QUOTATIONS

THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE

NEARLY a quarter of a century ago, on January 19, 1903, a small group of scientific investigators in New York met at the call of Professor Graham Lusk and the late Dr. S. J. Meltzer to consider the organization of active workers in experimental biology and medicine. This was the meeting that initiated the Society for Experimental Biology and Medicine under the presidency of Dr. Meltzer. The main object of the organization was the cultivation of the experimental method of investigation in the sciences of experimental biology and medicine. Membership in the group was limited to persons who had completed some meritorious independent experimental research in that field of study. The programs, from the start, consisted in brief presentations of the essential features of experimental investigations, and frequently of demonstrations of actual experiments. The membership soon outgrew its confinement to "Greater New York" and spread throughout the country. One reason for the success that has attended the development of this society lies perhaps in the significant circumstance that it has aimed to bring together workers in many fields, such as physiology, biochemistry, biology, bacteriology, pharmacology and experimental medicine, at a time when rapidly developing specialization had already begun to segregate investigators into small groups. The new society thus represented a wholesome reintegrating force and provided a stimulus for the discussion of "borderline" and interrelated problems. It has become an influence tending to overcome the danger of narrowness in the present-day outlook on the natural sciences with which medicine is so closely bound up. Another early object of the society was the development of high standards of presentation and scientific criticism. Incidentally, not a few significant discoveries have been announced for the first time at its meetings. As might be expected, this movement was bound to be followed by similar endeavors elsewhere. Many of them have resulted in the organization of branches of the society. To-day ten branches are located all the way from New York to Peking; eight more are at present under contemplation. The contributions, in the form of brief, concise summaries, are embodied in the *Proceedings of the Society for Experimental Biology and Medicine*, which is available through subscription. This journal deserves the active support of members of the medical profession, who are likely to find it stimulating and informative. Published without special endowment and maintained by the contributions of scientific workers, it needs and enlists the help of those who can benefit by its program.—*The Journal of the American Medical Association.*

MUSCLE, YEAST AND CANCER CELLS

IN his comparative study on the carbohydrates and gaseous metabolism of isolated muscle, at rest and at work, Otto Meyerhof[1,2] finally established beyond all doubt the doctrine that utilization of oxygen by muscle takes place normally, not during the act of contraction but rather during the periods of relaxation and rest immediately following. It was further shown that the energy required for contraction is directly derived from the breakdown of glycogen into lactic acid, whereas during the recovery period the oxidation involves a twofold action, the burning of one part of sugar, or its lactic acid equivalent, to carbon dioxide and water, while three to six times the amount of lactic acid is built back to glycogen. In other words, the immediate source of the energy for contraction is gotten by an anaerobic reaction, while the recovery from the contraction in its normal and most efficient manner is accomplished by an aerobic chain of reactions which culminates in the saving of a large part of the carbohydrate that had been split during the anaerobic phase or the contraction period. A further study revealed the fact that the processes found to hold for muscle in action also take place during periods of complete normal rest, although with much less intensity, so that the resting level of lactic acid concentration, from 0.015 to 0.03 per cent. of the muscle's weight, represents not only the residue of a previous recovery period but also the continuous balance sheet of a never-ceasing anoxidative carbohydrate splitting and an equally continuous oxidative removal of the split bodies by the twofold process of one part burned to carbon dioxide and water and from three to six parts built back to glycogen.

It is obvious that the anoxidative phase of these events is an expensive, prodigal one, but one apparently capable of yielding quickly and abundantly the free energy that is needed to enable the muscle cells to raise tension and to contract as quickly as they do; whereas the oxidative phase is one that not only frees the cells of the split products that accumulate during the anoxidative phase, clearing the decks for the next action, as it were, but does it in the manner of a salvager, rescuing at the same time as much of

1 Meyerhof, O., "Die Energie Umwandlungen im Muskel," *Arch. f. d. ges. Physiol.*, *182*: 232, 284 and *185*: 11, 1920; *188*: 114, and *191*: 125, 1921; *195*: 22, 1922; Meyerhof, Lohmann, u. Meier, "Synthese des Kohlehydrats im Muskel," *Biochem. Zeitschr.*, *157*: 459, 1925.

2 Hill, A. V., u. Meyerhof, O., "Über die Vorgänge bei der Muskelkontraktion," *Ergeb. d. Physiol.*, *22*: 299, 1923. (This joint review should be consulted for earlier literature and contributary evidence.)

the material as may be for future use. It will be noted that the breathing of the muscle cells is bound up with the aerobic phase only. Since the anaerobic splitting depends upon the action of ferments, this phase has been referred to as the phase of fermentative breakdown; the aerobic is often referred to as simply the respiratory phase.

