SOME HIGHLIGHTS OF THE EARLY PERIOD OF BIOENERGETICS

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The period from 1927 to 1939 marks the beginning of the modern development of bioenergetics. The principal discoveries during that period were the isolation of phosphocreatine, ATP and pyridine nucleotides and the elucidation of the intermediate steps of alcoholic and lactic fermentation. I shall try to say something about this preliminary period which ended with the recognition of the role of pyridine nucleotides in the oxidation-reduction reactions of fermentation and the role of triosephosphate oxidation in the regeneration of ATP.*

The Hexosephosphates

One might properly begin this discussion with a consideration of the phosphate compounds that have been isolated from muscle and that play a role in lactic fermentation. A list in chronological order is given in Table 1. Embden and Zimmerman isolated the same hexosemonophosphate and diphosphate esters from muscle that had previously been isolated from yeast by Harden and Young. This was the first indication that there might be similarities between alcoholic and lactic fermentation. At that time it was not known how these esters were formed, since ATP which is necessary for their formation from glucose had not been discovered and the reaction of glycogen with inorganic phosphate to form glucose-1-phosphate had not been described. In fact, Meyerhof and

Table 1

The isolation of phosphorus compounds involved in lactic acid fermentation in muscle.

Compound	Year	Author and reference number
Hexosediphosphate	1924	Embden and Zimmerman[1]
Hexosemonophosphate	1927	Embden and Zimmerman[2]
5′-adenylic acid	1927	Embden and Zimmerman[3]
Phosphocreatine	1927	Fiske and Subbarow[4]
Adenosinetriphosphate	1929	Fiske and Subbarow[5] Lohmann[6]
L-α-glycerophosphate	1933	Meyerhof and Kiessling[7]
Phosphoglyceric acid	1933	Embden, Deuticke and Kraft[8]
Phosphoenolpyruvic acid	1934	Lohmann and Meyerhof[9]
Dihydroxyacetonephosphate	1934	Meyerhof and Lohmann[10]
Glucose-1-phosphate	1936	Cori and Cori[11]
Diphosphopyridine nucleotide	1936	Warburg and Christian[12]
1,3-diphosphoglyceric acid	1939	Negelein and Brömel[13]

Lohmann repeatedly expressed the opinion that the isolated esters were not on the direct pathway from carbohydrate to lactate but were stabilization products of more labile forms. One of the principal reasons for this assumption was the observation that the addition of the isolated hexosemonophosphate or diphosphate

* The European laboratories chiefly associated with these investigations were those of Embden, Meyerhof, Parnas, v. Euler and Warburg.

to muscle extract or yeast maceration juice often resulted in slower fermentation than that observed with carbohydrate. The idea that these esters were not true intermediates persisted until 1936 and had a strong influence on contemporaries. For example, EGGLETON and EGGLETON[14] in their first paper on phosphagen suggested that the acid-labile substance which they had observed while analysing a muscle extract for inorganic phosphate might be the unstable "active" hexosemonophosphate postulated by MEYERHOF. Furthermore, when LIPMANN and LOHMANN[15] found that hexosediphosphate added to frog muscle extract was converted to an ester difficult to hydrolyse in acid (later shown to be phosphoglyceric acid), LOHMANN[16] cited this as evidence for the conversion to a stable form. Perhaps a quotation from a paper by MEYERHOF and KIESSLING[17], entitled "The main pathway of lactate formation in muscle," which appeared in 1935 will make clear what they had in mind (my translation) ... "The energy of splitting of ATP ... is not lost during phosphate transfer, but is preserved in the main in the synthesized product. In this way there would first be formed a sugar phosphate of higher energy content than the stable hexosephosphates, having the character of a radical. This is probably the decisive factor for the reactivity of the newly formed product. However, if during the lifetime of the radical no reaction takes place, ... the primary product is converted to the relatively stable hexosephosphates." Shortly before this statement appeared the following phosphate transfer reactions had been described—between ATP and creatine by LOHMANN[18], between phosphoenolpyruvic acid and AMP by PARNAS[19], between ATP and glucose by EULER and ADLER[20], and between ATP and hexosemonophosphate by DISCHE.[21] In other words, the role of ATP as an energy transfer system had been clearly recognized by that time. What bothered MEYERHOF was that a strict stoichiometry of these reactions had not been demonstrated, especially with glycogen as the phosphate acceptor and ATP as the phosphate donor.

