Factors That Control the Effect of pH on Glycolysis in Leukocytes*

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SUMMARY

Stimulation of glycolysis accompanies a rise in pH in intact polymorphonuclear leukocytes and supernatant preparations derived from homogenates of these cells. The curve of lactate production plotted against pH for the cell-free system was steepest between pH 6.5 and 7.0. Our studies indicate that phosphofructokinase is the key control point, and a secondary locus of control may be at glyceraldehyde phosphate dehydrogenase or diphosphoglycerate kinase. The over-all effect of pH on glycolysis appears not to be dependent on the concentrations of cofactors known to affect phosphofructokinase. In the case of inorganic phosphate, the concentration of neither the monobasic nor the dibasic species is involved in the effect of pH.

It has been repeatedly observed that a rise in pH increases glycolysis in intact organisms and in a great variety of systems in vitro. The mechanism of this phenomenon has not been investigated extensively, but recent studies with human red blood cells (1) and with extracts of rat diaphragm muscle (2) have led to the suggestion that the phosphofructokinase step is a primary site of the pH effect. Furthermore, it has been proposed (2) that this effect may be due to pH-dependent changes in the inhibition of phosphofructokinase by ATP.

We have studied in detail the effects of changes in pH on the glycolytic activity of intact guinea pig polymorphonuclear leukocytes and of extracts prepared from these cells. These changes were of the order of 1 pH unit and were in the physiological range. The effects that we observed were large and demonstrable under aerobic or anaerobic conditions. The evidence presented here supports the view that the response of the phosphofructokinase reaction is of greatest importance, but the over-all effect of pH on glycolysis is probably also dependent upon changes in a later reaction. The mechanism of pH control of phosphofructokinase does not appear to depend upon changes in the concentration of various cofactors known to be capable of influencing this enzyme.

METHODS AND PROCEDURES

Preparation of Cells and Supernatant Fraction—An exudate rich in polymorphonuclear leukocytes was obtained from the peritoneal cavity of guinea pigs approximately 18 hours after the intraperitoneal injection of 12% casein solution (3). All procedures after harvesting and prior to incubation were carried out in the cold. The cells were washed once in physiological sodium chloride solution and once in Krebs-Ringer phosphate (pH 7.4).

To prepare a cell-free extract with high glycolytic activity we used a slight modification of the technique of Beck and Valentine (4). Freshly harvested cells were washed and then suspended (20% by volume) in 4 ml of neutral isotonic potassium chloride. Approximately 25 mg of nicotinamide were added and the cells were homogenized for a few minutes in a Teflon Potter-Elvehjem tissue grinder. The homogenate was centrifuged at 1,500 g for 7 min, the sediment was resuspended in the original volume of potassium chloride, and the homogenization was repeated. This resulted in the disruption of 60 to 90% of the cells in the original suspension. The supernatant fluids were combined and centrifuged at 28,000 × g for 30 min to obtain a clear supernatant fraction containing approximately 2 to 4 mg of protein and 20 μmoles of nicotinamide per ml.

Incubation.—In the experiments with whole cells, 5 to 10 ml of cold 20% cell suspensions in Krebs-Ringer phosphate medium were pipetted into 50-ml Erlenmeyer flasks and substrates were added as necessary. The final concentration of cells was usually between 15 and 19% by volume. In the experiments with the supernatant fraction the final incubation mixture (also in 50 ml Erlenmeyer flasks) was the same as that described by Beck (4) and contained (in addition to substrate) 10 mM potassium phosphate buffer, 1 mM sodium ATP, 1 mM NAD, and 5 mM

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justed within a few minutes to the desired level with NaOH.

At the end of the incubation period (20 to 60 min), the pH was measured inorganic phosphate by the technique of Lopez and Lowry (7).

analyzed the supernatant fraction itself in the final incubation mixture was usually obtained for 60 min.