With this cycle of alternating fermentative breakdown and respiratory recovery established for the skeletal muscle cell, the question arose as to whether the phenomena involved represented properties peculiar only to muscle or whether they were properties of other living cells as well.

Since the work of Pasteur the so-called anaerobic character of certain organisms has been known. Certain varieties of the yeast plant thrive amazingly well in the absence of air. Indeed the bottom wirts of the highly cultivated beer and vinous yeasts have been regarded as utilizing no oxygen whatever. The energy for growth in these cases is obviously derived from the anoxidative splitting of higher carbon compounds to carbon compounds of lesser complexity. On the other hand, yeasts such as the press-yeast, bakers' yeast and the wild yeasts continue to grow in the presence of oxygen, although their fermentation capacity at the same time is reduced. The problem of the part played by oxygen in the growth and fermentative action of yeast therefore had been recognized and studied not only by the more modern students of fermentation but also by Pasteur. But as Meyerhof points out, a definitive answer to the question could not have been obtained by the use of the cruder methods these workers had at their disposal; an employment of the more modern methods of micro-analysis such as were used in the study of muscle metabolism, however, ought to yield a less conflicting body of data. Such an application Meyerhof and his associates[3] have now made to the study of a number of various fermentation bacteria.

In these studies it is shown that even in the cases of the so-called anaerobic forms there is an actual utilization of oxygen, although small in amount, whenever this gas is admitted to the wirt in proper media. But however small or large the amount of oxygen utilization is, whether the form studied is of the "aerobic" press-yeast or bakers' yeast, or whether the form is of the "anaerobic" races, for example, the bottom wirt of beer and vinous yeasts, the same two processes of metabolism found for muscle cells are here also found. One process, the anoxidative, concerns itself with the fermentative breakdown of carbohydrate into ethyl alcohol, pyruvinic acid, acetaldehyde, lactic acid, acetic acid, etc., the other process, the oxidative, concerns itself with the complete oxidation of a part of the carbohydrate and the rescuing of another part from the fermentative breakdown. But more than this, when the ratio of the total number of molecules of split products removed to the number of molecules oxidized is determined for the various forms of bacteria, the oxidative quotient, as it is called, is shown to be of the same magnitudes as were found in the case of muscle, that is, between 3 and 6. In other words, for every molecule of carbohydrate oxidized to carbon dioxide and water 3 to 6 molecules are rescued from the fermentative breakdown. This, then, explains why the amount of fermentation products is less when oxygen is admitted to fermenting yeasts, and at the same time demonstrates that fermentation bacteria are only different from muscle in their metabolism chiefly in that the two major processes of metabolism have each undergone transformation (Umstimmung), the fermentative process having been greatly augmented, the oxidative salvaging process having been greatly depressed or partly lost.

As to how this transformation may have come about has been largely answered by both O. Warburg and O. Meyerhof and their associates in a series of independent studies. It was found by the latter[4] that so little as .0002 normal hydrocyanic acid present in the media of aerobic races of yeast reduced their oxidative power nearly 90 per cent., but their anoxidative fermentative power only as little as 10 per cent., and that by successive cultures these yeasts so transformed would produce permanent anaerobic strains of the plants. On the other hand, by treating anaerobic races with substances that stimulate their breathing capacity, permanent strains of aerobic plants could be cultivated. With increased utilization of oxygen increased salvage of carbohydrate was ensured and thus a corresponding decrease in the apparent fermentative splitting resulted.

Preceding and contemporary with these investigations on yeast two series of studies, one by O. Meyerhof and his coworkers,[5] the other by O. Warburg

[3] Meyerhof, O., "Über den Einfluss des Sauerstoffs auf die alkoholische Gärung der Hefe," *Biochem. Zeitschr.*, *162*: 43, 1925; and *Die Naturwissenschaften*, Jahrg. 14, p. 1175 (Dec.), 1926; also, Meyerhof und Finkle, "Über Berziehungen des Sauerstoffs zur bakterialen Milchsäuregärung," *Chem. d. Zelle u. Gewebe*, *12*: 157, 1926.

[4] Meyerhof, O., "Über den Einfluss des Sauerstoffs auf die alkoholische Gärung der Hefe," *Die Naturwissenschaften*, Jahrg. 13, p. 980 (Dec. 4), 1925; "Über den Zusammenhang der Spaltungsvorgänge mit der Atmung in der Zelle," *Ber. d. deutschen chem. Gesellsch.*, Jahrg. 58, p. 991, May, 1925.