EMBDEN, on the other hand, assumed that the phosphate esters he had isolated were on the direct pathway to lactate and were the immediate precursors of lactate during muscular contraction. In order to emphasize this fact he coined the name "lactacidogen" which he applied first to hexosediphosphate and later —when it was shown that the diphosphate does not occur in untreated muscle*—to hexosemonophosphate. Embden and collaborators measured the lactacidogen content of muscle under a variety of conditions, but their original method of determination was inadequate. It consisted in incubating minced muscle in 1% bicarbonate solution for 2 hours at 37° and measuring the inorganic phosphate before and after incubation. The difference was assumed to represent hexosemonophosphate. It was shown by LOHMANN[16] by means of hydrolysis curves in 1 N HCl at 100° that most of the inorganic phosphate liberated during this incubation came from a compound which—unlike hexosemonophosphate—was easily hydrolyzable and which he first identified as inorganic pyrophosphate.**

Table 2

Autolysis of phosphate compounds of muscle.

Minced rat muscle was incubated for 2 hrs. at 37° in 1 per cent sodium bicarbonate solution. A trichloroacetic acid filtrate was analyzed for total P, inorganic plus phosphocreatine P, and ATP (calculated from 7 minute hydrolysis value in N HCl at 100°). Hexosemonophosphate was determined by a direct method. Values are given in mg P per 100 gm muscle. Data recalculated from Cori and Cori.[23]

	Before incubation	After incubation
Total P	200	200
Inorganic + phosphocreatine P	111	177
Residual organic P	89	23
Adenosinetriphosphate P	61	3
Hexosemonophosphate P	19	14
Undetermined P	9	6

* EMBDEN and ZIMMERMAN[1] isolated hexosediphosphate from a press juice of muscle incubated with fluoride. Fluoride inhibition discovered by Embden played a great role in the elucidation of the glycolytic pathway.

** When DAVENPORT and SACHS[22] showed that a trichloroacetic acid extract of muscle did not give a color reaction for free inorganic pyrophosphate, LOHMANN[6] recognized that it occurred in combination with adenylic acid, a compound which had previously been isolated from muscle by EMBDEN and ZIMMERMAN[3]. In both isolation procedures ATP had been exposed to an alkaline solution of barium or calcium salts which results in the splitting of ATP to AMP and inorganic pyrophosphate. Independently and nearly simultaneously FISKE and SUBBAROW[5] reported the isolation and identification of adenosinetriphosphate from muscle. The great rapidity of publication of papers in Germany during that period offered a great advantage in questions of priority.

Table 3

Effect of stimulation on phosphate distribution in muscle

Frog gastrocnemius (Eggleton, Lohmann) and rat gastrocnemius (Cori) were stimulated tetanically for about 15 seconds. Hydrolysis was in 1 N NCl at 100°. Values are given in mg P per 100 gm muscle

	Eggelton and Eggleton[27]		Lohmann[16]		Cori and Cori[28]	
	Resting	Stimulated	Resting	Stimulated	Resting	Stimulated
Inorganic P	23	45				
Phosphocreatine P	70	41				
Sum	93	86	94	84	98	89
7′ hydrolysis P			126	112	137	125
180′ hydrolysis P			141	126	160*	150*
Total P	169	168	157	159	171	172
Hexosemonophosphate P					7	22

*240 min. hydrolysis

The lactacidogen story is thus seen to be intimately connected with the discovery of ATP.

At that time we had developed a method for the direct determination of hexosemonophosphate which was based on fractionation of barium salts and determination of the ester by two independent methods, one based on reducing power and the other on phosphate content.[23]

An experiment using this method is shown in Table 2. It can be seen that the increase in inorganic P during incubation, what EMBDEN called lactacidogen, is derived mostly from ATP as LOHMANN had found and very little, actually less than 10 percent, comes from hexosemonophosphate.