Table I

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Duration</th>
<th>Gas</th>
<th>Medium glucose</th>
<th>pH range</th>
<th>Lactate production</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>min</td>
<td></td>
<td>mM</td>
<td></td>
<td>nmol mg⁻¹ protein min⁻¹</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>Air</td>
<td>5</td>
<td>7.0-6.9</td>
<td>12.9</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>N₂</td>
<td>5</td>
<td>7.7-6.8</td>
<td>21.2</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>Air</td>
<td>0</td>
<td>8.0-7.2</td>
<td>14.5</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>N₂</td>
<td>0</td>
<td>7.9-6.8</td>
<td>16.0</td>
</tr>
</tbody>
</table>

a Initial and final pH values are given.
b Lactate production for each period was calculated by subtracting zero time value. The data are expressed as rates, for convenience. They should not be strictly interpreted as such although, as noted in Fig. 7, virtual linearity was normal obtained for 60 min.

c Number of pairs of flasks.

MgCl₂. When the substrate was phosphoglyceric acid, 1 mM NADH was used instead of NAD. The dilution of the supernatant fraction in the final incubation mixture was usually 1:5.

After the addition of substrate, the pH of the flasks was adjusted within a few minutes to the desired level with NaOH or HCl. Aliquots were taken for analysis (zero time) and the flasks were incubated in a shaking water bath at 37°. At the end of the incubation period (20 to 60 min), the pH was measured again and the protein was precipitated with 6% (final concentration) ice-cold perchloric acid.

Analytical Methods—Protein was measured by the method of Lowry et al. (5), glucose by the glucose oxidase method (6), and inorganic phosphate by the technique of Lopez and Lowry (7). ATP, ADP, and AMP, as well as lactate and all of the other glycolytic intermediates reported in this study, were determined enzymatically by standard methods (8) by means of spectrophotometric readings at 340 nm. 1 The absorbance for NADH was taken as 0.22 × 10⁶ m⁻¹ cm⁻¹. Measurements of pH were made with a Beckman pH meter, model G, and a dipping glass electrode.

Reagents—Substrates, cofactors, and enzymes were all purchased from Boehringer and Soehne or Sigma and, except as described below, were used as supplied.

Table II

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Lactate production</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic glucose (25)</td>
<td>158 ± 28</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anaerobic, glucose (13)</td>
<td>151 ± 31</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aerobic, no glucose (4)</td>
<td>116 ± 10</td>
<td>0.04</td>
</tr>
<tr>
<td>Anaerobic, no glucose (7)</td>
<td>101 ± 15</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

a For further details see text.
b Lactate production in more acid medium was set at 100 in each experiment. Means and standard deviations are given.
c P has the usual connotation of statistical probability. N.S. indicates "not significant."

In every experiment with glucose, lactate production was greater in the more alkaline medium; for the aerobic experiments the mean value for lactate was 158 ± 28% of that in the more acid medium, and in the anaerobic experiments this value was 151 ± 31%. In both groups of experiments the effect of pH was significant (P < 0.01). When no glucose was present in the medium, a much smaller rise in lactate production was observed in the aerobic, more alkaline medium (116 ± 10% of the value at lower pH), and there was no pH effect in the anaerobic flasks.

Effect of pH on Lactate Production from Glucose by Supernatant Fraction of Leukocytes—In 19 experiments supernatant fractions were incubated anaerobically with 5 mM glucose for 60 min at different pH levels. In almost all cases there was a slight fall in pH during the period of incubation and the mean reduction was 0.31 ± 0.03 pH unit. The results are summarized in Fig. 1, with the mean pH during incubation plotted on the abscissa. The effect of pH on lactate production (nmole·mg⁻¹ protein) by a supernatant fraction from leukocytes is shown.

FIG. 1. Influence of pH on lactate production (nmole·mg⁻¹ protein) by a supernatant fraction from leukocytes. Sixty observations were made in the course of 19 separate experiments. The pH values shown are the estimated mean pH during the period of incubation. These mean pH values were grouped in ranges of 0.1 unit from 6.1 to 8.0, each dot representing from one to nine observations. The curve is drawn by inspection. For conditions of incubation see text.
striking effect of pH on lactate production in this system is evident.

