The distribution of alanine aminotransferase isozymes in several tissues from several species has been studied. In glycolytic tissues, such as skeletal and cardiac muscle, cytosolic alanine aminotransferase was the predominant form. In gluconeogenic tissues, such as liver and kidney, the concentration of the cytosolic alanine aminotransferase was much more variable; its presence, however, may be correlated with the presence of phosphoenolpyruvate carboxykinase in the same compartment.

The particulate enzyme was found associated only with the matrix of the mitochondria. It was present only in those gluconeogenic tissues that can utilize alanine for glucose production, e.g., rat liver and pig liver and kidney; it was absent from rat kidney which cannot convert alanine to glucose. These observations, together with the kinetic parameters of the two isozymes, suggest that in vivo, mitochondrial alanine aminotransferase is involved in the conversion of alanine to pyruvate, while the cytosolic isoenzyme is mainly involved in the formation of alanine from pyruvate.

The existence of two alanine aminotransferases has been suggested by various reports (2-5). In rat liver the presence of a low, particulate activity, associated with the mitochondria, has generally been ignored because it contributes so little to total alanine aminotransferase activity or has been attributed, by some, to cytosolic contamination of mitochondrial preparations or to the broad specificity of other transaminases. Unfortunately, studies to prove that the two activities may be identified as isoenzymes have been lacking because the marked instability of the mitochondrial alanine aminotransferase from rat liver has prevented its isolation (4, 5). Now, however, we have been able to enrich the mitochondrial enzyme from porcine liver and kidney because of its relatively high concentration and somewhat greater stability (6, 7). The kinetic, physical, and electrochemical characteristics of the purified mitochondrial enzyme are consistent, although not identical, with those previously published for crude preparations obtained from rat liver and more important, quite different from the properties of the enzyme found in the cytosol (7).

In the present study, we have studied the intracellular distribution of the two aminotransferase activities in rat and porcine tissues which are indeed specific for alanine and have confirmed that this activity is distributed only between the cytosol and mitochondria. Furthermore, the mitochondrial form is localized in the matrix space of these particles.

Isoenzymes appear to create functional cellular compartments in prokaryotes lacking subcellular structures and to facilitate the exchange of metabolites between membrane-bound, subcellular structures in eukaryotes. From the study of the distribution of the two alanine aminotransferase isoenzymes in the tissues of several species we have concluded that these enzymes may play unique metabolic roles in cellular metabolism.

**MATERIALS AND METHODS**

**Animals**—Male Holtzman rats (200 to 250 g), Hampshire or Chester White barrows (70 to 100 kg), New Hampshire x Single Comb White crossbred chickens (1200 to 1500 g), and Hartley strain guinea pigs (350 to 400 g) were used in these experiments. All were fed standard commercial diets, fasted overnight, and killed by exsanguination.

**Preparation of Cell Fractions**—The tissues were immediately excised and placed in a cold medium composed of 0.225 M mannitol, 0.075 M sucrose, 0.01 M Tris, pH 7.8, and 0.05 mM EDTA (8). All operations were performed at 0-4°C. After blotting dry, a portion of tissue was weighed and homogenized with the aid of a glass homogenizer with a loose fitting Teflon pestle in 9 volumes of the same medium. The cell debris was sedimented by centrifugation at 300 x g for 10 min, resuspended twice in the same medium, resedimented, and, for estimation of enzyme activities, resuspended in a volume of a “suspension” medium equal to that of the initial volume of homogenization medium. The suspension medium was composed of 0.05 M KPO4, pH 7.8, 0.025 M L-alanine, 0.002 M L-cysteine, and 50% glycerol (v/v) (8). The other fractions were recovered from the appropriate supernatant layers in a similar manner: the mitochondria were sedimented at 6,500 x g for 10 min, the fluffy layer at 15,000 x g for 15
The intracellular distribution of alanine aminotransferase, glutamate dehydrogenase, lactate dehydrogenase, and glucose-6-phosphatase activities in rat and pig livers

