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METABOLISM OF SULFUR-CONTAINING AMINO ACIDS

Martha H. Stipanuk

Division of Nutritional Sciences, Cornell University, Ithaca, New York 14853

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INTRODUCTION

It has long been recognized that L-methionine (Met) is metabolized by transmethylation and transsulfuration, but recent studies have provided more information about the regulation of flux through these pathways and about the fate of the transferred methyl group and sulfur atom. The role of the polyamine pathway and the possible role of a transamination pathway in Met metabolism were demonstrated more recently. L-Cysteine (Cys) metabolism has received relatively little attention, but the interpretation of several recent studies in light of the older literature provides some new insights. The intent of this review is to provide an overview of current knowledge about pathways of sulfur-containing amino acid metabolism in mammalian tissues and the physiological regulation

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of flux through these pathways. Most of the research on sulfur-containing amino acid metabolism has focused on the liver and, hence, so does this review. However, the relative roles of the liver and other tissues in the metabolism of Met and Cys in vivo have not been well established, so extrahepatic tissues may also play a significant role in Met and Cys metabolism.

METHIONINE METABOLISM

The Formation and Utilization of S-Adenosylmethionine

The first step in Met metabolism is the formation of the high-energy sulfonium compound, S-adenosyl-L-methionine (AdoMet). AdoMet is both the methyl donor for transmethylation reactions and the precursor of decarboxylated AdoMet [dAdoMet; S-adenosyl(5')-3-methylthiopropylamine], which is the aminopropyl donor for the synthesis of polyamines. Met adenosyltransferase (EC 2.5.1.6) catalyzes the formation of AdoMet by transfer of the adenosyl moiety of ATP to the sulfur atom of Met. Multiple isozymes of Met adenosyltransferase exist in mammalian tissues (112, 113, 116, 134, 138, 139, 206, 209, 216). Three isozymes (I, II, and III) have been identified in rat liver (206). Met adenosyltransferase-I (α) shows Michaelis-Menten kinetics with a K_m for Met of 41 μM, is slightly inhibited by AdoMet, and comprised about 15% of the total Met adenosyltransferase activity in rat liver preparations when activity was assayed at 25 μM Met. Met adenosyltransferase-II (γ), which also appears to be the isozyme found in normal rat kidney, has a Met concentration required for half-maximal velocity [$S_{0.5}$ (Met)] of 8 μM, is strongly inhibited by AdoMet, and comprised about 5% of the total activity in rat liver. The predominant isozyme in rat liver, Met adenosyltransferase-III (β), has a $S_{0.5}$ (Met) of 215 μM and demonstrates positive cooperative modulation by AdoMet at physiological metabolite concentrations (50–150 μM Met, 50–200 μM AdoMet). Thus, the velocity of AdoMet synthesis in extraheptic tissues would be expected to be nearly maximal, relatively unaffected by an increase in Met concentration, and sensitive to feedback/product inhibition by AdoMet. In contrast, the velocity of AdoMet synthesis by the high-K_m hepatic isozyme should increase in response to elevated Met and AdoMet levels, permitting rapid clearance of excess Met by the liver.

The Met adenosyltransferase isozyme pattern is altered in fetal and neoplastic liver and in liver of patients with hereditary tyrosinemia, with a marked reduction in levels of the high-K_m isozyme, MAT-III (112, 113, 116, 139, 216). Gaull et al (71) and Finkelstein et al (62) studied children with low levels of hepatic Met adenosyltransferase activity (8–18% of control values for adults) concomitant with the presence of normal amounts of enzyme in erythrocytes, cultured fibroblasts, and lymphoid cell lines. Despite persistent hypermethioninemia, these patients were free of adverse symptoms. Although he-

patic Met adenosyltransferase activity in one child was 8% of the control level when activity was assayed at 1 mM Met, it was 39% of control levels when the assays were performed with 6–12 μM Met. It seems probable that these children lacked active Met adenosyltransferase-III, but had normal levels of the low-K_m isozymes.

AdoMet serves as the methyl donor for essentially all known biological methylation reactions with the notable exception of those involved in methylation of L-homocysteine (Hcy). The co-product of transmethylation, S-adenosyl-L-homocysteine (AdoHcy), is hydrolyzed to yield Hcy, which can be remethylated to Met or condensed with serine to form cystathionine. Formation of cystathionine commits the Met molecule to catabolism by the transsulfuration pathway. These transmethylation reactions and the transsulfuration pathway are depicted in Figure 1.

A second fate of AdoMet involves its decarboxylation to form dAdoMet, which is the donor of aminopropyl groups for synthesis of spermidine and

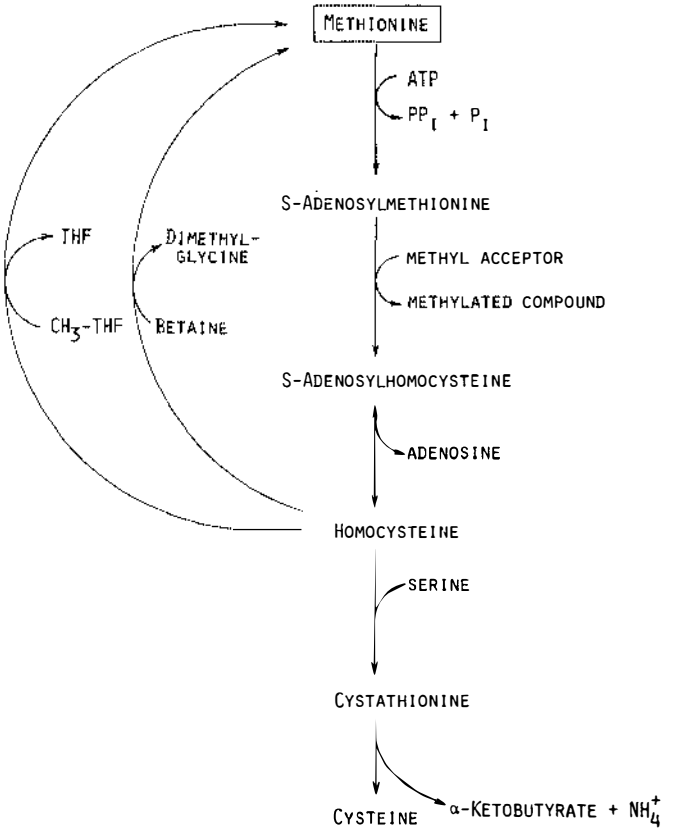

Figure 1 The transmethylation-transsulfuration pathway.

spermine. Polyamine synthesis also results in the formation of 5'-methylthioadenosine (MTA) from dAdoMet. The sulfur and methyl group of MTA may be reincorporated into Met by the MTA salvage pathway, whereas the aminopropyl group does not appear to be recycled. The reactions involved in polyamine synthesis and MTA salvage are summarized in Figure 2.

Few estimates have been made of the relative flux of AdoMet through these two pathways. Recycling of Hcy and of MTA to Met can lead to underestimation of the magnitude of AdoMet flux through either transmethylation reactions or the polyamine pathway. Giulidori et al (72) measured the $^{14}CO_2$ produced by intact rats given intravenous S-adenosyl-[1-^{14}C]Met or S-adenosyl-[3,4-^{14}C]Met. They suggested that 30% of the irreversibly catabolized AdoMet was used for the aminopropylation pathway following decarboxylation. About 70% of the AdoMet apparently was catabolized by the transsulfuration pathway following transmethylation, as there was no evidence for nonenzymatic decomposition of AdoMet. These estimates are probably maximal for decarboxylation-aminopropylation and minimal for transmethylation because the authors made no corrections for Hcy recycling or for incomplete or differential recovery of the carbon atoms as CO_2. The recovery of the 1-carbon should have been substantially greater than that of the 3- and 4-carbons because of direct decarboxylation of AdoMet or of α-ketobutyrate compared to metabolism of the 3- and 4-carbons via the tricarboxylic acid cycle.

Iizasa & Carson (89) estimated the relative rates of polyamine synthesis and transmethylation from AdoMet in malignant human and murine cell lines deficient in MTA phosphorylase. These cells did not detectably cleave MTA

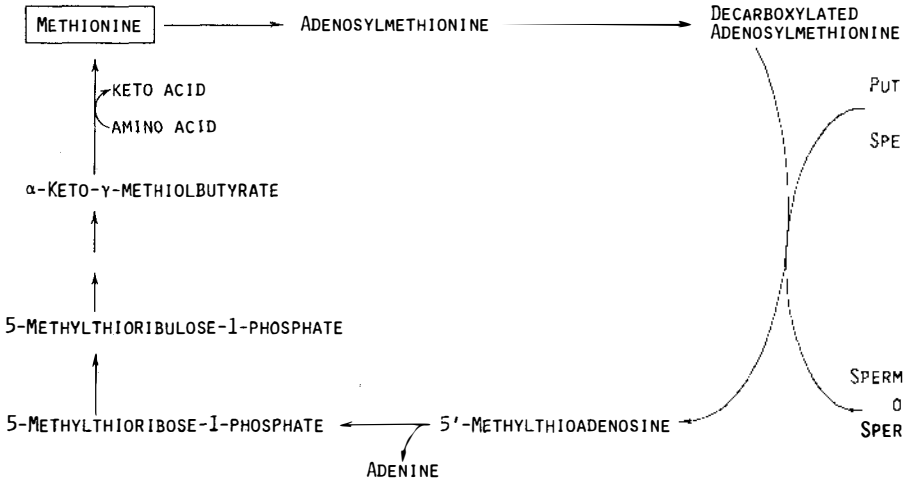

Figure 2 The polyamine pathway.

and did not appreciably metabolize Hcy. Both MTA and Hcy were excreted into the growth medium. During exponential growth of lymphoblasts, the MTA excretion rate was 80–130 and the Hcy excretion rate was 210–290 $pmol \cdot h^{-1} \cdot 10^6$ $cells^{-1}$; thus, MTA excretion represented about 30% of the AdoMet consumption in these rapidly growing cells. Both the rates of MTA and Hcy production would be expected to be substantially lower in non- or slowly dividing cells.

The Transmethylation and Transsulfuration Pathway

METHYLATION REACTIONS The methyl group of AdoMet is transferred to a nitrogen, oxygen, or sulfur atom of a wide range of compounds in reactions catalyzed by numerous methyltransferases. The major use of labile methyl groups appears to be for the formation of creatine from guanidinoacetate. Mudd & Poole (132) reported urinary excretions of creatinine that were approximately 15–16 $mmol \cdot day^{-1}$ in men and 10 $mmol \cdot day^{-1}$ in women, whereas other methylated compounds excreted in urine, including creatine, only accounted for 1.6–2.6 meq of labile methyl $groups \cdot day^{-1}$.

Loss of labile methyl groups via oxidation of the carbon to C-1 intermediates at oxidation levels of formaldehyde, formate, or CO_2 appears to occur primarily via formation and degradation of sarcosine, as shown in Figure 3 (129, 225a, 229). Based on sarcosine excretion by a female sarcosinuric patient, Mudd et al (129) estimated that about 1.5–3.0 mmol of labile methyl groups were oxidized via the sarcosine pathway each day when the subject was on a relatively normal dietary intake; total daily utilization of Met methyl groups in transmethylation reactions was estimated to be 13–14 meq. Intake of labile methyl groups (Met or choline) beyond the apparent requirement of approximately 14 meq per day resulted in nearly equimolar increases in sarcosine production beyond those accounted for by choline degradation; this sarcosine was presumably synthesized via the glycine methyltransferase reaction. De novo synthesis of methyl groups via the tetrahydrofolate (THF) system appeared to be minimal when labile methyl intake was sufficient or excessive. The labile methyl group intake beyond which additional methyl groups were used for sarcosine production was in agreement with the sum of methyl group utilization for various methylation reactions under basal conditions; this agreement suggests that Mudd and coworkers have accounted for most, if not all, of the major routes of Met methyl group utilization (129, 132). It seems clear that the major daily requirement for labile methyl groups is for creatine formation and that the major mechanism for removal of excess methyl groups is via sarcosine production and degradation.

