Interrelationship of Carbohydrate Metabolism and Alkaline Phosphatase Synthesis in *Bacillus licheniformis* 749/c*

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Membrane-bound alkaline phosphatase of *Bacillus licheniformis* 749/c is derepressed by glucose in complex and chemically defined media. In the presence of lactate, pyruvate, or succinate the synthesis is repressed. The lactate repression neither affects total protein synthesis nor inhibits penicillinase synthesis. Thus, carbon sources specifically influence alkaline phosphatase synthesis. Although variations in the inorganic phosphate content of the growth media directly affect alkaline phosphatase synthesis, the intracellular inorganic and total phosphate pools appear to be unrelated to its repression or derepression. During lactate repression there is preferential incorporation of lactate molecules into glycogen, whereas no such incorporation could be detected from glucose. Net glycogen synthesis remains the same in glucose- or lactate-grown cells. It is postulated that, in phosphate-deficient growth medium, gluconeogenic metabolism regulates alkaline phosphatase synthesis.

Alkaline phosphatase of *Bacillus subtilis* SB 15 is derepressed by depriving the cells of a source of inorganic phosphate in the growth media (1). To date, genetic regulation of alkaline phosphatase in *bacilli* has been proposed to be identical with that in *Escherichia coli* (2). In spite of extensive study on the genetic regulation of alkaline phosphatase in *E. coli*, the nature of the actual repressor or inducer remains unknown. There is one structural gene (*pho A*), which specifies the structure of the enzyme molecule and there are two regulator genes, *pho R* and *pho S*. The former is located close to the structural gene, 10.5 in the genetic map and *pho S* is located remotely at 73.5. Besides, there is another regulatory gene *pho T* which is functionally separable from *pho R*. Since the initial suggestion that the conversion of inducer to repressor only occurs in the presence of inorganic phosphate (3), the role of the latter in the regulation of alkaline phosphatase remains critically important. However, it has been perceived that the effect of inorganic phosphate may be expressed in diverse ways. Most significant is the recent report that the *pho S* and *pho T* genes are primarily involved with the regulation of the transport of inorganic phosphate (4).

The physiological control of alkaline phosphatase synthesis appears to be diverse and complex. It has been reported that alkaline phosphatase synthesis of *B. subtilis* SB 15 is derepressed by glucose and repressed by lactate when the organism is grown in media containing a low amount of inorganic phosphate (1). The alkaline phosphatase synthesis of a radiation-resistant mutant of *E. coli* is also influenced by carbohydrate material in the growth media (5). It has been suggested that carbohydrate metabolism regulates alkaline phosphatase synthesis. Implicit in this suggestion is the possibility that alkaline phosphatase has some significant function in carbohydrate metabolism of *B. subtilis*. Our working hypothesis was that the metabolic reactions involving carbohydrate material regulate alkaline phosphatase via the regulation of an intracellular phosphate pool (6).

Our aim is to test this working hypothesis and to show that the effect of carbon sources on alkaline phosphatase synthesis is specific. Furthermore, we will attempt to correlate specific reactions of carbohydrate metabolism to the lactate repression of alkaline phosphatase synthesis.

**Materials and Methods**

*Organism, Media, Inocula—* *Bacillus licheniformis* strain 749/c, a mutant constitutive for the production of penicillinase, was maintained on sporulation agar (7). The organism was grown at 30° with constant shaking in Bacto-casitone medium which was treated with magnesium mixture (8) to remove inorganic phosphate. The final composition of the medium per 1000 ml was as follows: Tris(hydroxymethyl)aminomethane, 6 g; 1 ml of salt mixture (7); NaCl, 5 g; inorganic phosphate-free Bactocasitone, 10 g; MgSO₄·7H₂O, 0.3 g; and CaCl₂, 0.1 g. The pH of the medium was adjusted to 7.0. The latter two components were autoclaved separately and were added to the medium immediately prior to use. A variety of other carbon sources (e.g. glucose, glyceral, lactate, pyruvate, or succinate) were added under sterile conditions as required. The media, with or without the addition of disodium hydrogen phosphate (2 mM), will be referred to as high phosphate (HP) and low phosphate (LP), respectively.