The lactacidogen controversy continued until 1932. Using a more specific method for the determination of hexosemonophosphate[24], Embden and collaborators[25] reasserted that a muscle fixed at the height of contraction showed a decrease of hexosemonophosphate and an increase in inorganic phosphate and lactate. A muscle plunged into liquid air contracts before it is frozen through. EMBDEN and his collaborators called this the contracting muscle because they thought that they were fixing a muscle at the height of a single contraction, whereas a muscle which had been previously fatigued by a short tetanus so it would not contract in liquid air they called the resting muscle. Actually it is the other way around, because the changes produced by the preceding stimulation were not wiped out when the muscle was fixed in liquid air. Furthermore, as LOHMANN[16] showed with different methods of fixation of muscle, freezing in liquid air *per se* did not produce significant changes in hexosemonophosphate.*

In Table 3 are shown experiments by the EGGLETONS and by LOHMANN on frog gastrocnemius. Both authors designated the muscle fixed directly in liquid air as resting muscle. On this basis, isometric tetanic contraction produces a marked decrease in phosphagen and a somewhat smaller increase in inorganic phosphate. The difference of about 10 mg P per 100 gm muscle represents esterification, and, as LOHMANN's data show, a substance difficult to hydrolyse in N HCl at 100° accumulates (cf. Total P—180 min. hydrolysis P of 16 for resting and 33 for stimulated muscle.) That this substance is largely hexosemonophosphate is shown by the data in Table 3 for stimulated rat muscle. The phosphate changes in Table 3 are quite similar to those reported by EMBDEN, but the interpretation given them by EMBDEN could not be sustained, although there can be little doubt that hexosemonophosphate is an intermediate of lactate formation.**

Epinephrine, in contrast to stimulation,

* Fixation of muscle so as to maintain the *status quo* has long been a problem, first emphasized by FLETCHER and HOPKINS[26] who recommended crushing the muscle in ice-cold alcohol.

** The lactacidogen controversy cannot diminish in any way the importance of Embden as a scientist. It is told here for two reasons. One is that it illustrates a type of subconscious psychological error that even the best scientists can be subject to. The other is that these prolonged and often intense controversies – which have now largely disappeared – served some useful purpose by stimulating new work.

Table 4

Effect of epinephrine on phosphate distribution in rat muscle and in isolated frog muscle.

Epinephrine (0.02 mg) was injected subcutaneously in rats 60 minutes before removal of gastrocnemius. Frog sartorius was incubated anaerobically for 60 minutes at 20° in 3×10^{-4} M iodoacetate (IAA) without and with 1×10^{-5} M epinephrine. Analyses were carried out as in Table 2, except that true inorganic P was determined after precipitation with magnesia mixture.
Values are given in mg P per 100 gm muscle.

	Rats (Cori and Cori[29])		Frogs (Cori and Cori[30])	
	Control	Epinephrine	IAA	IAA + epinephrine
Inorganic P	28	23	29	22
Phosphocreatine P	59	59	42	38
Adenosine-triphosphate P	66	69	39	43
Hexosemono-phosphate P	9	17	11	19

did not produce any change in phosphocreatine or ATP, but did produce a decrease in inorganic P and a corresponding increase in hexosemonophosphate (Table 4). Since the same changes were observed in an iodoacetate-poisoned muscle where no resynthesis of ATP could occur, it was concluded that hexosemonophosphate was formed by a reaction between glycogen and inorganic phosphate. Subsequent work which will not be detailed here showed this supposition to be correct.

With the knowledge gained about the enzymatic reactions involved in the formation of glucose-6-phosphate—from glycogen plus inorganic phosphate via glucose-1-phosphate or from glucose plus ATP—the idea that glucose-6-phosphate is a stabilization product of a reactive intermediate was given up. These two reactions initiate the phosphate cycle in lactic and alcoholic fermentation, respectively.

The Phosphate Cycle

Another concept which played a great role in the development of bioenergetics was the idea of a phosphate cycle as the driving force of lactic fermentation. In order to trace the development of this idea, we have to consider the early work with phosphocreatine and ATP, the ammonia formation in muscle studied extensively by PARNAS and his school[31], the alactic contraction of iodoacetate-poisoned muscle discovered by LUNDSGAARD[32], and the impact of a new glycolytic scheme proposed by EMBDEN, DEUTICKE, and KRAFT.[8]