Data from studies with intact rats are also consistent with metabolism of excess Met methyl carbon via the combined action of Met adenosyltransferase (probably isozyme-III), glycine methyltransferase (EC 2.1.1.20), and sarco-

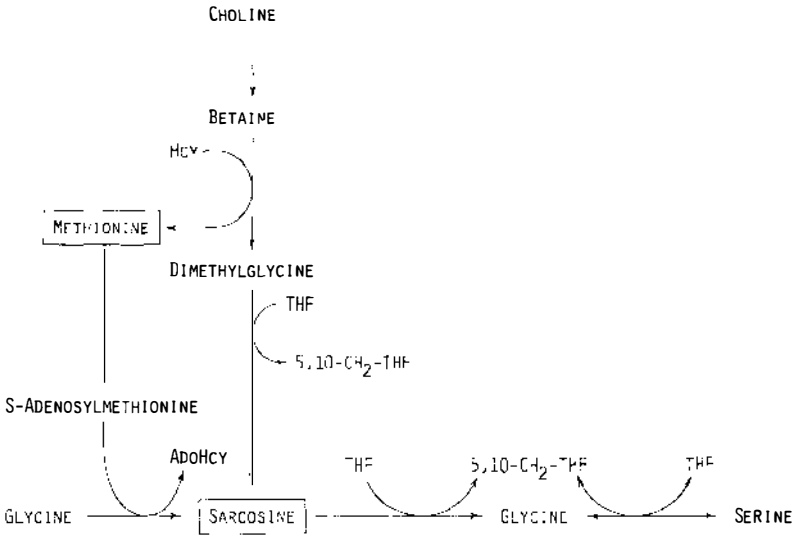

Figure 3 Pathway for methyl group oxidation.

sine dehydrogenase (EC 1.5.99.1). In intact rats given intraperitoneal injections of [Me-^{14}C]Met, up to 40% of the label incorporated into hepatic proteins was recovered in serine and a smaller amount was found in Cys (2, 3). The labeling of serine presumably occurred via conversion of sarcosine to glycine and $N^{5,10}$ methylene-tetrahydrofolate (methylene-THF) (225a, 229)] in the reaction catalyzed by sarcosine dehydrogenase, followed by conversion of glycine and methylene-THF to serine in the reversible reaction catalyzed by serine hydroxymethyltransferase (EC 2.1.2.1). A small amount of label was presumably incorporated into Cys by utilization of the labeled serine in the transsulfuration pathway. As would be expected if production of sarcosine is dependent upon the availability of excess labile methyl groups, both the conversion of the Met methyl carbon to CO_2 and the incorporation of the methyl carbon into serine were decreased when the rats were fed choline-devoid or Met-deficient diets (2).

Recently, Wagner (225b) reported that glycine methyltransferase is allosterically inhibited by the polyglutamate form of N^5-methyltetrahydrofolate (methyl-THF), which accumulates in the cell during Met deficiency. Thus, regulation of glycine methyltransferase may play a role in conservation of labile methyl groups when Met intake is inadequate.

Oxidation of excess labile methyl groups via sarcosine production and degradation appears to be dependent upon the methylation of glycine rather than upon phosphatidylcholine turnover, both of which generate sarcosine from the methyl group of AdoMet. Case et al (26) showed that phosphatidylcholine turnover did not account for a significant amount of Met methyl group oxidation

in the intact rat. Additionally, phosphatidylcholine biosynthesis by methylation of phosphatidylethanolamine or by incorporation of pre-formed choline appears to be regulated to maintain a relatively constant level of phosphatidylcholine in tissues (29, 159). As expected, increased incorporation of label from [Me-^{14}C]Met into tissue phosphatidylcholine was observed in rats fed choline-devoid diets, whereas decreased incorporation was observed in rats fed Met-deficient diets (2, 3). This is in marked contrast to the similar effects that changes in either Met or choline intake had on the conversion of the methyl carbon of Met to serine, sarcosine, or CO_2.

METABOLISM OF S-ADENOSYLHOMOCYSTEINE AdoHcy is hydrolyzed to adenosine (Ado) and Hcy by AdoHcy hydrolase (EC 3.3.1.1). This reaction is apparently the sole means of intracellular removal of AdoHcy in mammalian tissues (44, 46). The reaction is reversible with the equilibrium far in the direction of synthesis (K_{eq} = 1 μM), but hydrolysis occurs in vivo when Ado is removed by Ado deaminase (EC 3.5.4.4) or Ado kinase (EC 2.7.1.20) and when Hcy is removed by cystathionine β-synthase (EC 4.2.1.22), betaine-Hcy methyltransferase (EC 2.1.1.5), or Met synthase (tetrahydropteroylglutamate methyltransferase, EC 2.1.1.13). AdoHcy hydrolase contains tightly bound NAD^+, which participates in the catalytic process (69). The $S_{0.5}$ of the rat or mouse liver enzyme for AdoHcy has been reported to range from 0.75 to 20 μM when measured with low concentrations of enzyme (41, 69, 95, 219) and to be 120 μM at cellular concentrations of enzyme (219); tissue concentrations of AdoHcy range from <0.8 to 56 nmol·g^{-1} (43, 61, 83, 221, 226).

Hydrolysis of AdoHcy is inhibited by the presence of either product, Hcy or Ado, and inhibition is accompanied by the accumulation of AdoHcy and AdoMet (84, 168). Purine nucleoside toxicity (observed in children with Ado deaminase deficiency or purine nucleoside phosphorylase deficiency and in patients treated with 9-β-D-arabinofuranosyladenine) as well as the growth inhibitory properties of MTA may be mediated partially through inhibition of AdoHcy hydrolase (16, 21, 53, 68, 94, 106, 160). Inhibition of AdoHcy hydrolase may lead to decreased intracellular Met synthesis from Hcy and altered folate metabolism due to the methyl trap effect (16, 21), inhibition of intracellular transmethylation reactions (22, 106), and inhibition of Ado kinase (68).

The cellular concentration of AdoHcy itself or the ratio of AdoMet to AdoHcy may serve as a feedback regulator of biological methylation reactions. Most methyltransferases that utilize AdoMet as the methyl donor are inhibited by AdoHcy, and the inhibitory constants vary over a wide range (K_i for AdoHcy = 1–35 μM; K_m for AdoMet = 1–570 μM) (22, 23, 83, 84, 98). Whether or not regulation of methyltransferase reactions by AdoHcy occurs under physiological conditions is questionable, because the ratio of the concen-

tration of AdoHcy to that of AdoMet is relatively low compared to that required for inhibition of methyltransferases, and the activity of AdoHcy hydrolase is higher than that of Met adenosyltransferase in most tissues (43, 45, 61, 83, 226). However, when AdoHcy levels in perfused rat liver or in intact rats or mice were increased as a result of inhibition of AdoHcy hydrolase by Ado, Hcy, or 9-β-D-arabinofuranosyladenine, a parallel increase in AdoMet levels was generally seen; the increased levels of AdoMet were probably the result of decreased utilization of AdoMet by methyltransferases that were inhibited by AdoHcy (46, 78, 84). However, when high amounts of both Ado and Hcy were added, a further increase in the concentration of AdoHcy without a parallel increase in the concentration of AdoMet was observed; this increase was presumably due to synthesis of AdoHcy by reversal of the hydrolase reaction (84).

Data from studies with rat hepatocytes and from in vitro experiments with nearly cellular levels of enzyme (10 μM) and of substrates (2 μM Ado, 50 μM AdoHcy) suggest that a substantial portion of cellular AdoHcy hydrolase exists as a stable complex with Ado (219, 220). This enzyme does not appear to participate in the metabolic hydrolysis of AdoHcy but functions instead as an Ado-binding protein in intact cells. The Ado sequestered by the enzyme was not available for synthesis of AdoHcy in the presence of Hcy or for deamination by Ado deaminase (219).

REMETHYLATION OF HOMOCYSTEINE TO SYNTHESIZE METHIONINE The transmethylation-transsulfuration pathway has a branch point at the level of Hcy, as shown in Figure 1. Hcy may be remethylated to Met in the reaction catalyzed by Met synthase or in that catalyzed by betaine-Hcy methyltransferase. It may also be used for resynthesis of AdoHcy by reversal of the hydrolysis catalyzed by AdoHcy hydrolase, as discussed above, or irreversibly converted to cystathionine via the reaction catalyzed by cystathionine β-synthase. This branch point is an important regulatory locus (64, 129, 132).

Met synthase is widely distributed in mammalian tissues (59, 97, 230). It is responsible for the de novo synthesis of Met methyl groups from one-carbon units in the THF coenzyme system. It utilizes methyl-THF as the methyl donor and methylcobalamin as a tightly bound coenzyme. A catalytic amount of AdoMet is required, which apparently is involved in generating the active form of the B_{12}-coenzyme or in stimulating methyltransferase activity (19, 20, 123, 124). The K_m of rat liver Met synthase for Hcy is 60 μM (55).

Met synthase is clearly important in Hcy metabolism. This is evidenced by the elevated levels of homocyst(e)ine and normal or low concentrations of Met that are found in plasma of human patients with inborn errors of metabolism affecting the availability of methyl-THF or active B_{12}-coenzyme and, hence, the activity of Met synthase (77, 85, 131, 169, 177). The inactivation of Met

synthase by exposure of intact animals to nitrous oxide decreased tissue concentrations of Met and AdoMet and impaired essential methylation reactions (119, 120, 223).

In Met deficiency and in vitamin B_{12} deficiency (which presumably mimics a Met deficiency at the cellular level) methyl-THF accumulates in the cell at the expense of other forms of folate (170, 174, 225b). This decreased use of methyl-THF is caused by a lack of active Met synthase (vitamin B_{12} deficiency) or by a lack of Hcy, the methyl group acceptor (Met deficiency). Addition of Met, by increasing the availability of Hcy or by increasing the concentration of AdoMet, results in demethylation of methyl-THF. AdoMet inhibits the conversion of methylene-THF to methyl-THF by methylene-THF reductase (EC 1.1.99.15), a reaction that is essentially irreversible under physiological conditions (36, 109, 225). Inhibition of the reductase occurred at concentrations of AdoMet that were somewhat greater than the normal range for tissue concentrations, and this inhibition was reversed by the presence of AdoHcy (15, 109). Activation of Met synthase by AdoMet is unlikely to play a role in the demethylation of methyl-THF, because Met synthase was fully stimulated at normal tissue concentrations of AdoMet and was unaffected by addition of AdoHcy (15).

Demethylation of methyl-THF causes a redistribution of THF derivatives to other coenzyme forms and allows flux of one-carbon units to other reactions; it also increases the hepatic concentration of total folate and causes a large increase in the hepatic levels of pteroylpolyglutamates (30, 42, 105). Methyl-THF is a poor substrate for rat liver pteroylpolyglutamate synthetase. Thus, methyl-THF taken up from the plasma must be converted to THF via the methyltransferase reaction before it can be converted to a pteroylpolyglutamate, the form of folate that is preferentially retained by tissue (30, 118, 225, 225b). A direct stimulatory effect of Met on the transport of folates in mammalian cells has also been suggested (91).