The chemically defined medium contained (NH₄)₂SO₄, 15.2 mM; MnSO₄·2H₂O, 0.0005 mM; FeSO₄·7H₂O, 0.0035 mM; MgSO₄, 2.06 mM; L-glutamic acid, 10 mM; glucose, 0.1%; Tris buffer, 100 mM; and K₂HPO₄, 5 mM. The pH of this medium was adjusted to 7.1. The inoculum which was prepared by growing a heat-shocked spore suspension (9) in the above medium for 30 h at 35° with constant shaking, was diluted 10-fold and grown for 8 h.

**Enzyme Assay—** Aliquots of cell samples from the culture were...
Enzyme assays or may be quickly frozen in dry ice for future use. The methods of assays of alkaline phosphatase (8) and penicillinase (10) were described earlier. The results were expressed as units of alkaline phosphatase (nanomoles of p-nitrophenol produced per min) and penicillinase (micromoles of benzyl penicillin hydrolyzed per h) activity per mg dry weight of the cell.

Protease activity was estimated in the culture supernatant. Two methods could be followed to remove amino acids from the culture supernatant. Ammonium sulfate (50 g) was slowly added to 100 ml of culture supernatant; the precipitate, which formed after incubation with constant shaking for 2 h at room temperature (22°) and stationary at 4° for 2 h, was collected by centrifugation at 10,000 x g for 10 min. The other method removed the amino acids by dialysis. However, it was observed that handling large volumes of material could be avoided by following the former method; furthermore, prolonged dialysis led to partial loss of enzyme activity. The precipitate was dissolved in and dialyzed against Tris buffer (pH 7.5) containing salts (MgSO₄, 0.03%; CaCl₂, 0.01%; NaCl, 0.23% (Tris/salts)). The dialyzed solution was concentrated and filtered through an Amicon ultrafiltration apparatus (UM-10 membrane). Aliquots of the filtrate were used to assay the protease activity at 37°, using azocoll as the substrate (11). The soluble colored material, produced from the proteolytic action (contaminated in the sample) on the insoluble azocoll, was separated by filtration through a Millipore filter (0.45 μ) and measured at 520 nm in a Gilford spectrophotometer (model 200). The nonspecific protease activity (11) was expressed as milligrams of azocoll proteolyzed (units) per h per mg cell dry weight.

Effect of Different Carbon Sources on Alkaline Phosphatase Synthesis in Chemically Defined Medium - The effects of the various carbon sources were studied in a chemically defined medium. Growth after transfer of inoculum into defined media containing glucose, glycerol, lactate, or pyruvate, with and without the addition of 5 mm inorganic phosphate, is shown in Fig. 1.

In the media containing inorganic phosphate, growth in the presence of lactate or pyruvate was 35 to 40% lower than that in the presence of glucose or glycerol. Withdrawal of inorganic phosphate from the growth media slowed the growth to almost 10% of that in media containing inorganic phosphate (Fig. 1); the total amount of growth during 8 h equals only one generation. Alkaline phosphatase synthesis in chemically defined medium (Fig. 2), in contrast to that in complex medium, showed practically no lag before the onset of synthesis. In the presence of lactate or pyruvate the enzyme synthesis started after a lag which was shorter (1 h) than that in complex medium (5 h). Changes in the concentrations of carbon sources greater than 1% did not appreciably affect synthesis.

This mixture was incubated at 37° for 1 h and at 4° for 24 h. The supernatant and precipitate which formed as a result of the reaction were separated by centrifugation at 1000 x g for 20 min at 4°. The resulting pellet was washed twice with PBS and finally dissolved in NaOH (0.05 n). The radioactivity present in this precipitate represented the glycogen. The specificity of the Con A-glycogen complex formation was determined by estimating the amount of binding after the addition of methyl-a-D-mannopyranoside (1 mg; Sigma) to the reaction mixture. This reagent inhibits complex formation because of its high binding affinity for Con A (16).

**RESULTS**

**Effect of Different Carbon Sources on Alkaline Phosphatase Synthesis in Chemically Defined Medium** - The effects of the various carbon sources were studied in a chemically defined medium. Growth after transfer of inoculum into defined media containing glucose, glycerol, lactate, or pyruvate, with and without the addition of 5 mm inorganic phosphate, is shown in Fig. 1.

