The metabolism of glycine is characterized largely by synthetic reactions. Even the catabolism of glycine appears to foster synthetic reactions because its cleavage leads to the formation of a one-carbon tetrahydrofolate compound which can serve in a variety of synthetic pathways. In non-ketotic hyperglycinaemia the activity of the glycine cleavage reaction is defective. This has been demonstrated in vivo and in vitro using liver and brain.

Non-ketotic hyperglycinaemia is an inborn error of metabolism in which large amounts of glycine are found in body fluids and there is no demonstrable accumulation of organic acids. It is in this way distinguishable from the ketogenic hyperglycinaemia syndrome which occurs with propionic acidaemia and other disorders of organic acid metabolism.

Non-ketotic hyperglycinaemia was first described in detail by Gerritsen et al. (1965). The patient is generally first seen with overwhelming illness early in life. Patients who survive generally have extreme degrees of cerebral defect. However, the disorder is probably heterogeneous and patients with mild degrees of mental retardation have been seen. The fundamental defect appears to be in the glycine cleavage reaction (Ando et al., 1968; Tada et al., 1969).

**METABOLISM OF GLYCINE**

Glycine is the simplest of the amino acids, having only two carbon atoms, an amino group and a carboxyl group. It is a non-essential amino acid and can be synthesized in man. The daily intake of an average adult is 3–5 g. The taste of glycine is sweet. The amino acid is also glucogenic. This may be demonstrated by feeding the amino acid to a starved animal and examining for glycogen in the liver.

Glycine is involved in a variety of synthetic reactions (Nyhan, 1982), including the synthesis of proteins, which accounts for about 50% of the metabolism of administered glycine (Ratner et al., 1940). The extent of conversion to protein serine is about four times that of direct incorporation into protein glycine (Bakay and Nyhan, 1970; Winnick et al., 1948), an index of the importance of the glycine–serine interconversion (Figure 1).

When labelled glycine is fed, there is a lag of 6–8 h before glycogen is formed, suggesting that glycine must first be converted to other molecules, which are subsequently converted to glucose. Furthermore, twice as much of the α-carbon of glycine as of the carboxyl carbon appears in glycogen, suggesting a conversion to serine. There is also a lag of 6–8 h before glycine nitrogen appears in urinary urea. This suggests further that glycine is to a considerable extent first involved in synthetic reactions.

The interconversion of glycine and serine is the most important pathway in the catabolism of glycine. In man, labelled serine appears in the blood promptly after the injection of labelled glycine (Ando et al. 1968; Nyhan and Childs, 1964).

When glycine is labelled in the 2 position with carbon-14, the label is found in the 2 and 3 positions of serine (Ando et al., 1968; Sakami, 1949). The proportions of carbon 2 of glycine converted to carbon 2 and carbon 3 of serine are about equal.

The system involved in the conversion of glycine to serine (Richert et al., 1962; Sagers and Gunsalus, 1961) is tetrahydrofolate (FH4) dependent and proceeds as follows:

\[
\begin{align*}
\text{NH}_2\text{CH}_2\text{COOH} + \text{FH}_4 + \text{H}_2\text{O} & \rightarrow \text{FH}_4\text{CH}_2\text{OH} + \text{CO}_2 + \text{NH}_3 \tag{1} \\
\text{FH}_4\text{CH}_2\text{OH} + \text{NH}_2\text{CH}_2\text{COOH} & \rightarrow \text{HOCH}_2\text{CHNH}_2\text{COOH} + \text{FH}_4 \tag{2}
\end{align*}
\]

Reaction 1 is not required for Reaction 2. Reaction 2, catalysed by serine hydroxymethyl transferase, can
Figure 1  The interconversion of glycine and serine. Abbreviations employed include: FH₄, tetrahydrofolic acid; and 1-C units, single carbon units. (Reprinted with permission from Ando et al., Pediatr. Res. 2 (1968) 254)

proceed using glycine and single carbon sources other than glycine. Reaction 1 could serve the catabolism of glycine independently of serine biosynthesis.

Four protein fractions catalyse the overall reaction (Klein and Sagers, 1966). The first enzyme catalyses the decarboxylation of glycine, and it is reversible. All four proteins are required to catalyse the overall conversion of glycine to CO₂, NH₃ and an FH₄ derivative. E₁ contains a bound pyridoxal phosphate. E₂ is a heat-stable protein. E₃ and E₂ are required for this decarboxylation. E₃ is a flavoprotein which is reduced in the presence of E₂ and glycine and transfers electrons to NAD (Baginski and Huennekens, 1966). E₄ transfers carbon 2 of glycine to FH₄. The glycine-serine interconversion follows the same sequence in mammalian liver. The process has been clarified largely through the work of Kikuchi and colleagues (Kawasaki et al., 1966; Kikuchi, 1973; Motokawa and Kikuchi, 1974; Yoshida and Kikuchi, 1972). It was first found that rat liver mitochondria can synthesize glycine by a CO₂ fixation reaction in which serine and ammonia yield two molecules of glycine. The β-carbon of serine and bicarbonate carbon were incorporated in a 1:1 ratio into the α- and carboxyl carbons of glycine. Methylene-FH₄ was effective in replacing serine in the synthesis of glycine. The enzyme preparation also catalysed the decarboxylation of glycine; the glycine cleavage required FH₄. The extracts also catalysed an exchange between the carboxyl carbon of glycine and CO₂. Pyridoxal phosphate is a component of the enzyme complex. These observations indicated the presence in mammalian liver of a system similar to that in P. glycinophilus.

The glycine cleavage system is entirely mitochondrial. The four protein components have now been designated P, H, T and L (Figure 2). The P-protein is the pyridoxal

Figure 2  The glycine cleavage reaction. (Reprinted with permission from Nyhan, in Stanbury, J., Wyngaarden, J. and Frederickson, D. (eds.) The Metabolic Basis of Inherited Disease, 5th ed., 1982)