Unlike Met synthase, which is widely distributed in mammalian tissues, betaine-Hcy methyltransferase is generally found in high concentrations only in mammalian liver (59). Activity has been found in kidney and pancreas of some species (131, 230); substantial levels of activity have been reported for both liver and kidney of human infants and children (131). The enzyme is specific for Hcy, but certain analogs of betaine can also serve as the methyl donor (5, 182). The reported K_m values of the human liver enzyme for Hcy and betaine are 120 and 100 μM, respectively, whereas those for the rat liver enzyme are 15–21 and 49–56 μM, respectively (57, 182).

Betaine-Hcy methyltransferase is inhibited in vitro by the presence of dimethylglycine and possibly by Met, both products of the reaction, and by preincubation with AdoMet (57, 65, 182). Substantial inhibition of the rat liver enzyme by 50 μM Met has been reported (57), but the human liver enzyme was

unaffected by Met (182). A protective effect of AdoHcy on the inactivation of betaine-Hcy methyltransferase by AdoMet has been demonstrated (64, 65); higher levels of AdoHcy that are clearly unphysiological appear to inhibit (competitively with Hcy) the methyltransferase (60).

Hepatic betaine-Hcy methyltransferase activity was increased in rats fed diets that contained no Met and also in those fed diets with high levels of protein or Met (58, 59). Supplemental betaine or choline also induces the enzyme (66, 74). Thus, the enzyme appears to respond to the increased need for labile methyl group transfer or conservation of Hcy when Met intake is low, to the need to metabolize Hcy when Met intake is high, and also to the need to dispose of betaine when betaine or choline intake is high.

The availability of betaine appears to influence conservation or recycling of the Hcy moiety of Met. This suggests that, at least when dietary Met is limited or when Hcy removal by other reactions is blocked, both betaine-Hcy methyltransferase and Met synthase are essential for adequate methylation of Hcy to Met. Addition of betaine to liver slices increased the recycling of the Hcy moiety of Met (8, 230). Betaine supplementation of the diet of fruit bats that had been treated with nitrous oxide (which severely inhibits Met synthase) resulted in reduced weight loss and delayed onset of neurological impairment (224). Furthermore, betaine therapy has been effective in decreasing the Hcy concentration and increasing the Met and Cys concentrations in plasma of patients with homocystinuria (186, 228).

CATABOLISM OF HOMOCYSTEINE—THE TRANSSULFURATION PATHWAY Cystathionine synthase catalyzes the replacement of the β-OH group of L-serine with Hcy to form cystathionine. Cystathionine synthase contains tightly bound pyridoxal 5'-phosphate and also possesses serine sulfhydrase activity (102, 103). The translational product of the synthase gene appears to be a polypeptide of 63,000 kd, which is initially assembled into a tetramer. This product is subject to limited post-translational proteolysis, which reduces the M_r of the original subunit to 48,000 and is associated with a change from a tetrameric to a dimeric structure, a 30-fold decrease in the K_m for Hcy, and a 60-fold increase in specific activity (103, 104, 183, 184). This active form of the enzyme has a K_m of 0.6–0.8 mM for Hcy and 0.1–0.4 mM for serine (103, 184). Proteolytic activation may be tissue specific; it has been observed in human and rat liver but not in human fibroblast extracts (103, 183, 184). Cystathionine synthase is also activated by AdoMet (63, 64), but the effects of proteolytic cleavage and activation by AdoMet are not additive (102). Activation by AdoMet does not appear to be related to the presence of a soluble effector and presumably involves some modification of the enzyme structure (63). Cystathionine synthase may also be activated in vitro by high levels of AdoHcy (60).

The AdoMet concentration may be an important physiological regulator of cystathionine synthase activity. Supplementation of a low Met diet with cyst(e)ine instead of Met results in less hepatic cystathionine synthase activity, which may occur as a result of less activation of the enzyme by AdoMet in vivo (67). The ability of Cys to replace a portion of the dietary Met may be due to this effect on cystathionine synthase activity, but a primary effect of Cys on utilization of Met for protein synthesis could also explain the reduced flux of Met to Cys (196). Patients with a genetic deficiency of Met adenosyltransferase activity have a concomitant decrease in cystathionine synthase activity, which is possibly due to the absence of activation by AdoMet. Although the hypothesis has not been tested, it is tempting to speculate that some of the beneficial effect of betaine therapy in patients with homocystinuria may be related to the resulting increase in Met and, hence, AdoMet levels, which could stimulate cystathionine synthase activity and increase the irreversible flux of Hcy through the transsulfuration pathway.

Finkelstein & Martin (64) studied the metabolism of Hcy using incubation systems reconstituted to contain enzymes (from tissue extracts) and reactants at concentrations that approximated those present in vivo. Systems were modeled on the liver of rats fed chow, 3.5% casein, or 55% casein. They measured flux of Hcy through the reactions catalyzed by Met synthase, betaine-Hcy methyltransferase, and cystathionine synthase by adding either 5-[Me-^{14}C]methyl-THF, [Me-^{14}C]betaine, or L-[3-^{14}C]serine to otherwise identical tubes and measuring the labeled product, Met or cystathionine. When the system was modeled on the liver of chow-fed rats, the activities of Met synthase, betaine-Hcy methyltransferase, and cystathionine synthase accounted for 27, 27, and 46%, respectively, of the Hcy consumed. Inhibition of Met synthase or betaine-Hcy methyltransferase shifted relative flux through the three pathways in a manner suggesting that Met synthase had the highest affinity for Hcy and that cystathionine synthase had the least. This suggestion is consistent with the reported K_m values for these two enzymes (55). The finding that 54% of the Hcy consumed was converted to Met is also consistent with estimates of the extent of remethylation of Hcy to Met in human subjects (129, 132), in the perfused rat liver (55) and in the intact rat (189), all of which were about 50%. Changes in flux through the three pathways in the systems modeled on the livers of rats fed 3.5% casein or 55% casein could be largely explained by changes in enzyme, substrate, and effector concentrations.

Cystathionase (cystathionine γ-lyase, EC 4.4.1.1) catalyzes the γ-cleavage of cystathionine to form Cys and α-ketobutyrate, the final step of the transsulfuration pathway. This pyridoxal 5'-phosphate-dependent enzyme also catalyzes the deamination of homoserine and the desulfhydration of cyst(e)ine (142, 237). The K_m for cystathionine of cystathionase purified from liver of

several species has been reported to be in the range of 0.3 to 3.5 mM (14, 222, 237).

The importance of the transsulfuration pathway in Met metabolism is suggested by a number of observations. The ability of Cys to replace a substantial portion of dietary Met on a nearly equimolar basis (187, 200) and the incorporation of Met or Hcy sulfur into Cys and, thence, into cysteinyl residues of protein and glutathione (9, 202, 211, 212) suggest that transsulfuration is a major pathway for metabolism of Met sulfur. Reduced levels of cystathionine synthase or cystathionase activity in humans with inborn errors of metabolism or in animals fed vitamin B_6–deficient diets result in elevated levels of homocyst(e)ine and cystathionine in plasma and urine (55, 130, 176, 185, 203). Inhibition of cystathionase with an irreversible inhibitor, propargylglycine, markedly reduced $^{35}SO_4$ excretion in rats given [^{35}S]Met or L-[^{35}S]cystathionine (but not in rats given [^{35}S]cysteine) and equally depressed the metabolism of L-[carboxy-*n*-propyl-1-^{14}C]cystathionine and [1-^{14}C]Met to $^{14}CO_2$ (47, 193, 195). Treatment of hepatocytes or intact rats with propargylglycine also resulted in the excretion or accumulation of labeled cystathionine formed from labeled Met (9, 193). The accumulation of homocyst(e)ine and cystathionine as well as the reduction in oxidation of Met to SO_4^{-2} and CO_2 when flux through the transsulfuration pathway is reduced clearly demonstrates the importance of this pathway in normal Met metabolism.

The Polyamine Pathway

FORMATION AND UTILIZATION OF DECARBOXYLATED S-ADENOSYLMETHIONINE The polyamine pathway is important for the synthesis of the polyamines, spermidine and spermine, and possibly for the synthesis of methylthio compounds. The importance of these compounds in cellular physiology is not yet well understood, but the present evidence suggests that they are essential for normal growth (208). As shown in Figure 2, polyamines are synthesized in mammalian cells from ornithine and AdoMet by the actions of ornithine decarboxylase and AdoMet decarboxylase, which provide putrescine and dAdoMet, and of spermidine synthase and spermine synthase, which catalyze the transfer of the aminopropyl group from dAdoMet to putrescine to form spermidine and to spermidine to form spermine (149, 166, 208). The MTA formed from dAdoMet during polyamine synthesis is salvaged by conversion of the methylthioribose moiety into Met and of adenine into adenine nucleotides (7, 96, 166). Polyamine degradation leads to formation of a number of derivatives, but there is no evidence for any reutilization of the aminopropyl group of polyamines (150, 172).

The activated aminopropyl group needed for polyamine synthesis is generated by decarboxylation of AdoMet in a reaction catalyzed by AdoMet decarboxylase (EC 4.1.1.50); this reaction commits the Met molecule to the

polyamine pathway. AdoMet decarboxylase contains a covalently linked pyruvoyl group, which is essential for enzymatic activity, and does not contain pyridoxal 5'-phosphate (39, 143, 145). The activity of AdoMet decarboxylase is regulated by changes in the concentration of putrescine, an activator of the enzyme. AdoMet decarboxylase is activated over a physiological range of putrescine concentrations (0–50 μM), probably by a decrease in the apparent K_m of the enzyme for AdoMet (157, 158, 163). Increased ornithine decarboxylase activity can indirectly increase the supply of dAdoMet by increasing the cellular concentration of putrescine, which, in turn, activates AdoMet decarboxylase (145, 149). This mechanism may ensure that a parallel supply of dAdoMet and putrescine is available and, therefore, that putrescine is efficiently converted to spermidine.

AdoMet decarboxylase activity is also regulated in mammalian tissues by changes in the amount of enzyme protein. The enzyme turns over rapidly with a $t_{1/2}$ of less than 2 h in most tissues (173). The amount of enzyme protein is increased in response to spermidine depletion and to a variety of physiological and nutritional treatments (86, 92, 122, 128, 144, 145, 148, 151, 152, 154, 178, 213). Some studies indicate that high levels of dAdoMet can inhibit AdoMet decarboxylase and limit its accumulation (144, 236), but physiological levels of dAdoMet are probably not high enough to have an effect.

It is likely that the supply of dAdoMet limits the rate of spermidine and spermine synthesis. Concentrations of dAdoMet in rat tissues have been reported to be 0.9–2.5 nmol per gram wet weight compared to AdoMet concentrations of 23–67 nmol per g wet wt (81, 147). The rapid utilization of dAdoMet (so that it does not accumulate in the cell) may be related to the coordinated regulation of putrescine and dAdoMet production (149), to the presence of spermidine synthase and spermine synthase activities at levels that are in substantial excess of that of AdoMet decarboxylase (161), and to the high affinities of the aminopropyltransferases for dAdoMet (K_m = 0.6 and 1.1 μM for spermine synthase and spermidine synthase, respectively) (140, 164).

Polyamine synthesis appears to be the major, if not the only, route for the further metabolism of dAdoMet. Decarboxylated AdoMet accumulated to levels that were many-fold the control levels in cells cultured in vitro and in ventral prostate of intact rats when its utilization was blocked by inhibition of ornithine decarboxylase or of spermidine synthase (35, 121, 144, 151, 152). In incubations of soluble protein from rat liver with putrescine (as substrate for spermidine synthase) and adenine (to inhibit MTA degradation by MTA phosphorylase), inhibition of AdoMet decarboxylase by methylglyoxal bis-(guanylhydrazone) (MGBG) blocked formation of labeled MTA from S-[8-^{14}C]adenosyl-L-methionine and of labeled spermidine from S-adenosyl-L-[2-^{14}C]methionine; the decreased production of MTA and spermidine was accompanied by a nearly equimolar decrease in disappearance of AdoMet (44). A

similar dose-dependent effect of MGBG on MTA synthesis was observed in studies with human lymphoblastoid cell lines (96).