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**Fig. 1. Growth of Bacillus licheniformis 749ic in chemically defined medium with and without the addition of inorganic phosphate (5 mm P).** Since there was very little cell growth in medium without the addition of inorganic phosphate, a high amount of starting inoculum (optical density 70) was needed for enzyme assays at different time intervals: ●, glucose with P; ■, without P; ▲, glycerol with P; ▲, without P; △, lactate with P; □, without P; ▽, pyruvate with P; ▾, without P. All carbon sources were added to a final concentration of 0.1%.
alkaline phosphate synthesis. Although net enzyme synthesis is apparently equivalent in both systems, the amount of enzyme formed per individual cell will be 10-fold higher in chemically defined medium because the net cell growth is only one-tenth of that in complex medium.

In low phosphate Bacto-casitone medium the abovementioned carbon sources influenced alkaline phosphatase synthesis in essentially the same manner as they did in chemically defined medium. The only difference is that in low phosphate Bacto-casitone medium without any additional carbon source, or inorganic phosphate, or both, the cell growth is the same as in the medium containing inorganic phosphate. These cells formed a basal level of alkaline phosphatase. Glucose and glycerol stimulated the alkaline phosphatase synthesis 2- to 3-fold above this basal level, whereas lactate, succinate, and pyruvate failed to do so.

Alkaline Phosphatase Synthesis in Cells Transferred from Media Containing One Carbon Source to Another—Alkaline phosphatase synthesis of the cells growing in medium containing one carbon source transferred to medium containing a different carbon source, was studied. It can be assumed that modification of the enzyme synthesis according to the carbon sources present in the second medium, results from the specific effect of these carbon sources. The cells, after 3 h of growth in media containing glucose or lactate, were transferred with sterile precautions into prewarmed (30°C) media containing lactate or glucose, respectively (Fig. 3). The growth after this transfer was slightly stimulated (Fig. 3, inset). Enzyme synthesis in control cells; i.e. glucose medium to glucose medium, started after a brief lag of 30 to 45 min. The cells transferred from glucose to lactate medium, on the other hand, showed a very small synthesis after a prolonged lag of 3 h. Lactate-pregrown cells, transferred into medium containing glucose, synthesized alkaline phosphatase after a lag of 1 h. In contrast, cells transferred from lactate to lactate medium, synthesized enzyme after a 2-h lag, and only produced 10% of the enzyme formed by the cells transferred into glucose medium. Penicillinase synthesis in glucose or lactate-pregrown cells, transferred to lactate or glucose media, and vice versa did not exhibit any difference. Thus, the remarkable effect of carbon sources on alkaline phosphatase synthesis did not affect the cell growth or the synthesis of another membrane-bound enzyme.

Effect of Changes in pH of Glucose Medium on Alkaline Phosphatase Synthesis—Growth of the cells in glucose medium caused an accumulation of acid which was counteracted by periodic addition of alkali. This pH adjustment in glucose medium caused a slight stimulation of growth and a 40% increase in the alkaline phosphatase synthesis. Penicillinase synthesis, on the contrary, remained unchanged by this pH variation (Fig. 4). Unlike the changes in the pH of glucose medium, the pH in media containing lactate or glycerol remained unaltered during cell growth. Therefore, the drop in the pH of the glucose growth medium cannot per se cause derepression of alkaline phosphatase.

Characterization of Alkaline Phosphatase as Vegetative Enzyme—Two types of alkaline phosphatase are known to exist; i.e., a vegetative enzyme and a sporulative one (17). It has been shown that the regulation of these two alkaline phosphatases differs. The vegetative enzyme unlike the sporulation enzyme is susceptible to repression in the presence of inorganic phosphate and is synthesized prior to the derepression of protease, which is the first enzyme to be derepressed in the sporulation cycle (17). Two experiments were done to determine which alkaline phosphatase is derepressed by glucose: (a) whether the enzyme could be repressed by inorganic phosphate or not, and (b) what the time of alkaline phosphatase derepression was relative to that of protease. The effect of inorganic phosphate on alkaline phosphatase synthesis can be seen in Fig. 5. The cells, after 2 and 5 h of growth in media containing glucose, were washed and resuspended into new media with and without the addition of inorganic phosphate.
The enzyme content in the washed cell could be estimated but, the amount of enzyme released varied in different periods of cell growth. Thus, the amount of enzyme estimated in the whole culture represented the sum of enzyme synthesized and secreted. Therefore, in order to determine the net amount of enzyme formed, it was imperative to estimate the amount of enzyme in the whole culture. Inorganic phosphate totally repressed the enzyme synthesis in both the cells transferred after 2 and 5 h of growth. The cells, after transfer into new medium (without inorganic phosphate), showed a lag of 30 to 45 min before regaining alkaline phosphatase synthesis. The rate of enzyme synthesis before and after transfer into new media remained unchanged following the brief lag.