### Table 1

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Rat Total</th>
<th>Rat Cytosol</th>
<th>Rat Microsomes</th>
<th>Rat Fluffy layer</th>
<th>Rat Mitochondria</th>
<th>Rat Nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total alanine aminotransferase</td>
<td>34.2 ± 4.0</td>
<td>29.0 ± 1.2</td>
<td>2.3 ± 0.2</td>
<td>0.28 ± 0.02</td>
<td>3.4 ± 0.6</td>
<td>0.39 ± 0.02</td>
</tr>
<tr>
<td>Glutamate dehydrogenase</td>
<td>46.7 ± 3.2</td>
<td>6.7 ± 0.3</td>
<td>30.4 ± 1.6</td>
<td>2.2 ± 0.04</td>
<td>31.6 ± 1.9</td>
<td>0.39 ± 0.10</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>45.0 ± 1.9</td>
<td>43.7 ± 1.9</td>
<td>1.3 ± 0.2</td>
<td>0.06 ± 0.05</td>
<td>0.25 ± 0.05</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Glucose-6-phosphatase</td>
<td>20.0 ± 0.9</td>
<td>0.60 ± 0.05</td>
<td>14.8 ± 0.8</td>
<td>1.6 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>Pig Alanine aminotransferase</td>
<td>13.8 ± 0.6</td>
<td>5.5 ± 0.3</td>
<td>0.27 ± 0.01</td>
<td>5.8 ± 0.8</td>
<td>0.19 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Glutamate dehydrogenase</td>
<td>86.1 ± 1.8</td>
<td>5.2 ± 0.4</td>
<td>72.2 ± 1.9</td>
<td>5.8 ± 0.8</td>
<td>5.1 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>60.8 ± 1.5</td>
<td>58.4 ± 3.7</td>
<td>0.49 ± 0.05</td>
<td>0.61 ± 0.04</td>
<td>0.61 ± 0.07</td>
<td>4.2 ± 0.2</td>
</tr>
<tr>
<td>Glucose-6-phosphatase</td>
<td>17.0 ± 0.9</td>
<td>0.85 ± 0.03</td>
<td>11.9 ± 0.7</td>
<td>1.7 ± 0.8</td>
<td>0.85 ± 0.05</td>
<td>1.7 ± 0.1</td>
</tr>
</tbody>
</table>

*Mean ± S.E. of four animals.

### RESULTS

Earlier studies suggested that no alanine aminotransferase was present in nonmitochondrial particles in rat liver (4, 5), however, the use of appropriate marker enzymes for the various cellular fractions was not reported in these studies. Therefore, we have reexamined the cellular distribution of alanine aminotransferase activities in both the rat and pig. The homogenates were fractionated by differential centrifugation as described above; solubilized glutamate dehydrogenase activity was used as a marker for mitochondrial breakage, lactate dehydrogenase activity was a measure of the contamination of the various fractions by the cytosol, and glucose-6-phosphatase was used as a marker for microsomal contamination.

It is clear from Table I that in rat liver most of the alanine aminotransferase activity is located in the soluble fraction of the cell (85%). Of the remaining activity, almost 70% is associated with the mitochondria, 6% with the fluffy layer, and 6% with the nuclear fraction. The distribution of glutamate dehydrogenase activity indicated that at least 15% of the mitochondria activity was present in the fluffy layer and 5% was sedimented with the nuclear fraction. That there was very little cytosolic contamination is indicated by the presence of less than 1% of the total lactate dehydrogenase activity in the mitochondrial or fluffy layer fractions. Although 15% of the microsomal marker activity was in the latter fractions, the possibility that the so-called mitochondrial activity was due to microsomal contamination is untenable because alanine ami...
Alanine aminotransferase activity was absent from isolated microsomes (Table 1). 1

Table I also shows the results obtained from an analysis of porcine liver. In this species only 40% of the total alanine aminotransferase activity recovered was found in the soluble fraction. As in rat liver, most of the particulate alanine aminotransferase activity (86%) was associated with the mitochondrial and flask layer fractions. Again, as in the rat, no alanine aminotransferase activity could be detected in the microsomal fraction.

