Is Metabolic Acidosis a Common Factor in Many Degenerative Diseases?

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Abstract

The possible role of the Electron Transport System in energy production at cell level is discussed along with an indication of the adaptability of LDH to different metabolic needs. There is a working hypothesis suggesting the connection between metabolic acidosis, lowered energy production and the appearance of different degenerative diseases. Tissue minerals may serve as a screening tool for the assessment of nutritionally, socially or environmentally induced metabolic acidosis.

The investigation into cell respiration by Otto Warburg goes back 75 years. Until that time cancer cells were distinguished from normal cells by morphological differences only. A crucial discovery was made by Warburg and his co-workers; they established the first functional qualitative difference between normal and cancerous cells — a biochemical change which is significant in cellular energy production.

Let us examine this process more closely. A normally functioning mitochondrion produces energy in two phases: a) by breaking down one mole of six carbon glucose into two moles of three carbon pyruvate, and b) then entering the Krebs cycle to produce the final breakdown products, carbon dioxide and water.

The energy produced is stored in energy rich phosphate bonds through oxidative phosphorylation of adenosine diphosphate into adenosine triphosphate (ADP to ATP).

In step (a) the net production of energy rich phosphate bonds will be about eight and in step (b) the net production of energy rich phosphate bonds will be about thirty, a total of thirty-eight.

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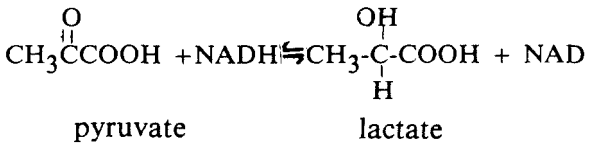
In glycolysis in the absence of oxygen, the Electron Transport System — ETS (which includes enzymes in which the co-enzyme part consists of molecules capable of providing an enol keto (quinol^quinone) structures, like tocopherols, ubiquinones, nicotinamide, ascorbic acid, and different dehydrogenases, as pointed out by Tamari and Rona*) will provide conditions in which dehydro-nicotinamide-adenine dinucleotide (NADH), the reduced form is reoxidized to NAD and the same cycle repeats itself again.

If for any reason the ETS stops fulfilling its role as in deficiency of a vitamin and/or mineral or the presence of toxic substances, then in order to maintain homeostasis in equilibrium, NADH will be oxidized by pyruvate in a reaction in which pyruvate will be reduced to lactate.



Lactate as the end product of glycolysis will provide approximately 20 percent of the expected total energy (8 phosphate bonds). Consequently, more glucose must undergo glycolysis to provide a given amount of energy under "anaerobic" as compared with "aerobic" conditions (Pasteur effect). Tissues that function under hypoxic circumstances tend to produce lactate .

So, lactate will be the end product of the glycolysis process if the ETS is inhibited from performing its function, either due to a deficiency state in different co-enzymes or trace elements, or because of the presence of toxic substances which are substituting or inhibiting the essential co-enzymes and/or trace elements.

The end result will express itself — as is pointed out by Goldblatt and Cameron[2] — in "oxygen" deficiency. The heart fibroblast tissue culture exposed to intermittent oxygen

deficiency for long periods, led to the production of transplantable cancer cells. In agreement with this experiment, when glycolysis cannot follow its normal course and continue into the Krebs cycle, the homeostatic process of survival switches the energy production to a more primitive level, where it is maintained by fermentation (lower energy and lactate production). According to Warburg, this metabolic change will occur if the exposure to a deficiency state or toxic environment continues for a long period of time .