The protease activity of the cells grown in Bacto-casitone medium alone and in the presence of glucose or lactate was determined after 5 and 7 h of growth. It is evident from the results presented in Table I that the protease activity of 7-h cells was double the amount present after 5 h of growth. This large increase in the enzyme activity of the 7th h sample indicates that protease was derepressed long after the de-repression of alkaline phosphatase activity. These manipulations did not affect penicillinase synthesis.

** FIG. 4.** Alkaline phosphatase (——) and penicillinase (— — —) synthesis in pH unadjusted and adjusted 0.1% glucose media: ●, pH adjusted; ○, pH unadjusted.

** FIG. 5.** The effect of inorganic phosphate on alkaline phosphatase (APase) synthesis in 0.1% glucose medium added at different intervals (indicated by arrows); ●, untreated; ▲, Δ, without and with phosphate at 2 h; ■, □, without and with phosphate at 5 h; (— — —), amount of enzyme lost by washing.

** FIG. 6.** The effect of lactate on the incorporation of radioactivity from U-14C-amino-acid mixture into trichloroacetic acid-precipitable protein of glucose-pregrown cells: ●, incorporation into untransferred cells; incorporation into cells transferred to 0.1% glucose medium without (●) and with (○) 40 µg/ml of chloramphenicol; incorporation into cells transferred to 2% lactate medium without (▲) and with (△) 40 µg/ml of chloramphenicol.

**Table 1**

<table>
<thead>
<tr>
<th>Carbon source</th>
<th>5 h</th>
<th>7 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (0.1%)</td>
<td>0.072</td>
<td>0.148</td>
</tr>
<tr>
<td>Lactate (2%)</td>
<td>0.069</td>
<td>0.138</td>
</tr>
<tr>
<td>Control*</td>
<td>0.071</td>
<td>0.146</td>
</tr>
</tbody>
</table>

* Control: medium without any additional carbon source.
and lactate transferred cells is identical and that this incorporation could be 80% halted by chloramphenicol. Thus, during repression of alkaline phosphatase synthesis in glucose cells transferred to lactate, protein synthesis appears to progress in the normal manner. Therefore, these results that lactate neither affects penicillinase synthesis nor inhibits total protein synthesis suggest that the effect on alkaline phosphatase synthesis is specific. It should be emphasized that the aim of this experiment is only to examine whether the repression of alkaline phosphatase synthesis by lactate is a consequence of an overall effect on total protein synthesis.

The results clearly eliminate this possibility.

**Glycogen Synthesis during Alkaline Phosphatase Derepression and Repression**—Table II shows the amount of $^{14}$C incorporated after 2-h incubation into glycogen from various $^{14}$C-labeled carbon sources. It is noted that the incorporation from $^{14}$C-lactate into glycogen is 70-fold greater than that from $^{14}$C-glucose or $^{14}$C-glycerol. The net amount of glycogen synthesized in the presence of glucose is 8% and glyceral is 20% lower than in the presence of lactate. The specificity of the lactate effect on glycogen synthesis was determined by quantitative estimations of the incorporations of radioactivity into glycogen while glucose-pregrown cells were transferred into lactate medium and vice versa. The results presented in Table III show that glucose-pregrown cells, transferred to $^{14}$C-lactate medium, incorporate 60-fold more radioactivity into glycogen than lactate-pregrown cells transferred into $^{14}$C-glucose medium. However, the glycogen content of lactate-pregrown cells is 38% higher than glucose-pregrown cells.