Because alanine aminotransferase activity appeared to be confined to the cytosolic and mitochondrial compartments it was feasible to use the short procedure described above to measure the distribution of the activities in other tissues and/or species. Table II shows the distribution of alanine aminotransferase, lactate dehydrogenase, and glutamate dehydrogenase in the cytosol and particulate fractions from rat and pig. In accord with the above results, at least 15% of the total alanine aminotransferase activity in rat liver is particulate bound. In pig liver, on the other hand, at least 50% of the total activity can be found in the particulate fraction. This distribution did not change significantly when mitochondrial breakage was taken into account (Table II). This difference between rat and pig is not due to susceptibility of the liver cells to homogenization as demonstrated by the similarity in completeness of release of lactate dehydrogenase activity. The similar distribution of glutamate dehydrogenase activity in the preparations indicates that there is little difference between the two species in the fragility of the mitochondria. The correspondence between the data of Tables I and II and the fact that the particulate enzyme probably is located only in the mitochondria indicate that the latter method can be used to measure the distribution of alanine aminotransferase activity between cytosol and mitochondria.

**Intramitochondrial Localization of Alanine Aminotransferase**—Although the results presented above make it unlikely that mitochondrial alanine aminotransferase activity can be attributed to contamination of these particles by other cellular fractions, the possibility remained that a nonspecific adsorption of the soluble enzyme occurs on the outer mitochondrial membrane, which in the pig could be of more quantitative significance than in the rat. Pig liver mitochondria, isolated by differential centrifugation, were fractionated into soluble, inner and outer membrane fractions by the method described above. Glutamate dehydrogenase activity was used as a marker for the matrix space, cytochrome oxidase activity for the inner membrane, and monoamine oxidase activity represented the outer membrane. The distribution of these enzymes (Table III) is in accord with that obtained by other authors for rat liver mitochondria. The sharpness of separations of these activities attests to the quality of the preparations.

Sixty per cent of the mitochondrial alanine aminotransferase activity was found in the soluble fraction; the remaining activity was almost completely recovered in the heavy fraction. The fact that no alanine aminotransferase was associated with the light fraction (outer membrane) makes it very unlikely that there was a nonspecific adsorption of the cytosolic enzyme on the outer membrane. This distribution pattern of alanine

1 Enrichment of crude mitochondrial preparations by rate-zonal centrifugation through a sucrose gradient has shown that no alanine aminotransferase activity is associated with either the lysosomes or peroxisomes. R. W. Swick, J. L. Stance, S. L. Nance, and J. P. Thomson, unpublished data.
enzymes were chosen on the basis of their participation in pathways which do or do not immediately involve the substrates of alanine aminotransferase.

Table IV shows the distribution of several enzymes compared to that of alanine aminotransferase expressed as the ratio of their activity in the cytosol to that in the mitochondria. Of those enzymes examined only the distribution of alanine aminotransferase is greatly different in rat and porcine liver. Therefore, it appears that there may be a unique difference in the distribution of alanine aminotransferase activities between the rat and pig.

**Kinetic Properties of Mitochondrial Alanine Aminotransferase**—Because the kinetic properties of two isoenzymes may help define and limit their roles in metabolism, we measured the Michaelis constants for mitochondrial alanine aminotransferase using a partially purified preparation. The enzyme, from porcine liver, was enriched more than 100-fold by ammonium sulfate fractionation, DEAE-cellulose chromatography, and gel filtration through Sephadex G-150. One major and two minor contaminating bands were obtained after acrylamide disc gel electrophoresis. Estimates were made of the reciprocal values of \( V_{max} \) for alanine and \( \alpha \)-ketoglutarate at four levels of the co-substrate (Figs. 1 and 2). A secondary plot of these values against the reciprocal of the co-substrate concentrations permits the estimation of \( V_{max} \) at infinite co-substrate concentration and calculation of the absolute \( K_m \) values. The Michaelis constants were \( 1.9 \pm 0.3 \) mM for alanine and \( 0.42 \pm 0.05 \) mM for \( \alpha \)-ketoglutarate. Somewhat higher values were reported when a crude mitochondrial extract was used (5). Nevertheless, the \( K_m \) value for alanine is more than an order of magnitude lower than that for the cytosolic alanine aminotransferase (4, 5). On the other hand, there is little difference between the isozymes in the \( K_m \) values for \( \alpha \)-ketoglutarate.

