After completing the classical course at Brown University and a year of study in a conservative theological seminary, he found further effort in this direction unsatisfying. In perplexity and mental agitation he retired to the open spaces of the Southwest, where he spent five months of vagrant wandering in northern

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[10] O. Meyerhof, *Biochem. Z.*, 162: 43, 1925.