The EGGLETONS[33] as well as FISKE and SUBBAROW[34] had observed the splitting of phosphocreatine during muscular contraction and its restitution during aerobic recovery. Calorimetric measurements in MEYERHOF's laboratory[35] had established that the hydrolysis of phosphocreatine yielded about 12,000 calories per mole.* When it was found by NACHMANSOHN[36] that a partial resynthesis of phosphocreatine could also occur under anaerobic conditions, for about 20 seconds following a 5 second tetanus, the question arose what was the energy source for this resynthesis. The answer brought to an end another of these long drawn out controversies. The EMBDEN School[38] had maintained that a considerable part of the lactate formed in a tetanus occurred after the relaxation but this was denied by MEYERHOF who attributed EMBDEN's result to excessive stimulation. However, LEHNARTZ[39] showed that even without overstimulation some lactate formation occurred after contraction and this was finally conceded by MEYERHOF[40] and used as an explanation for the anaerobic resynthesis of phosphocreatine and for the anaerobic restitution heat of HARTREE and HILL.[41]

A dramatic change in muscle physiology occurred when LUNDSGAARD[32] discovered the alactic contraction of iodoacetate-poisoned muscle. A. V. HILL[42] had established that the ratio, T·L/H (tension × length/initial heat) remained constant in a series of anaerobic isometric contractions and a similar relationship was shown by MEYERHOF and SCHULZ[40] for T·L/M, where M stands for lactic acid formation.** LUNDSGAARD[43]

* Thermodynamic considerations played a great role in the thinking of the MEYERHOF circle. This derived in part from the close scientific contact between A. V. HILL and MEYERHOF. The only book MEYERHOF ever published is dedicated to A. V. HILL as the "renewer of the thermodynamics of muscle". One of the main aims of this historically important book[37] was to account for the heat measurements of A. V. HILL on intact muscle during contraction in terms of individual chemical reactions.

** Previous measurements of TL/M for tetani were incorrect because the lactate production after contraction was not included. In the above paper new measurements are reported where this has been done.

now showed that in an iodoacetate-poisoned muscle, where no anaerobic resynthesis of phosphocreatine could occur, the ratio T·L/P (phosphocreatine breakdown) was constant over a wide range of tensions in contrast to what had been observed in unpoisoned muscle. Furthermore, the phosphocreatine splitting was energetically equivalent to lactate formation in an unpoisoned muscle. From these and other experiments LUNDSGAARD[43] concluded that the contraction energy is supplied directly and exclusively by the phosphocreatine breakdown while the energy from lactate formation is used for the resynthesis of phosphocreatine. However, this left ATP out of consideration, which according to measurements of MEYERHOF and LOHMANN[44] yields about as much heat on hydrolysis as phosphocreatine.

The discovery of the role of ATP and of other dialyzable and heat-stable cofactors in alcoholic and lactic fermentation has a rather long and checkered history and will be given here only in outline. It begins with the observation of HARDEN and YOUNG[45] in 1906 that there are two components necessary for glucose fermentation in yeast juice, one consisting of protein and the other of ultrafiltrable, heat-stable compounds, organic in nature, but of unknown composition. Some 12 years later MEYERHOF[46] showed that the glycolytic enzyme system of muscle also needed a "coferment" and that the boiled juices from yeast and from muscle could replace each other as a source of coferment. Earlier experiments by HARDEN and YOUNG on the purification of the coferment of yeast were continued after 1923 by EULER and MYRBÄCK who referred to it as "cozymase." Up to 1933 (see MYRBÄCK[47]), they assumed that the cozymase was an adenylic acid of special composition, not identical with adenylic acid from yeast nucleic acid but similar to that of muscle. The molecular weight was given as 350. The lack of pure preparations of cozymase caused considerable confusion for a while. LOHMANN[48] showed that when frog muscle extract was aged at 20° it lost the capacity to form lactic acid from added glycogen, but this capacity could be completely restored by adding back ATP and if the extract had also been dialyzed, by adding back Mg^{++} ions. The need for inorganic phosphate had been established previously. LOHMANN[48] referred to these 3 components as the coferment system of lactate formation and concluded that it was different from EULER's cozymase, although cozymase (probably contaminated with free AMP) could replace the coferment system under certain conditions. Further studies by LOHMANN[49] showed that when ATP was added to an aged muscle extract in which phosphocreatine had largely been broken down there was a resynthesis of phosphocreatine. This easily reversible 2-step reaction,

$$\text{ATP (or ADP)} + \text{creatine} \rightleftarrows \text{ADP (or AMP)} + \text{phosphocreatine}$$

became know as the LOHMANN reaction. Since phosphocreatine was not broken down in the absence of adenine nucleotides, it became clear that the splitting of ATP occurred first during muscular contraction followed immediately by the resynthesis of ATP from phosphocreatine through the LOHMANN reaction, thus masking the fact that the increase in inorganic P previously observed came not from phosphocreatine but from ATP. This led eventually to the famous challenge of A. V. HILL[50] to the biochemists to demonstrate this in a muscle fixed at the height of a single contraction.