SALVAGE OF METHYLTHIORIBOSE FOR RESYNTHESIS OF METHIONINE As indicated in Figure 2, the MTA formed from dAdoMet during polyamine synthesis is metabolized by MTA phosphorylase to adenine and 5-methylthioribose-1-phosphate (54, 70, 96). The primary fate of 5-methylthioribose-1-phosphate in cell-free homogenates of rat liver is the formation of Met (6, 7). Carbons from the ribose portion, the carbon and hydrogens of the methyl group, and the sulfur of MTA are all incorporated into Met. Thus, the pathway by which MTA is converted to Met involves modifications in the ribose portion of the molecule to form the α-aminobutyrate portion of Met rather than a transfer of the methylthio group to an acceptor molecule (7). The steps involved in the conversion of 5-methylthioribose-1-phosphate to Met have been partially elucidated (6, 214, 215). 5-Methylthioribose-1-phosphate undergoes isomerization to 5-methylthioribulose-1-phosphate (215), which is then converted to α-keto-γ-methiolbutyrate, the keto acid precursor of Met. The intermediates and reactions involved in this conversion have not been fully characterized; the pathway appears to include formation of a phosphate ester, removal of the phosphate to form an intermediate at the oxidation state of ribose, and subsequent stoichiometric consumption of O_2 and production of formate (215). The final step in the pathway for Met synthesis is the transamination of the keto acid, which may be catalyzed by glutamine aminotransferase (6).

This pathway for MTA metabolism is physiologically important for the removal of MTA as well as for the conservation of the adenine and methylthioribose moieties of AdoMet. MTA is a strong inhibitor of the aminopropyltransferases involved in polyamine production (80, 146), of AdoHcy hydrolase (53, 160), and of adenosine kinase (68). Inhibition is not seen in vivo because a low concentration of MTA (1–2 $nmol \cdot g^{-1}$ in most rat tissues) is normally maintained in mammalian tissues due to the action of MTA phosphorylase (147, 171).

The Transamination Pathway of Methionine Metabolism

Benevenga and coworkers (11, 24, 191) proposed that Met is metabolized by an alternate pathway that involves transamination as the initial step. Met is transaminated to α-keto-γ-methiolbutyrate (perhaps by cytosolic glutamine aminotransferase) in the presence of α-keto-γ-methiolbutyrate, pyruvate, the keto acids of the branched-chain amino acids, or phenylpyruvate (12, 114, 115, 127, 191). Apparently, the keto acid of Met is transported into the mitochondria on the pyruvate carrier (115) where it is decarboxylated (perhaps by the

branched-chain keto acid dehydrogenase complex) to give 3-methylthiopropionyl-CoA (40, 115, 191). 3-Methylthiopropionate (3-methylthiopropionyl-CoA) may be further metabolized to methanethiol, hydrogen sulfide, sulfate, carbon dioxide, and possibly formaldehyde and formate, but the details of these conversions have not been elucidated (12, 25, 31, 192).

The role of a pathway of Met metabolism that is independent of the formation of AdoMet is not well established in the intact cell or animal, but deserves further consideration. Metabolic studies with isolated rat hepatocytes support a role of the transamination pathway of Met metabolism (115), and continuous infusion tracer dilution studies in intact sheep support the existence of some alternate pathway of Met metabolism (12). Additional support for the transamination pathway comes from studies indicating that metabolites produced by the transamination pathway may be related to the marked toxicity of Met in the rat (190).

Evidence for an alternate pathway of Met metabolism must be considered in light of the many data indicating that only the transmethylation-transsulfuration pathway is quantitatively important in the oxidation of the sulfur atom and methyl group of Met. Many of the observations of increased oxidation of the methyl group of Met in rats fed diets with excess Met can be explained, at least partially, by increased flux of Met through the Met adenosyltransferase, glycine methyltransferase, and sarcosine dehydrogenase system (10, 25, 126, 136). Experiments with labeled AdoMet and labeled Met suggest that the sulfur atom and methyl and carboxyl carbons of these two compounds are similarly metabolized in the intact rat, which is consistent with the conversion of Met to AdoMet prior to its oxidation (72). "Abnormal" metabolites of Met that would be formed by the transamination pathway have not been observed in man and animals under conditions where "normal" metabolism is partially blocked and where plasma Met is elevated; in fact, intermediates of the transsulfuration pathway have been found in increased amounts under these conditions (56, 130, 155, 186).

CYSTEINE (AND METHIONINE SULFUR) METABOLISM

The Cysteinesulfinate Pathway: Taurine Production

Cys, whether from an exogenous source or formed from serine and the sulfur of Met by the transsulfuration pathway (or possibly by direct sulfhydration of serine), is metabolized by the animal to yield either taurine (2-aminoethanesulfonate) and CO_2 or sulfate, urea, and CO_2 (108, 111). Several pathways of Cys metabolism have been demonstrated, but the physiological roles of these are not well understood.

The cysteinesulfinate pathway of Cys metabolism is depicted in Figure 4.

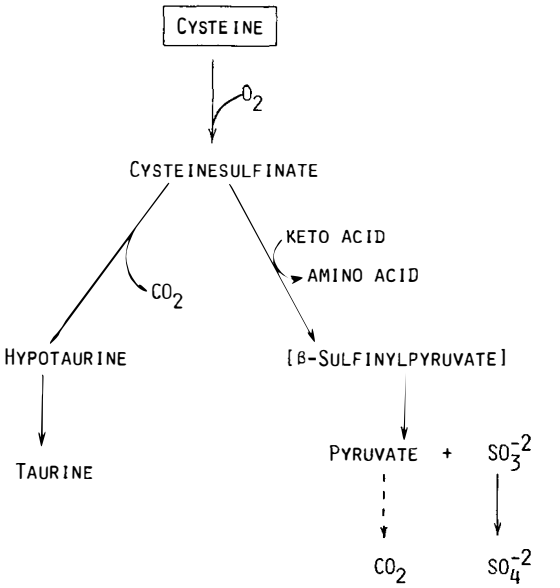

Figure 4 The cysteinesulfinate pathway.

The oxidation of Cys to cysteinesulfinate is catalyzed by Cys dioxygenase (EC 1.13.11.20), an iron-containing enzyme that seems to be specific for Cys, with an apparent K_m of 0.45 mM (232). Cysteinesulfinate may then be decarboxylated to hypotaurine (2-aminoethanesulfinate) by action of cysteinesulfinate decarboxylase (EC 4.1.1.29), a pyridoxal 5'-phosphate-dependent enzyme that has an apparent K_m for cysteinesulfinate of 0.045–0.17 mM and that can also use cysteic acid (cysteinesulfonate) as a substrate (75, 135). Brain glutamate decarboxylase (EC 4.1.1.15) can also catalyze the decarboxylation of cysteinesulfinate (135). Alternatively, cysteinesulfinate may undergo transamination or oxidative deamination to form the putative intermediate, β-sulfinylpyruvate, which spontaneously decomposes to yield pyruvate and sulfite (180).

About 70–90% of the cysteinesulfinate oxidized by rat hepatocytes or by intact rats or mice was converted to hypotaurine plus taurine (37, 38, 73, 199); this indicates that, under normal conditions, the rat or mouse metabolizes cysteinesulfinate primarily to taurine rather than to pyruvate and sulfite. Apparent flux of cysteinesulfinate through the transamination pathway in the intact mouse was increased when cysteinesulfinate decarboxylase was inhibited by β-methylene-DL-aspartate (73); this conversion of cysteinesulfinate to pyruvate and sulfite was presumably catalyzed by aspartate aminotransferase, which has a K_m for cysteinesulfinate of 3–25 mM (162, 231).

In mammals, hypotaurine is apparently oxidized to taurine via a poorly

characterized enzymatic reaction that appears to require NAD^+, Cu^{+2}, and O_2 (101, 137). The apparent K_m of the enzyme for hypotaurine is 0.20 mM (101, 137). The rates of hypotaurine oxidation catalyzed by rat or mouse tissues in vitro are too low to account for the rates observed in vivo (137, 153). Hypotaurine does not usually accumulate in mammalian tissues (82), but substantial levels have been found in rat liver after partial hepatectomy (204). Hypotaurine may also undergo transamination to sulfinylacetaldehyde, which presumably decomposes to sulfite and acetaldehyde, but this reaction appears to make a very minor contribution to hypotaurine metabolism in mammalian tissues (50, 51, 73).

The cysteinesulfinate pathway seems to be the major route of taurine formation in mammals. This conclusion is supported by the detection of labeled cysteinesulfinate and taurine in tissues of animals given labeled Cys (141), by the presence of the enzymes involved in the conversion of Cys to cysteinesulfinate and hypotaurine in most mammalian tissues (38, 233), and by the general association, both within and among species, of hepatic cysteinesulfinate decarboxylase activity with the capacity of the animal to synthesize taurine (38, 76, 234).

Hepatic Cys dioxygenase activity was elevated in rats fed diets with excess Met, Cys or protein (34, 99, 194, 199). These increases in Cys dioxygenase activity appeared to parallel an increase in the hepatic Cys concentration to 0.2–0.3 μmol per gram wet weight (control level, 0.1 $\mu mol \cdot g^{-1}$) and to precede an increase in hepatic taurine concentration to 6–8 μmol per gram wet tissue (control level, 3–4 $\mu mol \cdot g^{-1}$) (99).

In contrast to the increase in Cys dioxygenase activity, cysteinesulfinate decarboxylase activity in rat liver decreased to approximately 50% of control levels in rats fed excess protein or excess Cys (34, 117, 199). As expected, decreased cysteinesulfinate decarboxylase activity was associated with decreased oxidation of cysteinesulfinate in hepatocytes isolated from rats that had been fed a high-Cys diet (197). However, these hepatocytes oxidized Cys to CO_2 and to taurine as rapidly or more rapidly than did cells from control animals. Thus, the low cysteinesulfinate decarboxylase activity did not appear to be rate-limiting for Cys oxidation in hepatocytes from rats fed excess Cys.

Studies in animals have yielded conflicting results. Estimates of the oxidation of Cys or cysteinesulfinate to CO_2 in intact rats fed a high-Cys diet were the same as for control rats (199), whereas excess dietary Met or Cys generally led to an increase in the urinary excretion of Cys sulfur as taurine (34, 194). Rats fed excess protein had markedly reduced levels of hepatic cysteinesulfinate decarboxylase activity but elevated levels of urinary taurine (13). These observations seem to suggest that, in animals fed excess protein or sulfur-containing amino acids, either Cys is oxidized primarily by cysteinesulfinate-

independent pathways or increased Cys dioxygenase activity compensates for the decrease in cysteinesulfinate decarboxylase activity.

Taurine is used in conjugation reactions (i.e. bile acids) but does not otherwise appear to be further metabolized by mammalian tissues (52). Taurine that is not reabsorbed by the kidney is excreted as such in the urine (205); renal clearance of taurine in the rat appears to adapt to alterations in the sulfur amino acid and taurine content of the diet (28). Taurine is also secreted as taurine-conjugated bile acids and then degraded to sulfate by intestinal microorganisms (79, 201, 205). The sulfate formed in the intestine is largely reabsorbed and excreted in the urine with little sulfur being excreted in the feces (79, 107, 188). Most [^{35}S]taurine administered orally or intravenously to rats was excreted as [^{35}S]taurine rather than as [^{35}S]sulfate (79).