[5] Meyerhof u. Lohmann, "Über Atmung und Kohlehydratsumsatz tierischer Gewebe," *Biochem. Zeitschr.*, *171*: 381, 421, 1926; R. Takane, *ibid.*, *171*: 403, 1926.

and his coworkers,[6] demonstrated that the two metabolic processes, anoxidative-fermentative-splitting and oxidative-salvaging of the split carbohydrate, were characteristics of animal tissue cells other than muscle, and especially of growing tissues, such as mucous membrane, skin and glandular tissues, and curiously enough also of retinal tissue. All embryonic tissue showed a high rate of both the fermentative splitting and the oxidative salvaging processes.

When pathologic cells, such as carcinoma cells, were studied by Warburg and his associates, the remarkable facts were revealed that these cells exhibited an excessively high rate of fermentation, causing a vastly greater amount of sugar to be split to lactic acid than normal cells do, but on the other hand a greatly diminished power of utilizing oxygen. Indeed it was found that cancer cells could live and continue to split sugar in a nutrient solution in which the pressure of the oxygen had been reduced to 1/100000 vol. per cent.; the cells could live and recover completely if asphyxiated thus as long as forty-eight hours. Longer asphyxiation, however, proved to be fatal. It was shown that they utilized oxygen in small amount independently of high tension of the gas. That is, the oxygen utilization as in normal cells appears to be determined only by the physiological capacity to breathe. The high rate at which tumor cells are capable of splitting dextrose to lactic acid is shown by the fact that *in vitro,* in an hour, they can produce an amount of lactic acid equal to 10 per cent. of their own weight. It is emphasized that in these quantitative studies the weight of tumor cells always refers to masses of pure tumor cells and not the usual mixtures of tumor and non-pathological cells that are removed by the excisions of the surgeon. Experiments testing the blood passing into and that passing out of a tumor in the living animal supports the results obtained *in vitro.* The blood from a tumor vein is found in rats to have two to three times as much lactic acid as that from an artery.

These physiological experiments with normal and pathologic animal cells when compared with those on muscle and yeast show, as the authors point out,[4,6] that there is a striking similarity in the physiological transformation that tissue cells must undergo to become tumor cells on the one hand, and that the aerobic yeasts must undergo to become the anaerobic type on the other. That normal embryonic cells may be transformed into cancer cells by injury *in vitro* (arsenic and other poisons) has been shown by Carrel and by A. Fischer. The cells so injured when injected into chickens developed sarcomas. The injury in these cases consisted first in damaging the respiratory function of the cells, but being embryonic cells they already had their fermentation capacity highly developed. When injected into normal animals the cells were able to thrive by continuing their anaerobic fermentation, their supply of sugar being furnished by the host. That they could utilize little oxygen was rather an advantage than a disadvantage to them. Warburg points out that these results confirm the view long held that cancers are the result of injury to normally growing cells and that the injurious agent may be of manifold variety.

It would seem that the next step in the field of cancer research is to find out if possible how the cancer cell can be transformed back to the normal cell; how it may most easily be trained to improve its breathing capacity, and if possible to reduce its fermentative capacity. If such retransformation can be effected metastases would be rendered much more unlikely, for during the early stages of fixation comparative oxygen-want and diminished ability to get energy from anaerobic fermentative carbohydrate splitting would more likely lead to the death of the cells. Surgical removal of parent tumors then would mean more certain the removal of all the tumor-producing tissue, and in cases of the inoperable kind one could still hope to check the growth.

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[6] Warburg, Posener, u. Negelein, "Über den Stoffwechsel der Carcinomzelle," *Biochem. Zeitschr., 152*: 309, 1924; Warburg, "Über den heutigen Stand des Carcinomproblems," *Die Naturwissenschaften,* Jahrg. 15, p. 1 (Jan. 7), 1927.

SPECIAL ARTICLES

GRAPHIC TREATMENT OF EULER'S EQUATIONS

I WAS struck, some time ago, with the ease with which the familiar Eulerian tensor ($A = \Sigma m(y^2 + z^2)$, etc., $D = \Sigma myz$, etc.)

$$\begin{matrix} A & -F & -E \\ -F & B & -D \\ -E & -D & C \end{matrix}$$

usually reached analytically, can be written down from the mere inspection of an orthogonal volume. The angular momentum (H), the kinetic energy (T) and the torque of centrifugal forces (C) of a rotating rigid body are all in question, the last two taking the vector form $2T = \mathrm{H.w}$ and $\mathrm{C} = \mathrm{H} \times \mathrm{w}$, w being the vector angular velocity.

H.—In Figure 1 let m be any molecule of the body rotating clockwise about the x, y, z axes and for convenience let the unit of time be infinitely small so that w may be infinitesimal. The figure shows the component angular velocities ω_x, ω_y, ω_z, the corresponding tangential velocities $\omega_x r'$, $\omega_y x$, $\omega_z x$ and the