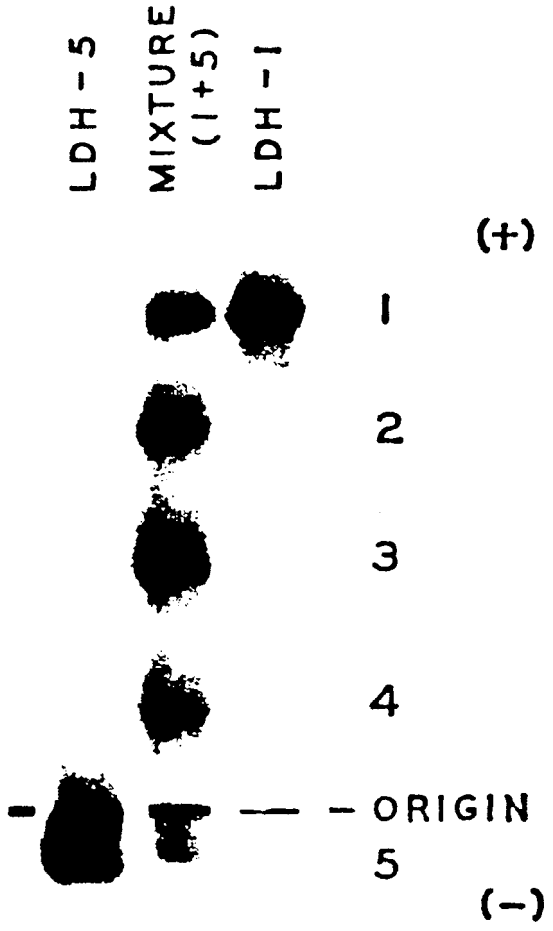


Figure 1

This photograph shows the LDH isozymes in each of three preparations after electrophoretic resolution in starch gel. On the right is LDH-1, on the left LDH-5, and in the middle are the isozymes resulting from a mixture of equal quantities of these two preparations. All five isozymes were generated in the mixture in the approximate ration of 1:4:6:4:1, the expected distribution after random reassociation of subunits. The total enzyme activity in the mixture was the sum of the activities of the single isozyme preparations. All three preparations were placed in *M* NaCl and frozen overnight before electrophoretic resolution.

At this point there is an important question to be asked: in cases where this described process can be detected, at what stage is it still reversible?

In the following, there is an attempt made to indicate this kind of possibility.

Over the years, enzymologists realized that the pure crystalline form of an enzyme may be substrate-specific, despite the difference in molecular forms'*. The most researched enzyme turned out to be lactate dehydrogenase (LDH). Under specific conditions it proved to be separated by electrophoresis into five isozymes, each of them having a particular migration pattern[5] characteristic of the organ of origin. In adult human heart and kidney the major isozymes are LDH-1, LDH-2, and LDH-3; whereas in adult human muscle and liver the dominant isozyme is LDH-5. Another type of pattern is exhibited by the spleen, LDH-3 being the predominant isozyme.

Apella et al.[6] studied the structure of the LDH isozymes and were able to separate them into four polypeptide chains of equal size, which could be separated into two elec-trophoretically distinct forms; A and B polypeptides derived from LDH-1 (AQB4) and LDH-5 (A_4B_0) were electrophoretically homogenous but containing different polypeptides. Markert[7] using a very simple and elegant technique, was able to prove that by mixing equal amounts of LDH-1 (polypeptide B) and LDH-5 (polypeptide A), all five isozymes appear on electrophoretic separation (Figure 1). The possible combination of four subunits (tetramers) of two polypeptides A and B are:

LDH-1	BBBB	A0B4
LDH-2	ABBB	A1B3
LDH-3	AABB	A2B2
LDH-4	AAAB	A3B1
LDH-5	AAAA	A4B0

Why should an enzyme exist in five forms, each of which can catalyze the same chemical reaction?

At present one can offer only a partial explanation which is based on a few but highly significant experimental findings. During the normal breakdown of glucose (glycolysis), the major fates of pyruvate are: (1) conversion to lactate — "anaerobic" glycolysis, and (2) conversion to carbon dioxide and water

— through the "Krebs cycle". In the case of skeletal muscle, energy is derived primarily from anaerobic glycolysis through the generation of ATP. NADH is formed during the production of ATP, and if NADH were not dehydrogenated (oxidized), glycolysis would cease. Since the major reaction for oxidizing NADH is the conversion of pyruvate to lactate", it is essential that skeletal muscle LDH be able to handle the large amount of pyruvate formed during vigorous muscular activity. In heart tissue, on the other hand, there is little need for anaerobic energy and most of the pyruvate enter the Krebs cycle. An appropriate type of LDH in the heart would be one that converts pyruvate to lactate at a slower rate.

The catalytic characteristics of the different isozymes have been measured in the presence of their normal substrates by several groups of investigators[8,9]; the major isozymes in the heart, containing predominantly B polypeptides are relatively slow in converting pyruvate to lactate , thereby permitting pyruvate metabolism to proceed via the Krebs cycle. By contrast, the muscle enzyme which contains mostly A polypeptides, converts pyruvate to lactate very quickly[15] enabling the muscle to function anaerobically. It is apparent that the catalytic properties of isozymes are suited to the *metabolic requirements* of their respective tissues.

One of the most revealing demonstrations of the functional significance of isozymes was obtained by Wilson et al.[10] during a survey of the LDH isozymes present in the breast muscle of birds. Birds like the pheasant, grouse and the domestic fowl, which fly only occasionally and in short bursts, have predominantly LDH-5. Their LDH isozyme patterns are similar to those observed in human skeletal muscle. During muscular activity, the lactate accumulates and with repeated activity muscle fatigue ensues.