Other possible pathways of taurine production from cysteine sulfur in mammalian tissues have been identified. One involves the reaction of 3'-phosphoadenosine-5'-phosphosulfate and serine to form cysteic acid, which may be decarboxylated to form taurine; this pathway appears to make a very minor, if any, contribution to taurine production in mammals (87, 125). Cysteinesulfinate may be oxidized nonenzymatically to cysteic acid, which may be decarboxylated by cysteinesulfinate decarboxylase to yield taurine; the rate of conversion of cysteinesulfinate to cysteic acid appears to be too slow for this route of taurine production to be significant (199, 210). Another pathway involves the production of cysteamine (2-mercaptoethylamine) followed by formation of hypotaurine via action of cysteamine dioxygenase (48, 88). Cysteamine production from Cys appears to be a branch of the coenzyme A synthetic pathway, with cysteamine being produced from pantetheine by action of pantetheinase; other possible routes of taurine production via cysteamine have also been proposed (27, 165). Further investigation of this potential route of taurine synthesis is needed.

The quantitative significance of taurine production in Cys metabolism in animals varies substantially among species. Indirect estimates based on the evolution of $^{14}CO_2$ by animals following intraperitoneal injections of [1-^{14}C]- or [3-^{14}C]-labeled cyst(e)ine indicate that about 70–80% of Cys is converted to taurine in the intact male rat (199, 233, 234), whereas only about 20% of the Cys that is oxidized is converted to taurine in the kitten (38). However, the rat, like other animals, excretes much more Cys sulfur as sulfate than as taurine (34, 108); this suggests that the estimate of 70–80% for Cys conversion to taurine in the rat may be high. Recent studies of Cys metabolism in hepatocytes suggest that only about 25% of Cys oxidation in rat liver involves production of hypotaurine and taurine (37).

Desulfuration Pathways of Cysteine Metabolism

Production of pyruvate and inorganic sulfur from Cys may occur by several pathways that do not involve conversion of Cys to cysteinesulfinate (195). In

contrast to the production of pyruvate and SO_3^{-2} (which is readily oxidized to sulfate by sulfite oxidase) from cysteinesulfinate, these desulfuration pathways all involve the release of Cys sulfur in a reduced oxidation state. Data from studies with rat liver mitochondria (227), the perfused rat liver (179), and hepatocytes (37, 197) suggest that a substantial amount of Cys may be metabolized by cysteinesulfinate-independent pathway(s). Wainer (227) demonstrated production of $^{35}SO_4$ by rat liver mitochondria incubated with [^{35}S]Cys at a rate that was not substantially decreased by addition of cysteinesulfinate. In experiments with livers from 72-hour starved rats, Simpson & Freedland (179) found that perfusion with 10 mM cysteinesulfinate in addition to 10 mM [U-^{14}C]Cys decreased the recovery of radioactivity in glucose by only 30%. The pattern for accumulation of nitrogenous products was markedly different when cells were incubated with 25 mM Cys than when they were incubated with 25 mM cysteinesulfinate. Increased production of urea and ammonia accounted for the nitrogen from ~80% of the oxidized Cys, whereas hypotaurine plus taurine accounted for 80–90% of the oxidized cysteinesulfinate (M. H. Stipanuk, unpublished observations). In other studies with rat hepatocytes, 25 mM cysteinesulfinate reduced recovery of the 1-carbon of Cys in CO_2 by 30–40% when the Cys concentration in the incubation medium was 0.2–1.0 mM, but by only 10% when the Cys concentration was 25 mM (M. H. Stipanuk, unpublished observations). Thus, high Cys concentrations may favor Cys catabolism by desulfuration pathways.

Pyruvate and reduced inorganic sulfur can be produced by the cleavage of cystine to pyruvate, ammonia, and thiocysteine, which is catalyzed by cystathionase, followed by further enzymatic or nonenzymatic reaction of thiocysteine with the enzyme or another thiol to reform a disulfide accompanied by release of sulfide (195, 235). The apparent K_m of rat liver cystathionase for L-cystine has been estimated to be about 0.03–0.07 mM compared with 0.8–3.5 mM for L-cystathionine and 15–20 mM for L-homoserine (222, 235, 237). Thus, cystine should compete favorably with other substrates for the enzyme. Pyruvate and sulfane sulfur can also be formed by transamination of Cys with α-ketoglutarate (or pyruvate) to form β-mercaptopyruvate, which may undergo desulfuration (or transsulfuration) catalyzed by β-mercaptopyruvate sulfurtransferase (4, 90, 218). The K_m of purified Cys:α-ketoglutarate aminotransferase for Cys is about 22 mM, whereas its K_m for aspartate is about 0.06–0.5 mM (4, 217). Thus, it is unlikely that Cys is a good substrate for transamination in vivo. Sulfide may also be formed from the substitution of the thiol group of Cys with a variety of thiol compounds to form the corresponding thioether in a reaction catalyzed by cystathionine synthase (18, 110, 156). However, cystathionine synthase apparently has a much higher K_m for Cys (36 mM) than for L-serine (2–8 mM) or Hcy (0.1–9 mM) (17, 103, 133).

All three of these pathways appeared to play a role in the production of acid-labile sulfide from Cys by liver and kidney homogenate systems designed

to approach physiological values for substrate concentrations and pH (195, 198), but the role of these pathways in the intact animal has not been assessed. Because of the existence of multiple pathways, blocking one pathway may have little effect on the overall ability of the animal to metabolize Cys. Patients with a genetic lack of β-mercaptopyruvate sulfurtransferase excrete low levels of the mixed disulfide of β-mercaptolactate and Cys, which suggests that at least a small amount of Cys is metabolized by transamination in vivo (32, 33). These patients excrete normal levels of urinary sulfate. Inhibition of cystathionase by propargylglycine had no effect on sulfate production from Cys (195), but metabolites potentially produced via action of cystathionase on Cys have been observed in urine of rats (49). Patients who have low levels of cystathionine synthase appear to convert Met and Cys to sulfate normally (155).

If sulfur were released from Cys as sulfane sulfur, the sulfide presumably would be oxidized to sulfate prior to its excretion. Inorganic sulfur metabolism has received little attention in recent years, but the elegant experiments of Koj et al (100), published in 1967, support a central role of thiosulfate in the oxidation of sulfide by animal tissues. Based on studies with $(^{35}S{\cdot}SO_3)^{-2}$ and $(S{\cdot}^{35}SO_3)^{-2}$, they proposed that thiosulfate is an intermediate in the formation of sulfate from sulfane sulfur. Their work clearly suggests that sulfide must be incorporated into thiosulfate (and that the outer S must become the inner S in SSO_3^{-2}) prior to its oxidation to sulfate and, also, that SO_3^{-2} formed from SSO_3^{-2} is not reincorporated into SSO_3^{-2} to any extent:

$$2HS^- + 2O_2 \rightarrow (SSO_3)^{-2} + H_2O \quad 1.$$

$$(SSO_3)^{-2} + 2GSH \rightarrow HS^- + HSO_3^- + GSSG \quad 2.$$

$$SO_3^{-2} + \tfrac{1}{2}O_2 \rightarrow SO_4^{-2} \quad 3.$$

The results obtained by Szczepkowski et al (207) in tracer experiments with intact rats suggest that thiosulfate is a normal intermediate in the production of sulfate from Cys in the animal. When a large excess of unlabeled thiosulfate was injected at the same time as [^{35}S]cystine, the excretion of radioactive sulfur as urinary thiosulfate was about 20-fold that of control rats who did not receive thiosulfate, and the excretion of radioactive sulfur as urinary sulfate was markedly reduced. The appearance of increased urinary levels of thiosulfate as well as of sulfite in individuals with sulfite oxidase deficiency due to inborn errors of metabolism (93, 175) or dietary molybdenum deficiency (1) also supports a central role of thiosulfate in sulfur metabolism. Because mammalian tissues do not have an enzymatic system for reducing sulfite or sulfate to sulfide, incorporation of ^{35}S from [^{35}S]Cys into thiosulfate also indicates that sulfur is released from Cys as sulfane sulfur.

Sulfane sulfur appears to be incorporated into some pool of reduced sulfur that has a relatively long half-life in the intact animal. In contrast to the rapid

excretion of label from injected $(S\cdot{}^{35}SO_3)^{-2}$ or ${}^{35}SO_4{}^{-2}$, labeled sulfur from injected $({}^{35}S\cdot SO_3)^{-2}$ or from metabolized [^{35}S]Met or [^{35}S]Cys is slowly excreted in the urine (34, 107, 181, 193, 194). Schneider & Westley (167) demonstrated the existence of a slowly metabolized pool of sulfur that was formed from the outer but not the inner sulfur of thiosulfate. They suggested, based on studies in intact rats, that elemental sulfur associated with protein and polythionate sulfur ($^-O_3SS_nSO_3^-$) are likely possibilities for the form of this retained intermediate that is subsequently slowly metabolized to provide reduced sulfur. Thus, it is conceivable that Cys is metabolized by pathways that involve release of sulfide followed by incorporation of the sulfur into some pool of reduced sulfur that has a relatively long half-life prior to its oxidation to sulfate.

SUMMARY AND CONCLUSIONS

Met metabolism occurs primarily by activation of Met to AdoMet and further metabolism of AdoMet by either the transmethylation-transsulfuration pathway or the polyamine biosynthetic pathway. The catabolism of the methyl group and sulfur atom of Met ultimately appears to be dependent upon the transmethylation-transsulfuration pathway because the MTA formed as the co-product of polyamine synthesis is efficiently recycled to Met. On the other hand, the fate of the four-carbon chain of Met appears to depend upon the initial fate of the Met molecule. During transsulfuration, the carbon chain is released as α-ketobutyrate, which is further metabolized to CO_2. In the polyamine pathway, the carboxyl carbon of Met is lost in the formation of dAdoMet, whereas the other three carbons are ultimately excreted as polyamine derivatives and degradation products.

The role of the transamination pathway of Met metabolism is not firmly established. Cys (which may be formed from the sulfur of Met and the carbons of serine via the transsulfuration pathway) appears to be converted to taurine and CO_2 primarily by the cysteinesulfinate pathway, and to sulfate and pyruvate primarily by desulfuration pathways in which a reduced form of sulfur with a relatively long biological half-life appears to be an intermediate. With the exception of the nitrogen of Met that is incorporated into polyamines, the nitrogen of Met or Cys is incorporated into urea after it is released as ammonium [in the reactions catalyzed by cystathionase with either cystathionine (from Met) or cystine (from Cys) as substrate] or it is transferred to a keto acid (in Cys or Met transamination).

Many areas of sulfur-containing amino acid metabolism need further study. The magnitude of AdoMet flux through the polyamine pathway in the intact animal as well as details about the reactions involved in this pathway remain to be determined. Both the pathways and the possible physiological role of alternate (AdoMet-independent) Met metabolism, including the transamination

pathway, must be elucidated. Despite the growing interest in taurine, investigation of Cys metabolism has been a relatively inactive area during the past two decades. Apparent discrepancies in the reported data on Cys metabolism need to be resolved. Future work should consider the role of extrahepatic tissues in amino acid metabolism as well as species differences in the relative roles of various pathways in the metabolism of Met and Cys.