The curve appears to be divided as follows. (a) Between pH 6.1 and 6.4 lactate production is minimal and pH exerts relatively little effect. (b) Between pH 6.5 and 7.0 lactate production rises precipitously with pH increase. (c) From pH 7.0 to 7.8 lactate production is maximal and pH again does not influence this function greatly.

Effect of pH on Concentrations of Glycolytic Intermediates in Intact Cells—Fig. 2 shows a plot of the relative cellular concentration of various intermediates in lactate production as affected by pH. The values for cells maintained at the higher pH are expressed as a percentage of values for cells at the lower pH (9, 10). The figure shows that a rise in initial pH from 6.7 to 7.6 produces a 90% increase in lactate production after 30 min of incubation. A “cross-over” point clearly occurs at the step between fructose-6-P and fructose-1,6-P₂.

Effect of pH on Concentration of Glycolytic Intermediates in Supernatant Fractions from Leukocytes when Glucose or Fructose-6-P Is Substrate—Data similar to those just described for whole cells are given for the supernatant fraction (Fig. 3). The results are more dramatic but confirm those of Fig. 2 in showing a change in the relative concentrations of intermediates after fructose-6-P.

It is noteworthy that this similarity to Fig. 2 exists despite the fact that in the cell-free system the concentrations of the phosphorylated intermediates were as much as two orders of magnitude greater than in the intact cells. Similar results were also obtained when fructose-6-P was used as a substrate.

Effect of pH on Production of Lactate and Hexose Monophosphates from Fructose Diphosphate in Supernatant Fraction.—The increase in relative concentrations of intermediates in alkaline compared to acid flasks at the step between fructose-6-P and fructose-1,6-P₂ could be due to acceleration of fructose diphosphatase activity at low pH. Although there is evidence that diphosphatase activity is very low in the leukocyte (12, 13), the possible role of this enzyme was evaluated by determining the effect of pH on the conversion of fructose-1,6-P₂ to hexose mono-

![Graph](http://www.jbc.org/content/244/2/386.f1)

**Fig. 2.** The relative concentrations in intact leukocytes of some glycolytic intermediates at two different pH levels. Mean values obtained after incubation at pH 6.7 are set at 100% in each experiment and those at 7.6 are given as the mean value ± S.E.M. The number of experiments (n) was 8. The initial glucose concentration was 5 mM and the period of incubation was 30 min. For further details see the text. The absolute values for intermediates at the lower pH (i.e. the 100% values on the figure) are as follows (nanomoles per mg of protein, mean ± S.E.M.): glucose-6-P (Glc-6-P), 1.06 ± 0.03; fructose-6-P (Fru-6-P), 0.70 ± 0.03; fructose-1,6-P₂ (Fru-1,6-P₂), 3.30 ± 0.16; triose-P (triose), 2.40 ± 0.36; lactate, 223 ± 33.

![Graph](http://www.jbc.org/content/244/2/386.f2)

**Fig. 3.** The relative concentrations of some glycolytic intermediates in a supernatant fraction from leukocytes incubated at two different pH levels (7.9 and 6.4). The conventions observed are those described in the legend to Fig. 2 and the data represent mean values (±S.E.M.) of nine observations. The initial glucose concentration was 5 mM and the period of incubation was 30 min. For further details see the text. The absolute values for intermediates at the lower pH (i.e., the 100% values on the figure) are as follows (nanomoles per mg of protein, mean ± S.E.M.): glucose-6-P (Glc-6-P), 315 ± 41; fructose-6-P (Fru-6-P), 100 ± 13; fructose-1,6-P₂ (Fru-1,6-P₂), 317 ± 14; triose-P (triose), 10.0 ± 1.1; lactate, 57.8 ± 4.3.