Another key reaction of the phosphate cycle was discovered by PARNAS, but before describing these experiments it will be helpful to consider the new glycolytic scheme published by EMBDEN, DEUTICKE and KRAFT[8] in 1933.* The main features of this scheme were a splitting of the 6 carbon chain of fructosediphosphate into one molecule each of dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, a dismutation between the two triosephosphates, yielding glycerophosphate and phosphoglyceric acid, a splitting of the latter to pyruvate and an oxidoreduction between glycerophosphate and pyruvate, yielding glyceraldehyde phosphate and lactate.

PARNAS and collaborators used the inhibition of ammonia formation from adenylic acid* as a criterion

* EMBDEN died shortly after the publication of this paper which gave a tremendous impetus for new work. Within a remarkably short time some of the intermediary reactions of glycolysis were elucidated, mainly by MEYERHOF and his collaborators. However, complete clarification did not arrive until the discovery of the pyridine nucleotides by WARBURG.[12]

* EMBDEN and ZIMMERMANN[3] found that the 5′-AMP which they had isolated from muscle formed inosinic acid and ammonia when added to minced muscle, thus accounting for the inosinic acid isolated from muscle by Liebig in 1847. Gerhard Schmidt[51] investigated the specificity of the deamination process with purified muscle adenylic deaminase. ATP and ADP in contrast to AMP are not attacked by Schmidt's deaminase.

of the integrity of the ATP system. They found[19] that in a minced muscle poisoned with iodoacetate addition of phosphoglyceric acid would inhibit ammonia formation and they attributed this to a reaction between phosphoglyceric acid or its derivative—shown to be phosphoenolpyruvic acid by LOHMANN and MEYERHOF[52]—and adenylic acid to form ATP.

The Parnas reaction,

phosphoenolpyruvate + ADP (or AMP) $\rightleftharpoons$ pyruvate + ATP (or ADP)

was the first reaction to become known in which ATP was formed at the expense of energy derived from glycolysis. The existence of a second reaction of this type was suspected, because according to the careful measurements of LUNDSGAARD[53] maximally 2 moles of phosphocreatine were resynthesized (via ATP and the LOHMANN reaction) per mole of lactate formed.

Apart from adding some intermediate steps, mainly by MEYERHOF and collaborators, the glycolytic scheme proposed by Embden required correction in only one respect. Although glycerophosphate is formed during an initial phase of glycolysis before pyruvate has accumulated, the main oxidation-reduction during the stationary phase is between glyceraldehyde phosphate and pyruvate. NEEDHAM and PILLAI[54] and MEYERHOF[55] made it probable that glyceraldehyde-3-phosphate was the form of sugar undergoing oxidation and that this step was connected with the uptake of inorganic phosphate and the formation of ATP. Complete clarification of the mechanism of this reaction came in 1939 when WARBURG and CHRISTIAN[56] crystallized the yeast enzyme catalyzing the oxidation of glyceraldehyde-3-phosphate. They showed that the reaction requiring inorganic P and diphosphopyridine nucleotide was reversible and that the products of the reaction were 1,3 diphosphoglyceric acid and reduced diphosphopyridine nucleotide. A separate protein catalyses the reaction

1,3 diphosphoglyceric acid + ADP $\rightleftarrows$ 3-phosphoglyceric acid + ATP

With the discovery of this reaction the phosphate cycle during lactic and alcoholic fermentation had been completed. Thus ended a most exciting period of biochemistry. It was then realized that further progress would come from the isolation of the individual catalysts that make up the multienzyme systems of fermentation and from study of the mechanism of each reaction. In the mean time, aerobic phosphorylation had been discovered which results, as does fermentation, in an uptake of inorganic phosphate and formation of ATP. The question was asked whether the oxidative phosphorylation which occurs anaerobically during fermentation is in any way a model reaction for that occurring during respiration or, if not, what further evolutionary change has taken place since it is generally believed that respiration appeared after fermentation. A discussion of these points is beyond the scope of this article and will undoubtedly be taken up by other speakers at this symposium.

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