**Intracellular Distribution of Alanine Aminotransferase in Several Tissues from Four Species**—The search for differences in the intracellular distribution of alanine aminotransferase was extended to other tissues and other species. Using differential centrifugation, we have demonstrated that alanine aminotransferase is also located in the cytosol and/or in the mitochondria in the guinea pig and chicken. Thus, the use of the short method gives a meaningful measure of the distribution of the transaminases between these cellular compartments. Glutamate dehydrogenase was measured as an index of the mitochondrial breakage, and the values for the mitochondrial alanine aminotransferase were calculated as before.

The results are shown in Table V. The total concentration of alanine aminotransferase activity in rat liver was 4 to 10 times higher than in other species, while the concentrations in pig,

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Cytosolic/mitochondrial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Rat</td>
</tr>
<tr>
<td></td>
<td>Pig</td>
</tr>
<tr>
<td></td>
<td>3.90 ± 0.27</td>
</tr>
<tr>
<td></td>
<td>4.79 ± 0.27</td>
</tr>
<tr>
<td>Malate dehydrogenase</td>
<td>9.43 ± 0.61</td>
</tr>
<tr>
<td></td>
<td>1.95 ± 0.33</td>
</tr>
<tr>
<td>Citrate cleavage enzyme</td>
<td>9.68 ± 0.57</td>
</tr>
<tr>
<td></td>
<td>11.84 ± 1.38</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>1.18 ± 0.53</td>
</tr>
<tr>
<td></td>
<td>1.75 ± 0.53</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>5.12 ± 0.81</td>
</tr>
<tr>
<td></td>
<td>0.84 ± 0.16</td>
</tr>
</tbody>
</table>

\( ^* \text{Mean ± S.E. of four animals.} \)

\( I/V \)

**Fig. 1.** Double reciprocal plot for the determination of the \( K_m \) for alanine for mitochondrial alanine aminotransferase. The kinetic method for the assay of enzyme activity was used (5): the incubation mixture was 0.1 M Tris-HCl buffer, pH 7.8, 0.15 mM NADH, and excess lactate dehydrogenase. The addition of alanine aminotransferase brought the final volume to 3 ml. The rate of oxidation of NADH with the time was recorded at 340 nm at 30°. The numbers in parentheses indicate the concentration (millimolar) of the fixed substrate (alanine); the negative abscissa intercept in the inset is \( 1/K_m \) for alanine.

**Fig. 2.** Double reciprocal plot for the determination of the \( K_m \) for \( \alpha \)-ketoglutarate for mitochondrial alanine aminotransferase. The assays were performed as described in the legend of Fig. 1. The numbers in parentheses indicate the concentration (millimolar) of the fixed substrate (\( \alpha \)-ketoglutarate). The negative abscissa intercept in the inset is \( 1/K_m \) for \( \alpha \)-ketoglutarate, \( \alpha KG \), \( \alpha \)K\( G \), \( \alpha \)K-glu.

Fig. 2. Double reciprocal plot for the determination of the \( K_m \) for \( \alpha \)-ketoglutarate for mitochondrial alanine aminotransferase. The assays were performed as described in the legend of Fig. 1. The numbers in parentheses indicate the concentration (millimolar) of the fixed substrate (\( \alpha \)-ketoglutarate). The negative abscissa intercept in the inset is \( 1/K_m \) for \( \alpha \)-ketoglutarate, \( \alpha KG \), \( \alpha \)K-glu.

The results are shown in Table V. The total concentration of alanine aminotransferase activity in rat liver was 4 to 10 times higher than in other species, while the concentrations in pig,

\( \text{guinea pig and chicken were not markedly different from each other. On the other hand, wide differences were observed in the intracellular distribution of the enzyme among these species. The ratio of cytosolic to mitochondrial activity was almost an order of magnitude lower in pig and guinea pig than it was in rat liver. In fowl it was 10\(^{-3}\) times that observed in the rat and 10\(^{-2}\) times that observed in pig and guinea pig. There was essentially no cytosolic alanine aminotransferase activity in chicken liver.} \)
It is also clear from Table V that these ratios mainly reflect widely different amounts of cytosolic alanine aminotransferase activity among the various species; only small differences were found in the activity associated with the liver mitochondria. The intracellular distribution of alanine aminotransferase activity in kidney was similar to that observed in the liver (except in the rat). On the other hand, in skeletal and cardiac muscles, the cytosolic form represented more than 90% of the total in all four species. This distribution is independent of that found in the liver and kidney, and of the total activity, which differs markedly from one species to another.