In order to identify whether the precipitated material examined here was glycogen, the labeled precipitate was treated with amyloglucosidase. In the event that the radioactive precipitate had been hydrolyzed, the resulting monosaccharides would be removed by dialysis. The results show that 76% of the radioactivity in the precipitate of lactate-grown cells was lost after amyloglucosidase treatment but no such loss could be detected without the enzyme treatment. In contrast, only 31% of the radioactivity was lost from the precipitate obtained from glucose-grown cells suggesting that the majority of the material formed from glucose may not be glycogen.

It is known (16) that concanavalin A specifically binds to glycogen, forming a precipitate which cannot be formed in the presence of $\alpha$-d-mannopyranoside because, its affinity being higher, the Con A-glycogen complex formation is prevented. The data presented in Table IV show that 74% of the radioactivity present in the material obtained from lactate and 60% from glucose-grown cells could be precipitated with Con A. This precipitation was prevented by $\alpha$-d-mannopyranoside treatment (data not shown).

It is evident from these results that the preferential incorporation of lactate into glycogen is coincidental to the lactate repression of alkaline phosphatase synthesis. This lactate effect is specific. It should be noted that, in contrast to the highly significant incorporation of lactate into glycogen, the net amount of glycogen formed in the presence of lactate or glucose is very similar but higher than that in the presence of glyceral. It does not appear from the result presented in Table III that lactate per se stimulates glycogen synthesis. Therefore, it is likely that glycogen synthesis proceeds through differing metabolic pathways but it is the specific gluconeogenic reaction(s) for the conversion of lactate to glycogen which influence alkaline phosphatase synthesis.

**Relationship of Inorganic Phosphate and Alkaline Phosphatase Synthesis in Complex Medium**—It was found that increased concentrations of inorganic phosphate in the growth medium prolong the lag phase and decrease the amount of alkaline phosphatase synthesized by the cells. It appears that the higher the inorganic phosphate content of the growth medium the greater is the sensitivity of enzyme synthesis to repression. Penicillinase synthesis is not affected by the variations in the inorganic phosphate content of the growth medium. One may presume from this result that the extracellular inorganic phosphate content somehow regulates the size of the intracellular inorganic phosphate pool which, in turn, regulates alkaline phosphatase synthesis. It is also likely that the effect of glucose and lactate arises simply from the metabolism of these components affecting the inorganic phosphate pool of the cell. Therefore, the changes in the phosphate pool were studied in the repressed and derepressed cells.

Precise interpretation of the phosphate pool fluctuation is beyond the scope of this paper. The results presented in Fig. 7 show that the "free phosphate pool" represents 10 to 15% of the "total phosphate pool." In the early log phase of growth, the "total phosphate pool" is formed from glucose and lactate was transferred into the cells.

### Table II

**Incorporation of [U-14C]glucose, glycerol, and lactate into glycogen of Bacillus licheniformis 749/c**

<table>
<thead>
<tr>
<th>Carbon source</th>
<th>Precipitated glycogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\mu$g glycogen/mg cell</td>
</tr>
<tr>
<td>[U-14C]Glucose</td>
<td>5.5</td>
</tr>
<tr>
<td>[U-14C]Glycerol</td>
<td>3.8</td>
</tr>
<tr>
<td>[U-14C]Lactate</td>
<td>6.0</td>
</tr>
</tbody>
</table>

$^t$ Amount of reducing sugar obtained from the glycogen precipitates determined by the procedure of Fong et al. (14) and expressed as micrograms of glycogen.

$^b$ Counts of radioactivity incorporated into 1 $\mu$g of precipitated glycogen.

### Table III

**Incorporation of [U-14C]lactate and glucose into glycogen of glucose- and lactate-pregrown cells, respectively**

<table>
<thead>
<tr>
<th>Carbon source</th>
<th>Precipitated glycogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\mu$g glycogen/mg cell</td>
</tr>
<tr>
<td>Lactate to [U-14C] glucose</td>
<td>5.2</td>
</tr>
<tr>
<td>Glucose to [U-14C] Lactate</td>
<td>3.5</td>
</tr>
</tbody>
</table>

$^t$ Amount of reducing sugar obtained from the glycogen precipitation determined by the procedure of Fong et al. (14) and expressed as micrograms of glycogen.

$^b$ Counts of radioactivity incorporated into 1 $\mu$g of precipitated glycogen.