Literature Cited

1. Abumrad, N. N., Schneider, A. J., Steel, D., Rogers, L. S. 1981. Amino acid intolerance during prolonged total parenteral nutrition reversed by molybdate therapy. *Am. J. Clin. Nutr.* 34: 2551–59
2. Aguilar, T. S. 1981. Importance of serine formation and choline supply in methionine methyl carbon oxidation in the rat. *Acta Cient. Venezolana* 32:314–23
3. Aguilar, T. S., Benevenga, N. J., Harper, A. E. 1974. Effect of dietary methionine level on its metabolism in rats. *J. Nutr.* 104:761–71
4. Akagi, R. 1982. Purification and characterization of cysteine aminotransferase from rat liver cytosol. *Acta Med. Okayama* 36:187–97
5. Awad, W. M. Jr., Whitney, P. L., Skiba, W. E., Mangum, J. H., Wells, M. S. 1983. Evidence for direct methyl transfer in betaine: homocysteine S-methyltransferase. *J. Biol. Chem.* 258:12790–92
6. Backlund, P. S. Jr., Chang, C. P., Smith, R. A. 1982. Identification of 2-keto-4-methylthiobutyrate as an intermediate compound in methionine synthesis from 5'-methylthioadenosine. *J. Biol. Chem.* 257:4196–4202
7. Backlund, P. S. Jr., Smith, R. A. 1981. Methionine synthesis from 5'-methylthioadenosine in rat liver. *J. Biol. Chem.* 256:1533–35
8. Barak, A. J., Beckenhauer, H. C., Tuma, D. J. 1982. Use of S-adenosylmethionine as an index of methionine recycling in rat liver slices. *Anal. Biochem.* 127:372–75
9. Beatty, P. W., Reed, D. J. 1980. Involvement of the cystathionine pathway in the biosynthesis of glutathione by isolated hepatocytes. *Arch. Biochem. Biophys.* 204:80–87
10. Benevenga, N. J. 1974. Toxicities of methionine and other amino acids. *J. Agric. Food Chem.* 22:2–9
11. Benevenga, N. J. 1984. Evidence for alternative pathways of methionine catabolism. *Adv. Nutr. Res.* 6:1–18
12. Benevenga, N. J., Eagen, A. R. 1983. Quantitative aspects of methionine metabolism. In *Sulfur Amino Acids, Biochemical and Clinical Aspects,* ed. K. Kuriyama, R. J. Huxtable, H. Iwata, pp. 327–41. New York: Liss
13. Benjamin, L. R., Steele, R. D. 1985. Hepatic cysteine sulfinate decarboxylase activity and urinary taurine excretion in rats fed varying levels of dietary protein. *Fed. Proc.* 44:1764 (Abstr.)
14. Bikel, I., Pavlatos, T. N., Livingston, D. M. 1978. Purification and subunit structure of mouse liver cystathionase. *Arch. Biochem. Biophys.* 186:168–74
15. Billings, R. E., Noker, P. E., Tephly, T. R. 1981. The role of methionine in regulating folate-dependent reactions in isolated rat hepatocytes. *Arch. Biochem. Biophys.* 208:108–20
16. Boss, G. R., Pilz, R. B. 1984. Decreased methionine synthesis in purine nucleoside-treated T and B lymphoblasts and reversal by homocysteine. *J. Clin. Invest.* 74:1262–68
17. Braunstein, A. E., Goryachenkova, E. V., Lac, N. D. 1969. Reactions catalyzed by serine sulfhydrase from chicken liver. *Biochim. Biophys. Acta* 171:366–68
18. Braunstein, A. E., Goryachenkova, E. V., Tolosa, E. A., Willhardt, I. H., Yefremova, L. L. 1971. Specificity and some other properties of liver serine sulfhydrase: Evidence for its identity with cystathionine β-synthase. *Biochim. Biophys. Acta* 242:247–60
19. Burke, G. T., Mangum, J. H., Brodie, J. D. 1970. Methylcobalamin as an intermediate in mammalian methionine biosynthesis. *Biochemistry* 9:4297–4302
20. Burke, G. T., Mangum, J. H., Brodie, J. D. 1971. Mechanism of mammalian cobalamin-dependent methionine biosynthesis. *Biochemistry* 10:3079–85
21. Cantoni, G. L., Aksamit, R. R., Kim, I.-K. 1982. Methionine biosynthesis and vidarabine therapy. *N. Engl. J. Med.* 307:1079
22. Cantoni, G. L., Chiang, P. K. 1980. The

role of S-adenosylhomocysteine and S-adenosylhomocysteine hydrolase in the control of biologic methylations. In *Natural Sulfur Compounds: Novel Biochemical and Structural Aspects,* ed. D. Cavallini, G. E. Gaull, V. Zappia, pp. 67–80. New York: Plenum

23. Cantoni, G. L., Richards, H. H., Chiang, P. K. 1979. Inhibitors of S-adenosylhomocysteine hydrolase and their role in the regulation of biological methylation. In *Transmethylation,* ed. E. Usdin, R. T. Borchardt, C. R. Creveling, pp. 155–64. New York: Elsevier/North Holland
24. Case, G. L., Benevenga, N. J. 1976. Evidence for S-adenosylmethionine-independent catabolism of methionine in the rat. *J. Nutr.* 106:1721–36
25. Case, G. L., Benevenga, N. J. 1977. Significance of formate as an intermediate in the oxidation of the methionine, S-methyl-L-cysteine and sarcosine methyl carbons to CO_2 in the rat. *J. Nutr.* 107:1665–76
26. Case, G. L., Mitchell, A. D., Harper, A. E., Benevenga, N. J. 1976. Significance of choline synthesis in the oxidation of the methionine methyl group in rats. *J. Nutr.* 106:735–46
27. Cavallini, D., Dupré, S., Federici, G., Solinas, S., Ricci, G., et al. 1978. Isethionic acid as a taurine co-metabolite. In *Taurine and Neurological Disorders,* ed. A. Barbeau, R. J. Huxtable, pp. 29–34. New York: Raven
28. Chesney, R. W., Gusowski, N., Dabbagh, S., Padilla, M. 1985. Renal cortex taurine concentration regulates renal adaptive response to altered dietary intake of sulfur amino acids. In *Taurine, Biological Actions and Clinical Perspectives,* ed. S. S. Oja, L. Ahtee, P. Kontro, M. K. Paasonen, pp. 33–42. New York: Liss
29. Chiang, P. K., Im, Y. S., Cantoni, G. L. 1980. Phospholipids biosynthesis by methylations and choline incorporation: Effect of 3-deazaadenosine. *Biochem. Biophys. Res. Commun.* 94:174–81
30. Chiao, F. F., Stokstad, E. L. R. 1977. Effect of methionine on hepatic folate metabolism in rats fed a vitamin B_{12}- and methionine-deficient diet. *Proc. Soc. Exp. Biol. Med.* 155:433–37
31. Cohen, L. M., Benevenga, N. J. 1985. Quantitation and identification of volatile sulfur evolved in the metabolism of 3-methylthiopropionate. *Fed. Proc.* 44: 800 (Abstr.)
32. Crawhall, J. C. 1978. β-Mercaptolactate-cysteine disulfiduria. In *The Metabolic Basis of Inherited Disease,* ed. J. B. Stanbury, J. B. Wyngaarden, D. S. Fredrickson, pp. 504–13. New York: McGraw-Hill. 4th ed.
33. Crawhall, J. C. 1985. A review of the clinical presentation and laboratory findings in two uncommon hereditary disorders of sulfur amino acid metabolism, β-mercaptolactate cysteine disulfideuria and sulfite oxidase deficiency. *Clin. Biochem.* 18:139–42
34. Daniels, K. M., Stipanuk, M. H. 1982. The effect of dietary cysteine level on cysteine metabolism in rats. *J. Nutr.* 112:2130–41
35. Danzin, C., Claverie, N., Wagner, J., Grove, J., Koch-Weser, J. 1982. Effect on prostatic growth of 2-difluoromethylornithine, an effective inhibitor of ornithine decarboxylase. *Biochem. J.* 202:175–81
36. Daubner, S. C., Matthews, R. G. 1982. Purification and properties of methylenetetrahydrofolate reductase from pig liver. *J. Biol. Chem.* 257:140–45
37. De La Rosa, J., Stipanuk, M. H. 1985. The oxidation of cysteine and cysteinesulfinate in rat and cat hepatocytes. *Fed. Proc.* 44:1591 (Abstr.)
38. De La Rosa, J., Stipanuk, M. H. 1985. Evidence for a rate-limiting role of cysteinesulfinate decarboxylase activity in taurine biosynthesis in vivo. *Comp. Biochem. Physiol.* 81B:565–71
39. Demetriou, A. A., Cohn, M. S., Tabor, C. W., Tabor, H. 1978. Identification of pyruvate in S-adenosylmethionine decarboxylase from rat liver. *J. Biol. Chem.* 253:1684–86
40. Dixon, J. L., Benevenga, N. J. 1980. The decarboxylation of α-keto-γ-methiolbutyrate in rat liver mitochondria. *Biochem. Biophys. Res. Commun.* 97: 939–46
41. Døskeland, S. O., Ueland, P. M. 1982. Comparison of some physicochemical and kinetic properties of S-adenosylhomocysteine hydrolase from bovine liver, bovine adrenal cortex and mouse liver. *Biochim. Biophys. Acta* 708:185–93
42. Eells, J. T., Black, K. A., Makar, A. B., Tedford, C. E., Tephly, T. R. 1982. The regulation of one-carbon oxidation in the rat by nitrous oxide and methionine. *Arch. Biochem. Biophys.* 219:316–26
43. Eloranta, T. O. 1977. Tissue distribution of S-adenosylmethionine and S-adenosylhomocysteine in the rat: Effect of age, sex and methionine administration on the metabolism of S-adenosylmethionine, S-adenosylhomocysteine and polyamines. *Biochem. J.* 166:521–29