<table>
<thead>
<tr>
<th>Experiment and pH</th>
<th>Time (min)</th>
<th>Starting fructose-1,6-P concentration (mM)</th>
<th>Hexose monophosphate formed (nmol/mg protein)</th>
<th>Lactate formed (nmol/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Alkaline</td>
<td>15</td>
<td>5.0</td>
<td>1.3</td>
<td>68</td>
</tr>
<tr>
<td>2. Alkaline</td>
<td>30</td>
<td>5.0</td>
<td>0.3</td>
<td>58</td>
</tr>
<tr>
<td>3. Alkaline</td>
<td>30</td>
<td>1.5</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>Acid</td>
<td>10</td>
<td>5.0</td>
<td>4</td>
<td>48</td>
</tr>
<tr>
<td>Acid</td>
<td>3</td>
<td>5.0</td>
<td>3</td>
<td>39</td>
</tr>
</tbody>
</table>

* The alkaline range was between 7.5 and 7.7 and the acid range was between 6.5 and 6.0.
phosphates and lactate. The results in three such experiments are summarized in Table III. It is evident that the quantity of hexose monophosphate formed, even though greater in the acid than in the alkaline medium, was extremely low by comparison with the lactate formed during the same period. These data therefore support the view that diphosphatase activity is negligible in this system and that the effects of pH are largely exerted on the phosphofructokinase reaction.

Effect of pH on Production of Lactate, at Steps beyond Phosphofructokinase—It should be noted in Table III that in each of three experiments lactate production is greater at the higher pH despite the circumvention of the phosphofructokinase step by the use of fructose-1,6-P2 as substrate. Additional studies were carried out to determine where such an effect might occur. Fig. 4 shows that an alkaline medium significantly enhances lactate production when glucose-6-P, fructose-6-P, or fructose-1,6-P2 is used as substrate (as already noted), but not when glyceraldehyde-3-phosphate is the starting point. This might suggest that a second enhancing effect of more alkaline media on lactate production (i.e. beyond phosphofructokinase) occurs at the aldolase step. In accord with this, we found that lactate production from 3-phosphoglyceric acid is significantly reduced in the more alkaline medium and, in a single experiment, similar results were obtained with 2-P-glyceric acid as substrate. As shown in Fig. 5, when this question was explored further by plotting relative concentrations of intermediates at the two different pH values the increase in lactate production from fructose-1,6-P2 caused by a rise in pH appeared, more probably, to occur subsequently to the aldolase reaction.

Since lactate production from excess 3-phosphoglyceric acid is reduced under alkaline conditions (Fig. 4), it would be reasonable to suppose that the locus of the pH effect on the conversion of fructose-1,6-P2 to lactate is either at the glyceraldehyde-3-P dehydrogenase or the diphosphoglycerate kinase step. To study the enhancement of lactate production from fructose-1,6-P2 in more detail, an experimental model was used in which a segment of the glycolytic sequence was isolated by blocking at the enolase step. Fructose-1,6-P2 (1.5 mM) was the substrate, and 6.7 mM NaF was added to inhibit the enolase reaction. The completeness of the inhibition was shown by the virtual absence of lactate production despite significant fructose-1,6-P2 utilization. When pyruvate was added as an acceptor for hydrogen from NADH formed in the glycolytic reaction, the dehydrogenase reaction lactate was produced. The measurement of this lactate formation could indicate the over-all conversion of glyceraldehyde-3-P to 1,3-P2 glyceric acid. Since the latter could not be measured by our methods, the only intermediates that were determined were fructose-1,6-P2, glyceraldehyde phosphate, and 3-P-glyceric acid. That there was no source of NADH other than that produced by the dehydrogenation of glyceraldehyde-3-P was shown in separate experiments with phosphoglycerate as substrate, in which lactate production was shown to be dependent upon the addition of NADH itself.

The data obtained in this system are shown in Fig. 6. They confirm the results previously summarized in Fig. 5, i.e. that stimulation by increased pH occurs subsequent to glyceraldehyde-3-P, and furthermore they show that this effect is apparently prior to 3-P-glyceric acid. The data clearly show an increased flow through the glyceraldehyde-3-P dehydrogenase step when the pH is raised but, since the concentration of the product of the reaction (1,3-P2-glyceric acid) was not measured, we cannot distinguish between the dehydrogenase reaction and the diphosphoglycerate kinase reaction as the locus of the pH effect.