### Table IV

**Identification of glycogen by concanavalin A precipitation**

<table>
<thead>
<tr>
<th>Source of glycogen $^*$</th>
<th>Total cpm added</th>
<th>Total cpm in Con A glycogen precipitation</th>
<th>Per cent glycogen bound to Con A</th>
</tr>
</thead>
<tbody>
<tr>
<td>[U-14C]Glucose control $^b$</td>
<td>136</td>
<td>No ppt</td>
<td></td>
</tr>
<tr>
<td>[U-14C]Glucose</td>
<td>136</td>
<td>82</td>
<td>60.0</td>
</tr>
<tr>
<td>[U-14C]Lactate control $^b$</td>
<td>7620</td>
<td>No ppt</td>
<td></td>
</tr>
<tr>
<td>[U-14C]Lactate</td>
<td>7620</td>
<td>5665</td>
<td>74.0</td>
</tr>
</tbody>
</table>

$^*$ Glycogen was extracted from the cells grown in media containing carbon sources as shown in the table.

$^b$ Control samples contained in addition to the other components, 1 mg of methyl-$\alpha$-d-mannopyranoside to inhibit a glycogen Con A precipitation.
The results presented in this paper clearly show that alkaline phosphatase synthesis in Bacillus licheniformis 749/c is derepressed by glucose and glycerol in chemically defined media. This derepression is quantitatively much smaller when the cells are growing in lactate, pyruvate, or succinate media. It is striking to note that the effect of glucose can be abolished by the addition of lactate or pyruvate. These carbon sources affect neither the synthesis of another membrane-bound protein (i.e. penicillinase) nor the total protein synthesis during the repression or derepression of alkaline phosphatase. Hence, glucose derepression or lactate repression of alkaline phosphatase synthesis does not appear to be a fortuitous phenomenon of cell metabolism. It is likely that unique metabolic reactions for lactate cause repression and for glucose cause derepression of alkaline phosphatase synthesis. Our ultimate aim is to identify the specific metabolic reaction(s) which have this regulatory role. Thus, it will be possible to establish a functional relationship between alkaline phosphatase synthesis and carbohydrate metabolism.

FIG. 7. The changes in the free inorganic phosphate (A) estimated in 100,000 × g supernatant of cell lysate and total phosphate (B) content estimated after perchloric acid hydrolysis of whole cells of Bacillus licheniformis 749/c grown in different media; 0, no additional carbon source; ●, 0.1% glucose; □, 2% lactate; ○, 2 mM Na₂HPO₄. Method of Ernster et al. (18) was followed for phosphate estimation.
in one regulatory gene affects the synthesis of two genetically
different enzymes; namely, alkaline phosphatase and phos-
phodiesterase (22). Thus, the interaction between different
regulatory and structural genes may be an effective way to
control the formation of alkaline phosphatase and other en-
zymes related to phosphate metabolism under differing meta-
bolic conditions; e.g. gluconeogenesis or glycolysis. In B.
subtilis, sporulation and vegetative alkaline phosphatase are
the products of the same gene. However, they are regulated
via different mechanisms (17). Inorganic phosphate does not
repress sporulation alkaline phosphatase synthesis and vege-
tative alkaline phosphatase-negative mutants produce small
amounts of sporulation alkaline phosphatase (17). These facts
do not explain the mechanism of lactate repression or glucose
derepression, however, they suggest that diverse regulatory
pheno menon are involved in controlling alkaline phosphatase
synthesis.

Before attempting to explain the precise regulatory role of
carbohydrate metabolism on alkaline phosphatase synthesis,
it is imperative that the nature of the pure alkaline phospha-
tase proteins formed in glucose- and lactate-grown cells be
known. Differences in the structure and properties of the
enzyme molecules may suggest that: (a) the protein molecule
undergoes a subtle change in conformation (e.g. allosteric),
or (b) that two different protein molecules are formed under
the conditions of glucose or lactate growth. Therefore, the
results of the studies on the purification and comparison of the
properties of the alkaline phosphatases from glucose- and
lactate-grown cells are presented in the accompanying paper.
Finally, experiments are in progress to prepare gluconeogen-
esis-negative mutants. These are needed to determine
whether there is any genetic basis in the regulation of alkaline
phosphatase synthesis and its relation to gluconeogenic me-
tabolism.

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