44. Eloranta, T. O., Kajander, E. O. 1984. Catabolism and lability of S-adenosyl-L-methionine in rat liver extracts. *Biochem. J.* 224:137–44
45. Eloranta, T. O., Kajander, E. O., Raina, A. M. 1976. A new method for the assay of tissue S-adenosylhomocysteine and S-adenosylmethionine: Effect of pyridoxine deficiency on the metabolism of S-adenosylhomocysteine, S-adenosylmethionine and polyamines in rat liver. *Biochem. J.* 160:287–94
46. Eloranta, T. O., Kajander, E. O., Raina, A. M. 1982. Effect of 9-β-D-arabinofuranosyladenine and erythro-9-(2-hydoxy-3-nonyl)adenine on the metabolism of S-adenosylhomocysteine, S-adenosylmethionine, and adenosine in rat liver. *Med. Biol.* 60:272–77
47. Engstrom, M. A. 1981. *Quantitative importance of an alternative route for methionine catabolism.* PhD thesis. Univ. Wisconsin, Madison
48. Federici, G., Ricci, G., Santoro, L., Antonucci, A., Cavallini, D. 1980. Cysteamine pathway of taurine biosynthesis. See Ref. 22, pp. 195–200
49. Fellman, J. H., Avedovech, N. A. 1982. Cysteine thiosulfonate in cysteine metabolism. *Arch. Biochem. Biophys.* 218: 303–8
50. Fellman, J. H., Roth, E. S. 1981. Hypotaurine aminotransferase. *Adv. Exp. Med. Biol.* 139:99–113
51. Fellman, J. H., Roth, E. S., Avedovech, N. A., McCarthy, K. D. 1980. Mammalian hypotaurine aminotransferase, isethionate is not a product. *Life Sci.* 27:1999–2004
52. Fellman, J. H., Roth, E. S., Fujita, T. S. 1978. Taurine is not metabolized to isethionate in mammalian tissue. See Ref. 27, pp. 19–24
53. Ferro, A. J., Vanderbark, A. A., MacDonald, M. R. 1981. Inactivation of S-adenosylhomocysteine hydrolase by 5'-deoxy-5'-methylthioadenosine. *Biochem. Biophys. Res. Commun.* 100:523–31
54. Ferro, A. J., Wrobel, N. C., Nicolette, J. A. 1979. 5-Methylthioribose 1-phosphate: A product of partially purified, rat liver 5'-methylthioadenosine phosphorylase activity. *Biochim. Biophys. Acta* 570:65–73
55. Finkelstein, J. D. 1974. Methionine metabolism in mammals: The biochemical basis for homocystinuria. *Metabolism* 23:387–98
56. Finkelstein, J. D. 1979. Regulation of methionine metabolism in mammals. See Ref. 23, pp. 49–58
57. Finkelstein, J. D., Harris, B. J., Kyle, W. E. 1972. Methionine metabolism in mammals: Kinetic study of betaine-homocysteine methyltransferase. *Arch. Biochem. Biophys.* 153:320–24
58. Finkelstein, J. D., Harris, B. J., Martin, J. J., Kyle, W. E. 1982. Regulation of hepatic betaine-homocysteine methyltransferase by dietary methionine. *Biochem. Biophys. Res. Commun.* 108:344–48
59. Finkelstein, J. D., Kyle, W. E., Harris, B. J. 1971. Methionine metabolism in mammals: Regulation of homocysteine methyltransferases in rat tissue. *Arch. Biochem. Biophys.* 146:84–92
60. Finkelstein, J. D., Kyle, W. E., Harris, B. J. 1974. Methionine metabolism in mammals: Regulatory effects of S-adenosylhomocysteine. *Arch. Biochem. Biophys.* 165:774–79
61. Finkelstein, J. D., Kyle, W. E., Harris, B. J., Martin, J. J. 1982. Methionine metabolism in mammals: Concentration of metabolites in rat tissues. *J. Nutr.* 112:1011–18
62. Finkelstein, J. D., Kyle, W. E., Martin, J. J. 1975. Abnormal methionine adenosyltransferase in hypermethioninemia. *Biochem. Biophys. Res. Commun.* 66: 1491–97
63. Finkelstein, J. D., Kyle, W. E., Martin, J. J., Pick, A.-M. 1975. Activation of cystathionine synthase by adenosylmethionine and adenosylethionine. *Biochem. Biophys. Res. Commun.* 66:81–87
64. Finkelstein, J. D., Martin, J. J. 1984. Methionine metabolism in mammals: Distribution of homocysteine between competing pathways. *J. Biol. Chem.* 259:9508–13
65. Finkelstein, J. D., Martin, J. J. 1984. Inactivation of betaine-homocysteine methyltransferase by adenosylmethionine and adenosylethionine. *Biochem. Biophys. Res. Commun.* 118:14–19
66. Finkelstein, J. D., Martin, J. J., Harris, B. J., Kyle, W. E. 1983. Regulation of hepatic betaine-homocysteine methyltransferase by dietary betaine. *J. Nutr.* 113:519–21
67. Finkelstein, J. D., Mudd, S. H. 1967. Trans-sulfuration in mammals: The methionine-sparing effect of cystine. *J. Biol. Chem.* 242:873–80
68. Fox, I. H., Palella, T. D., Thompson, D., Herring, C. 1982. Adenosine metabolism: Modification by S-adenosylhomocysteine and 5'-methylthioadenosine. *Arch. Biochem. Biophys.* 215:302–8
69. Fujioka, M., Takata, Y. 1981. S-Adenosylhomocysteine hydrolase from

rat liver: Purification and some properties. *J. Biol. Chem.* 256:1631–35
70. Garbers, D. L. 1978. Demonstration of 5'-methylthioadenosine phosphorylase activity in various rat tissues. *Biochim. Biophys. Acta* 523:82–93
71. Gaull, G. E., Tallan, H. H., Lonsdale, D., Pyzyrembel, H., Schaffner, F., von Bassewitz, D. B. 1981. Hypermethioninemia associated with methionine adenosyltransferase deficiency: Clinical, morphologic, and biochemical observations on four patients. *J. Pediatr.* 98: 734–41
72. Giulidori, P., Galli-Kienle, M., Catto, E., Stramentinoli, G. 1984. Transmethylation, transsulfuration, and aminopropylation reactions of S-adenosyl-L-methionine in vivo. *J. Biol. Chem.* 259: 4205–11
73. Griffith, O. W. 1983. Cysteinesulfinate metabolism: Altered partitioning between transamination and decarboxylation following administration of β-methyleneaspartate. *J. Biol. Chem.* 258: 1591–98
74. Grzelakowska-Sztabert, B., Balińska, M. 1980. Induction of betaine: homocysteine methyltransferase in some murine cells cultured in vitro. *Biochim. Biophys. Acta* 632:164–72
75. Guion-Rain, M.-C., Portemer, C., Chatagner, F. 1975. Rat liver cysteine sulfinate decarboxylase: Purification, new appraisal of the molecular weight and determination of catalytic properties. *Biochim. Biophys. Acta* 384:265–76
76. Hardison, W. G. M., Wood, C. A., Proffitt, J. H. 1977. Quantitation of taurine synthesis in the intact rat and cat liver. *Proc. Soc. Exp. Biol. Med.* 155:55–58
77. Harpey, J.-P., Rosenblatt, D. S., Cooper, B. A., Moël, G. L., Roy, C., Lafourcade, J. 1981. Homocystinuria caused by 5,10-methylenetetrahydrofolate reductase deficiency: A case in an infant responding to methionine, folinic acid, pyridoxine, and vitamin B_{12} therapy. *J. Pediatr.* 98:275–78
78. Helland, S., Ueland, P. M. 1983. S-Adenosylhomocysteine and S-adenosylhomocysteine hydrolase in various tissues of mice given injections of 9-β-D-arabinofuranosyladenine. *Cancer Res.* 43:1847–50
79. Hepner, G. W., Sturman, J. A., Hofmann, A. F., Thomas, P. J. 1973. Metabolism of steroid and amino acid moieties of conjugated bile acids in man. II. Cholytaurine (taurocholic acid). *J. Clin. Invest.* 52:433–40
80. Hibasami, H., Borchardt, R. T., Chen, S. Y., Coward, J. K., Pegg, A. E. 1980. Studies of inhibition of rat spermidine synthase and spermine synthase. *Biochem. J.* 187:419–28
81. Hibasami, H., Hoffman, J. L., Pegg, A. E. 1980. Decarboxylated S-adenosylmethionine in mammalian cells. *J. Biol. Chem.* 255:6675–78
82. Hirschberger, L. L., De La Rosa, J., Stipanuk, M. H. 1985. Determination of cysteinesulfinate, hypotaurine and taurine in physiological samples by reversed-phase liquid chromatography. *J. Chromatogr.* 343:303–13
83. Hoffman, D. R., Cornatzer, W. E., Duerre, J. A. 1979. Relationship between tissue levels of S-adenosylmethionine, S-adenosylhomocysteine, and transmethylation reactions. *Can. J. Biochem.* 57:56–65
84. Hoffman, D. R., Marion, D. W., Cornatzer, W. E., Duerre, J. A. 1980. S-Adenosylmethionine and S-adenosylhomocysteine metabolism in isolated rat liver: Effects of L-methionine, L-homocysteine, and adenosine. *J. Biol. Chem.* 255:10822–27
85. Hollowell, J. G. Jr., Hall, W. K., Coryell, M. E., McPherson, J. Jr., Hahn, D. A. 1969. Homocystinuria and organic aciduria in a patient with vitamin-B_{12} deficiency. *Lancet* 2:1428
86. Hopkins, D., Manchester, K. L. 1980. Control of activity of S-adenosylmethionine decarboxylase in muscle by spermidine. *FEBS Lett.* 109:299–302
87. Huovinen, J. A., Gustafsson, B. E. 1967. Inorganic sulphate, sulphite and sulphide as sulphur donors in the biosynthesis of sulphur amino acids in germ-free and conventional rats. *Biochim. Biophys. Acta* 136:441–47
88. Huxtable, R., Bressler, R. 1976. The metabolism of cysteamine to taurine. In *Taurine,* ed. R. Huxtable, A. Barbeau, pp. 45–57. New York: Raven
89. Iizasa, T., Carson, D. A. 1985. Differential regulation of polyamine synthesis and transmethylation reactions in methylthioadenosine phosphorylase deficient mammalian cells. *Biochim. Biophys. Acta* 844:280–87
90. Ishimoto, Y. 1979. Transaminative pathway of cysteine metabolism in rat tissues. *Physiol. Chem. Phys.* 11:189–91
91. Jägerstad, M., Åkesson, B., Fehling, C. 1980. Effect of methionine on the metabolic fate of liver folates in vitamin B_{12}-deficient rats. *Br. J. Nutr.* 44:361–69
92. Jänne, J., Pösö, H., Raina, A. 1978. Polyamines in rapid growth and cancer. *Biochim. Biophys. Acta* 473:241–93