The Role of Cofactors in Control of Phosphofructokinase by pH—Several cofactors are known to influence the activity of phosphofructokinase, including P4, ATP, ADP, and AMP (14, 15). We therefore undertook to determine whether the effect of pH could be explained by changes in the concentration of one or more of these substances. The rate of lactate production by the supernatant cell fraction (5 mM glucose as substrate) was determined when the starting pH was 7.6 or 6.6. Concomitant changes in the concentrations of ATP, ADP, and AMP were also measured.
The results of an experiment are shown in Fig. 7. These are typical of six such experiments. The enhancement of lactate production at the higher pH was accompanied by a reduction, or by no change in the concentrations of cofactors that are known to stimulate phosphofructokinase (ADP, AMP), and by an increase in the cofactor that is known to inhibit the enzyme (ATP) (14, 15). The levels of Pi did not change significantly under any conditions that we studied (see legend to Fig. 7). Since the levels of these substances in our system were similar to those studied by others (14, 15), the pH effect on the phosphofructokinase reaction in this complex system can probably not be ascribed to phenomena involving these cofactors.

Further evidence that Pi and the nucleotides do not mediate the pH effect in the cell-free system that we used was provided by experiments in which the concentrations of ATP, Pi, ADP, AMP, and cyclic AMP were varied over a relatively wide range in acid and alkaline media. Results representative of three such experiments are shown in Fig. 8. Despite large variations in the concentration of these cofactors lactate production from glucose was always greater at the higher pH levels.

It has recently been suggested that an increased concentration of HPO$_4^{2-}$, rather than total Pi, might be responsible for the enhancement of glycolysis under more alkaline conditions (16). To test this hypothesis a series of experiments was carried out in which the pH and the concentration of Pi were so arranged that the concentration of divalent phosphate was slightly higher in the acid than in the alkaline medium. A representative experiment is shown in Table IV. Comparison of the results in Columns A and B shows that lactate production from glucose in the supernatant fraction was markedly reduced in the acid medium despite the slightly higher concentrations of HPO$_4^{2-}$ in the latter. That inhibition by the relatively higher concentrations of H$_2$PO$_4^{-}$ was
also not responsible for the reduced lactate production in the acid medium was shown by the results of the experiments in Column C, in which it is shown that a rise in pH once again enhances lactate production despite a concentration of HPO\textsubscript{4}\textsuperscript{2-} equal to or slightly greater than that found in the acid medium of Column B.

### DISCUSSION

Our results show that the glycolytic activity of the guinea pig polymorphonuclear leukocyte is greatly influenced by the pH of the medium. This effect appears to be a general biological phenomenon, because a similar influence of pH on the rate of glycolysis has been described in many different cellular and subcellular systems, including human red blood cells (1, 17), frog muscle (18), cell-free extract of rat muscle (2), intact muscle, kidney and liver slices, and epididymal fat pad from the rat (19), cat brain slices (20), perfused rat heart (21-23), and Ehrlich ascites tumor cells (24).

Although there has been speculation about the possible site and mechanism of this effect, relatively little experimental evidence on this problem has been published. Murphy (25) noted that the addition of inosine prevented the inhibiting effect of low pH on glycolysis in erythrocytes; he concluded that, since inosine provides substrate to the Embden-Meyerhof pathway at the level of triose phosphate, the pH effect was probably between glucose-6-P and triose phosphate, and he suggested that phosphofructokinase was a likely site. On the basis of their study of the relative effects of pH on lactate production from pyruvate and glucose in rat diaphragm, Gevers and Dowdle (19) also led to suggest that the site of action was at, or before, the dehydrogenation of triose phosphate.

More recently, studies by Minakami and Yoshikawa (1) have shown that in human red cells increased lactate production in alkaline media is associated with a stimulation at the phosphofructokinase step. This is true also in the perfused intact rat heart (23). Our experiments with guinea pig leukocytes confirm this finding in both intact cells and supernatant fractions. However, by the use of glycolytic substrates other than glucose, we have added evidence in the supernatant preparation that the glyceroldehyde phosphate dehydrogenase or the diphosphoglycerate kinase steps are also facilitated by alkaline media. Uí (2) reported that a rise in pH had only a slight effect on lactate production from fructose-1,6-P\textsubscript{2} in a cell-free extract of rat diaphragm but he used initial pH values of 7.6 and 7.2 and did not report the final pH values. We suspect that additional experiments at more widely separated pH values might have shown the effect that we report here.