In contrast, LDH-1 is the major isozyme in the breast muscle of the storm petrel and the hummingbird, birds which excel in their capacity for long and sustained flight. In the breast muscle of these birds, as in the human heart, it is imperative that lactate production be maintained in a relatively low range.

Rabinowitz and Dietz[11] recently published a study demonstrating the changes induced in the LDH isozyme pattern by reduced oxygen tension. It enhanced not only the LDH-5 fraction, but also caused morphological changes in cultured lymphocytes, and resulted in the appearance of precancerous cells.

Binette et al. confirmed that there is a shift of the LDH isozymes in experimental animals under hypoxia from LDH-1 (aerobic) to LDH-5 (anaerobic). Moreover, the reversibility of this trend after removal of the animals to room air is reported. These findings seem not only to confirm the claims made by Warburg that tissues under hypoxic conditions (oxidation inhibited by the presence of poisons or by deficiency of certain vitamins and/or trace elements) switch from normal oxidative phosphorylation via the Krebs cycle to anaerobic glycolysis resulting in lactate formation, but also hold out the possibility that the change is reversible. A critical question may be asked at this point. If this trend can be detected, *after how much time is this process reversible* after being induced by different factors?

Time seems to be of considerable importance due to the fact that when cancer cells are already formed, "cancer cells cannot regain normal respiration even in the course of many decades"[13]. If there was a method of following the metabolic process in which systemic lactic acid production could be monitored, the process might yet be stopped and reversed at the pre-cancerous stage.

There is a working hypothesis suggesting [1] that hypoxic conditions will result in lowering the intracellular pH level to a degree which is not compatible with normal cellular function.

This supposition is supported by studies 15-17 indicating the presence of an elevated serum lactate in different malignancies and other degenerative diseases (Table I). At the same time a very severe pH drop occurs in lactic acidosis .

In the case of lactic acidosis, the homeostatic mechanism might take over, attempting to neutralize the accumulated acid (lactic) via salt formation. If such a working hypothesis were correct, an intracellular increase of alkali minerals, for example calcium and magnesium, could be expected. If tissue deposition of calcium and/or magnesium may occur via the vascular system, as in the above hypothesis, then

TABLE I

ELEVATED BLOOD LACTATE LEVELS

DISEASE	LACTIC ACID mg/dl	REFERENCE
Malignant Neoplasm of Stomach	21.5 + /-5.7	15
Malignant Neoplasm of Small Intestine	21.5 + /-5.7	15
M.N. of Large Intestine	21.5 + /-5.7	15
M.N. of Bronchus and Lung	13.7 + /-3.6	15
M.N. of Breast	26.8 + /-4.0	15
M.N. of Testis	13.6 + /-2.8	15
Reticulum Cell Sarcoma	23.2 + A2.9	15
Hodgkins's Disease	23.2 + A2.9	15
Multiple Sclerosis	increased	16
Anxiety Neurosis	increased	17
NORMAL VALUES	11.7 + /-0.72	

TABLE II

ELEVATED SERUM CALCIUM LEVELS IN DEGENERATIVE DISEASES

DISEASE	REFERENCE
Malignant Neoplasm of Liver	18
M.N. of Pancreas*	19
M.N. of Bronchus and Lung*	20
M.N. of Breast*	20,24
M.N. of Bladder*	19
M.N. of Esophagus*	19
Multiple Myeloma*	21
Rheumatoid Arthritis	22
Osteoporosis	23
Sarcoidosis*	24

* Elevated serum CALCIUM without evidence of direct bone involvement.

elevated blood calcium may confirm this process. Data from Table II do indeed indicate an increased serum calcium in many degenerative diseases like malignant neoplasm of different organs and others, many of them without evidence of direct bone involvement *°~.

Monitoring of the tissue deposition of alkali minerals (for screening purposes) would require the usage of a tissue which can serve as a reliable indicator of intracellular ion levels and which is stable and easily accessible. As blood and urine do not fulfill these conditions the best choice we have is hair tissue^ . Hair tissue seems to be a very sensitive indicator of minute changes in tissue levels of alkali (and other) minerals. The "early detection" of this kind of tissue mineral build-up might serve as an indicator enabling necessary changes to be made in order to reverse this process.

The above hypothesis raises many questions as to the ways and means by which a nutritionally, environmentally, and socially induced degenerative process might be (a) detected, (b) halted, and (c) reversed.

It would be promising indeed, were the scientific/medical community to take up the challenge of investigating these unanswered questions, and by doing so make a great contribution in the prevention of the appearance of many degenerative diseases.

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