**DISCUSSION**

Our studies of the intracellular distribution of the alanine aminotransferase isoenzymes show that in skeletal and cardiac muscle the predominant form of the transaminase is the cytosolic enzyme while the mitochondrial activity is very low. The concentration of alanine and pyruvate in resting muscle is 0.32 and 0.1 µmol/g, respectively, and during exercise may increase to 1.62 and 4 µmol/g (22). The Michaelis constant of cytosolic alanine aminotransferase for pyruvate is 0.9 mM (23) and the pyruvate concentration varies about this value while that of alanine is from 30 to 100 times lower than its Kₘ value (34 mM), thus suggesting that the reaction will proceed in the direction of alanine formation. This is consistent with the known formation and release of alanine from muscle during gluconeogenesis (e.g. Refs. 24-26).

A different situation appears to obtain in gluconeogenic tissues. In liver and kidney of almost every species examined the intramitochondrial enzyme was present in an amount that was similar from species to species while the concentration of the cytosolic enzyme varied widely. This suggests that the mitochondrial form, which has a Michaelis constant of approximately 2 mM for alanine, is involved in the transformation of alanine to pyruvate. This conversion, which eventually results in the formation of glucose, occurs in those tissues in which no cytosolic alanine aminotransferase is present, e.g. chicken liver (27). Furthermore, the rate of glucose formation is similar in liver preparations from rat and guinea pig (28) where the amounts of mitochondrial alanine aminotransferase are also similar although the total enzyme activity is 5 times greater in the rat. On the other hand, those tissues lacking mitochondrial alanine aminotransferase, e.g. rat kidney cortex, are unable to convert alanine to pyruvate (29) although cytosolic alanine aminotransferase is present and alanine can be formed from pyruvate (30). A mechanism for the recovery of reducing equivalents from alanine may also be available. An "alanine dehydrogenase" system has been proposed whereby alanine aminotransferase and glutamate dehydrogenase are linked to produce NADH (31) and such an enzyme-enzyme complex has recently been formed in vitro (32). Because the glutamate dehydrogenase is confined to the mitochondria it would seem reasonable that a more effective coupling would be achieved when the conversion of alanine to pyruvate occurs within this organelle.

The concentration of cytosolic alanine aminotransferase varies from species to species; therefore, we have considered the intracellular distribution of other enzymes involved in this pathway. Two ancillary enzymes in the gluconeogenic pathway were similar in the pig and rat (Table IV). In Table VI, we have compared the distributions between cytosol and mitochondria of alanine aminotransferase and phosphoenolpyruvate carboxykinase; the ratios for the latter enzyme were recalculated from data available in the literature. The similarity of the ratios for the two enzymes in each species is striking, suggesting that cytosolic alanine aminotransferase is present only in those gluconeogenic tissues in which phosphoenolpyruvate carboxykinase occurs in the same compartment.

A reason for this parallel distribution is suggested by an analysis of the interconversions through which substrates may go in order to enter the gluconeogenic pathway via pyruvate (Figs. 3 and 4). In those species, such as the rat, in which phosphoenolpyruvate carboxykinase is located mainly in the cytosol (36), oxalacetate, formed in the mitochondria, must first be converted to malate or aspartate in order to cross mitochondrial membranes (31, 38). When alanine is the
Intracellular distribution of alanine aminotransferase and phosphoenolpyruvate carboxykinase activities in the liver of different species

<table>
<thead>
<tr>
<th>Species</th>
<th>Alanine aminotransferase</th>
<th>Phosphoenolpyruvate carboxykinase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cytosol/ mitochondrial</td>
<td>Per cent in cytosol</td>
</tr>
<tr>
<td>Rat</td>
<td>5.12</td>
<td>82</td>
</tr>
<tr>
<td>Pig</td>
<td>0.84</td>
<td>45</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>0.48</td>
<td>67</td>
</tr>
<tr>
<td>Fowl</td>
<td>0.0045</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*a Calculated from the cited experiments.