Experiments with the cell-free extract, in which very high concentrations of substrates are used, must of course be interpreted cautiously, for there is no assurance that they faithfully reflect phenomena in whole cells. Nevertheless, the possibility of a pH effect beyond phosphofructokinase seems to us to be attractive because (as shown in Fig. 2) we do not find a significant increase in triose-P concentration in whole cells exposed to alkaline media, even though there is a relatively large increase in lactate production. The data in the experiments with the supernatant fraction (Fig. 3) also tend to support this possibility by showing that the relative increase in lactate production in alkaline media is several times greater than the relative increase in triose-P concentration.

Studies of the effects of pH on the activity of phosphofructokinase are quite consistent with the view that acceleration of this reaction is primarily responsible for the enhancing effect of alkaline media on glycolysis. The enzyme appears to be extraordinarily sensitive to pH and, under the conditions studied, it exhibits a steep sigmoidal pH activation curve over a pH range comparable to that used in these experiments (14, 26). The mechanism by which pH exerts its effect, however, is not entirely clear. It has been shown (2, 27) that the position of the pH activation curve of phosphofructokinase is greatly influenced by the concentrations of ATP at which the reaction is carried out, but the results given in Fig. 7 show that changes in the concentration of ATP, or of any of the cofactors known to oppose the influence of ATP, cannot be the explanation of the pH effect in the soluble fraction of the broken cells that we examined. Uí has suggested that the inhibiting action of ATP may be dependent upon pH (2), and presumably the same possibility could be suggested for the relieving action of ADP, AMP, and P\textsubscript{i} on this inhibition. However, our results in Fig. 8 argue against such a view for the complex system or the whole cell for they show that the differences between lactate production at two pH values are not conspicuously influenced by varying the concentrations of these cofactors over a relatively wide range. Although evidence of this type is admittedly not critical, it does suggest that the pH effect in these systems may be directly on the K\textsubscript{m} of phosphofructokinase for one or both of its substrates rather than on its affinity for any of the several substances known to exert allosteric effects on the purified enzyme.

Although the effect of anaerobiosis on glycolysis also appears to be exerted on phosphofructokinase (10, 28-30) it is of great interest that the controlling influence of pH is still demonstrable in anaerobic media. Our results with anaerobic leukocytes (Table II) confirm similar observations with rat diaphragm briefly reported by Gevers and Dowdle (19) and are also supported by extensive studies of our own with the same preparation. On the other hand, Uí (2) recently reported no significant difference in lactate production by rat diaphragms incubated anaerobically for 90 min at initial pH values of 7.4 and 8.0. However, no final pH values are given and, since pH is likely to fall very rapidly in the bicarbonate buffer that he used, we suggest that the initial differences in pH in Uí's experiments may not have been sustained long enough to have produced a significant effect. In any event, in our hands a clear effect of pH was demonstrated in leukocytes incubated anaerobically when initial pH differences were greater than those used by Uí and incubation times shorter (Table I). Such a result would be consistent with some current views of the mechanism of the Pasteur effect, which consider the latter to be due to changes in the concentrations of P\textsubscript{i} and the nucleotide cofactors controlling phosphofructokinase (15). We have shown in this paper that the pH effect is different, because it is apparently independent of cofactor concentration and is perhaps exerted directly on the enzyme. Thus, it would be predictable that changes in pH would have a controlling effect on glycolysis even when the latter has been enhanced by anaerobiosis.

The physiological implications of pH control of glycolysis are potentially very significant. This mechanism may well act as a brake on the intracellular lactate acidosis in anaerobic states, particularly in working muscles (30). It probably also accounts for the lactate and pyruvate acidemia in acute alkalosis in the intact organism (31) and may thereby provide a kind of feedback control of
blood and intracellular pH in alkalotic states. Furthermore, pH control of phosphofructokinase activity may explain the hyperglycemic effects of acidosis and the inhibiting effects of low pH on the action of insulin on isolated muscle (32).

REFERENCES
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