When phosphoenolpyruvate carboxykinase is located in the mitochondrial compartment, as in avian liver (35, 39), the carbon chain can cross the mitochondrial membrane as phosphoenolpyruvate, which is freely diffusible (40). Glucose formation from lactate in avian liver is not affected by aminooxyacetate (41), indicating that, in this case, no transamination is involved in the transfer of carbon chains across the mitochondrial membrane. Where phosphoenolpyruvate is found in both compartments, as in the guinea pig, glucose synthesis from lactate is only partially blocked by aminooxyacetate (28).

When alanine or pyruvate is the gluconeogenic substrate, the transfer of reducing equivalents could occur via the cyclic interconversion of oxalacetate, malate, and aspartate. It has been shown, however, that the transport of aspartate into mitochondria is quite limited (42), as is the equilibration of α-ketoglutarate and glutamate across the membrane (43). Perhaps this, the lower alanine aminotransferase activity, and the lack of a urea cycle in avian tissues all contribute to the inability of the chicken to function well on carbohydrate-free diets (44).

The presence of cytosolic alanine aminotransferase only in those gluconeogenic tissues in which aspartate aminotransferase is needed in the same compartment for the transfer of carbon chains across the mitochondrial membrane suggests some sort of coordination between the two cytosolic transaminases. They have two co-substrates in common and both are normally near equilibrium in vivo (45). It is, therefore, possible that the flow of metabolites through alanine aminotransferase can change the flow through aspartate aminotransferase by varying the ratio of the common co-substrates in the cytosol independently of their ratio in the mitochondria. In this way, alanine aminotransferase may regulate the supply of oxalacetate to phosphoenolpyruvate carboxykinase and the availability of aspartate in the cytosol for urea synthesis.

Several studies have demonstrated the important role of alanine in homeostasis and the wide variations in its concentration in blood. The role of the liver in dampening these variations is analogous to the situation encountered in the hepatic uptake of glucose (46). Alanine is actively transported and its intracellular concentration has been calculated to be approximately 2 mM (47). Under normal conditions twice as much alanine will be transaminated via the mitochondrial enzyme as via the cytosolic isozyme if equilibration of substrates between compartments is assumed. However, the presence of the cytosolic enzyme with its high K_m for alanine allows the utilization of this substrate by the liver at the highest alanine concentrations, as well, such as are obtained during

---

**Fig. 3.** Proposed pathway of glucose formation from alanine when phosphoenolpyruvate carboxykinase is a cytosolic enzyme (A) or a mitochondrial enzyme (B). Enzymes involved are (1) lactate dehydrogenase, (2) cytosolic alanine aminotransferase, (3) mitochondrial alanine aminotransferase, (4) pyruvate carboxylase, (5) mitochondrial aspartate aminotransferase, (6) cytosolic aspartate aminotransferase, (7) phosphoenolpyruvate carboxykinase, (8) glyceraldehyde 3-phosphate dehydrogenase, (9) cytosolic malate dehydrogenase, and (10) mitochondrial malate dehydrogenase. PEP, phosphoenolpyruvate; OAA, oxalacetate; α-KG, α-ketoglutarate; MAL, malate; PYR, pyruvate.

**Fig. 4.** Proposed pathway of glucose formation from lactate when phosphoenolpyruvate carboxykinase is a cytosolic enzyme (A) or a mitochondrial enzyme (B). Enzymes and abbreviations as identified in Fig. 3.
maximum gluconeogenic stimulation or during studies with isolated, perfused livers. This allows the liver to "buffer" effectively wide variations in the concentration of alanine.

It is apparent from the diagrams that the intramitochondrial transamination of alanine to pyruvate yields the simplest pathways and balanced schemes. This hypothesis is consistent with the known events in gluconeogenesis. The possible involvement of the alanine aminotransferase isozymes in the regulation of gluconeogenesis, as demonstrated by in vitro experiments, will be considered in a subsequent publication.

Acknowledgment—The authors are grateful to Mr. Terry Burk for excellent technical assistance.

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