93. Johnson, J. L., Waud, W. R., Rajagopalan, K. V., Duran, M., Beemer, F. A. 1980. Inborn errors of molybdenum metabolism: Combined deficiencies of sulfite oxidase and xanthine dehydrogenase in a patient lacking the molybdenum cofactor. *Proc. Natl. Acad. Sci. USA* 77:3715–19
94. Kajander, E. O. 1982. Inactivation of liver S-adenosylhomocysteine hydrolase in vitro of rats treated with erythro-9-(2-hydroxynon-3-yl)-adenine. *Biochem. J.* 205:585–92
95. Kajander, E. O., Raina, A. M. 1981. Affinity-chromatographic purification of S-adenosyl-L-homocysteine hydrolase: Some properties of the enzyme from rat liver. *Biochem. J.* 193:503–12
96. Kamatani, N., Carson, D. A. 1981. Dependence of adenine production upon polyamine synthesis in cultured human lymphoblasts. *Biochim. Biophys. Acta* 675:344–50
97. Keating, J. N., Weir, D. G., Scott, J. M. 1985. Demonstration of methionine synthetase in the intestinal mucosal cells of the rat. *Fed. Proc.* 44:1396 (Abstr.)
98. Kerr, S. J. 1972. Competing methyltransferase systems. *J. Biol. Chem.* 247: 4248–52
99. Kohashi, N., Yamaguchi, K., Hosokawa, Y., Kori, Y., Fujii, O., Ueda, I. 1978. Dietary control of cysteine dioxygenase in rat liver. *J. Biochem.* 84:159–68
100. Koj, A., Frendo, J., Janik, Z. 1967. [^{35}S]Thiosulphate oxidation by rat liver mitochondria in the presence of glutathione. *Biochem. J.* 103:791–95
101. Kontro, P., Oja, S. S. 1980. Hypotaurine oxidation by mouse tissues. See Ref. 22, pp. 201–12
102. Koraćević, D., Djordjević, V. 1977. Effect of trypsin, S-adenosylmethionine and ethionine on L-serine sulfhydrase activity. *Experientia* 33:1010–11
103. Kraus, J., Packman, S., Fowler, B., Rosenberg, L. E. 1978. Purification and properties of cystathionine β-synthase from human liver: Evidence for identical subunits. *J. Biol. Chem.* 253:6523–28
104. Kraus, J. P., Rosenberg, L. E. 1983. Cystathionine β-synthase from human liver: Improved purification scheme and additional characterization of the enzyme in crude and pure form. *Arch. Biochem. Biophys.* 222:44–52
105. Krebs, H. A., Hems, R., Tyler, B. 1976. The regulation of folate and methionine metabolism. *Biochem. J.* 158:341–53
106. Kredich, N. M., Hershfield, M. S., Johnston, J. M. 1979. Role of adenosine metabolism in transmethylation. See Ref. 23, pp. 225–30
107. Krijgsheld, K. R., Frankena, H., Scholtens, E., Zweens, J., Mulder, G. J. 1979. Absorption, serum levels and urinary excretion of inorganic sulfate after oral administration of sodium sulfate in the conscious rat. *Biochim. Biophys. Acta* 586:492–500
108. Krijgsheld, K. R., Glazenburg, E. J., Scholtens, E., Mulder, G. J. 1981. The oxidation of L- and D-cysteine to inorganic sulfate and taurine in the rat. *Biochim. Biophys. Acta* 677:7–12
109. Kutzbach, C., Stokstad, E. L. R. 1971. Mammalian methylenetetrahydrofolate reductase: Partial purification, properties, and inhibition by S-adenosylmethionine. *Biochim. Biophys. Acta* 250:459–77
110. Lak, N. D., Goryachenkova, E. V., Braunstein, A. E. 1970. Investigation of substrate specificity of serine sulfhydrase from the hen liver and its relation to some inhibitors. *Biokhimia* 35:270–77
111. Laster, L., Mudd, S. H., Finkelstein, J. D., Irreverre, F. 1965. Homocystinuria due to cystathionine synthase deficiency: The metabolism of L-methionine. *J. Clin. Invest.* 44:1708–19
112. Liau, M. C., Chang, C. F., Belanger, L., Grenier, A. 1979. Correlation of isozyme patterns of S-adenosylmethionine synthetase with fetal stages and pathological states of the liver. *Cancer Res.* 39:162–69
113. Liau, M. C., Chang, C. F., Giovanella, B. C. 1980. Demonstration of an altered S-adenosylmethionine synthetase in human malignant tumors xenografted into athymic nude mice. *J. Natl. Cancer Inst.* 64:1071–75
114. Livesey, G. 1984. Methionine degradation: "anabolic and catabolic." *Trends Biochem. Sci.* 9:27–29
115. Livesey, G., Lund, P. 1980. Methionine metabolism via the transamination pathway in rat liver. *Biochem. Soc. Trans.* 8:540–41
116. Lombardini, J. B., Sufrin, J. R. 1983. Chemotherapeutic potential of methionine analogue inhibitors of tumor-derived methionine adenosyltransferases. *Biochem. Pharmacol.* 32:489–95
117. Loriette, C., Pasantes-Morales, H., Portemer, C., Chatagner, F. 1979. Dietary casein levels and taurine supplementation: Effects on cysteine dioxygenase and cysteine sulfinate decarboxylase activities and taurine concentration in brain, liver and kidney of the rat. *Nutr. Metab.* 23:467–75

118. Lumb, M., Deacon, R., Perry, J., Chanarin, I., Minty, B., et al. 1980. The effect of nitrous oxide inactivation of vitamin B_{12} on rat hepatic folate: Implications for the methylfolate-trap hypothesis. *Biochem. J.* 186:933–36
119. Lumb, M., Sharer, N., Deacon, R., Jennings, P., Purkiss, P., et al. 1983. Effects of nitrous oxide–induced inactivation of cobalamin on methionine and S-adenosylmethionine metabolism in the rat. *Biochim. Biophys. Acta* 756:354–59
120. Makar, A. B., Tephly, T. R. 1983. Effect of nitrous oxide and methionine treatments on hepatic S-adenosylmethionine and methylation reactions in the rat. *Mol. Pharmacol.* 24:124–28
121. Mamont, P. S., Danzin, C., Wagner, J., Siat, M., Joder-Ohlenbusch, A.-M., Claverie, N. 1982. Accumulation of decarboxylated adenosyl-L-methionine in mammalian cells as a consequence of the inhibition of putrescine biosynthesis. *Eur. J. Biochem.* 123:499–504
122. Mamont, P. S., Joder-Ohlenbusch, A.-M., Nussli, M., Grove, J. 1981. Indirect evidence for a strict negative control of S-adenosyl-L-methionine decarboxylase by spermidine in rat hepatoma cells. *Biochem. J.* 196:411–22
123. Mangum, J. H., North, J. A. 1971. Isolation of a cobalamin containing 5-methyltetrahydrofolate-homocysteine transmethylase from mammalian kidney. *Biochemistry* 10:3765–69
124. Mangum, J. H., Smith, M. R., Awad, W. M. Jr. 1985. Methionine biosynthesis: The purification and characterization of methionine synthetase. *Fed. Proc.* 44:1214 (Abstr.)
125. Martin, W. G., Sass, N. L., Hill, L., Tarka, S., Truex, R. 1972. The synthesis of taurine from sulfate. IV. An alternate pathway for taurine synthesis by the rat. *Proc. Soc. Exp. Biol. Med.* 141:632–33
126. Mitchell, A. D., Benevenga, N. J. 1976. Importance of sarcosine formation in methionine methyl carbon oxidation in the rat. *J. Nutr.* 106:1702–13
127. Mitchell, A. D., Benevenga, N. J. 1976. The role of transamination in methionine oxidation in the rat. *J. Nutr.* 108:67–78
128. Moore, P., Swendseid, M. E. 1983. Dietary regulation of the activities of ornithine decarboxylase and S-adenosylmethionine decarboxylase in rats. *J. Nutr.* 113:1927–35
129. Mudd, S. H., Ebert, M. H., Scriver, C. R. 1980. Labile methyl group balances in the human: The role of sarcosine. *Metabolism* 29:707–20
130. Mudd, S. H., Levy, H. L. 1978. Disorders of transsulfuration. See Ref. 32, pp. 458–503
131. Mudd, S. H., Levy, H. L., Morrow, G. III. 1970. Deranged B_{12} metabolism: Effects on sulfur amino acid metabolism. *Biochem. Med.* 4:193–214
132. Mudd, S. H., Poole, J. R. 1975. Labile methyl balances for normal humans on various dietary regimens. *Metabolism* 24:721–35
133. Nakagawa, H., Kimura, H. 1968. Purification and properties of cystathionine synthetase from rat liver: Separation of cystathionine synthetase from serine dehydratase. *Biochem. Biophys. Res. Commun.* 32:208–14
134. Oden, K. L., Clarke, S. 1983. S-Adenosyl-L-methionine synthetase from human erythrocytes: Role in the regulation of cellular S-adenosylmethionine levels. *Biochemistry* 22:2978–86
135. Oertel, W. H., Schmechel, D. E., Weise, V. K., Ransom, D. H., Tappaz, M. L., et al. 1981. Comparison of cysteine sulphinic acid decarboxylase isoenzymes and glutamic acid decarboxylase in rat liver and brain. *Neuroscience* 6:2701–14
136. Ogawa, H., Fujioka, M. 1982. Induction of rat liver glycine methyltransferase by high methionine diet. *Biochem. Biophys. Res. Commun.* 108:227–32
137. Oja, S. S., Kontro, P. 1981. Oxidation of hypotaurine in vitro by mouse liver and brain tissues. *Biochim. Biophys. Acta* 677:350–57
138. Okada, G., Teraoka, H., Tsukada, K. 1981. Multiple species of mammalian S-adenosylmethionine synthetase: Partial purification and characterization. *Biochemistry* 20:934–40
139. Okada, G., Watanabe, Y., Tsukada, K. 1980. Changes in patterns of S-adenosylmethionine synthetases in fetal and postnatal rat liver. *Cancer Res.* 40:2895–97
140. Pajula, R.-L., Raina, A., Eloranta, T. 1979. Polyamine synthesis in mammalian tissues: Isolation and characterization of spermine synthase from bovine brain. *Eur. J. Biochem.* 101:619–26
141. Pasantes-Morales, H., Chatagner, F., Mandel, P. 1980. Synthesis of taurine in rat liver and brain in vivo. *Neurochem. Res.* 5:441–51
142. Pascal, T. A., Tallan, H. H., Gillam, B. M. 1972. Hepatic cystathionase: Immunochemical and electrophoretic studies of the human and rat forms. *Biochim. Biophys. Acta* 285:48–59

143. Pegg, A. E. 1977. Evidence for the presence of pyruvate in rat liver S-adenosylmethionine decarboxylase. *FEBS Lett.* 84:33–36
144. Pegg, A. E. 1984. The role of polyamine depletion and accumulation of decarboxylated S-adenosylmethionine in the inhibition of growth of SV-3T3 cells treated with α-difluoromethylornithine. *Biochem. J.* 224:29–38
145. Pegg, A. E. 1984. S-Adenosylmethionine decarboxylase: a brief review. *Cell Biochem. Funct.* 2:11–15
146. Pegg, A. E., Borchardt, R. T., Coward, J. K. 1981. Effects of inhibitors of spermidine and spermine synthesis on polyamine concentrations and growth of transformed mouse fibroblasts. *Biochem. J.* 194:79–89
147. Pegg, A. E., Coward, J. K. 1981. Inhibition of aminopropyltransferases. *Adv. Polyamine Res.* 3:153–61
148. Pegg, A. E., Hibasami, H. 1980. Polyamine metabolism during cardiac hypertrophy. *Am. J. Physiol.* 233:E372–78
149. Pegg, A. E., Hibasami, H., Matsui, I., Bethell, D. 1981. Formation and interconversion of putrescine and spermidine in mammalian cells. *Adv. Enzyme Regul.* 19:427–51
150. Pegg, A. E., McCann, P. P. 1982. Polyamine metabolism and function. *Am. J. Physiol.* 243:C212–21
151. Pegg, A. E., Pösö, H., Shuttleworth, K., Bennett, R. A. 1982. Effect of inhibition of polyamine synthesis on the content of decarboxylated S-adenosylmethionine. *Biochem. J.* 202:519–26
152. Pegg, A. E., Tang, K.-C., Coward, J. K. 1982. Effects of S-adenosyl-1,8-deamino-3-thiooctane on polyamine metabolism. *Biochemistry* 21:5082–89
153. Pierre, Y., Loriette, C., Chatagner, F. 1980. Metabolism of hypotaurine in some organs of the rat. See Ref. 22, pp. 195–200
154. Piik, K., Rajamäki, P., Guha, S. K., Jänne, J. 1977. Regulation of L-ornithine decarboxylase and S-adenosyl-L-methionine decarboxylase in rat ventral prostate and seminal vesicle. *Biochem. J.* 168: 379–85
155. Poole, J. R., Mudd, S. H., Conerly, E. B., Edwards, W. A. 1975. Homocystinuria due to cystathionine synthase deficiency: Studies of nitrogen balance and sulfur excretion. *J. Clin. Invest.* 55: 1033–48
156. Porter, P. N., Grishaver, M. S., Jones, O. W. 1974. Characterization of human cystathionine β-synthase: Evidence for the identity of human L-serine dehydratase and cystathionine β-synthase. *Biochim. Biophys. Acta* 364:128–39
157. Pösö, H., Hannonen, P., Himberg, J.-J., Jänne, J. 1976. Adenosylmethionine decarboxylase from various organisms: Relation of the putrescine activation of the enzyme to the ability of the organism to synthesize spermine. *Biochem. Biophys. Res. Commun.* 68:227–34
158. Pösö, H., Pegg, A. E. 1981. Differences between tissues in response of S-adenosylmethionine decarboxylase to administration of polyamines. *Biochem. J.* 200:629–37
159. Pritchard, P. H., Vance, D. E. 1981. Choline metabolism and phosphatidylcholine biosynthesis in cultured rat hepatocytes. *Biochem. J.* 196:261–67
160. Ragione, F. D., Pegg, A. E. 1983. Effect of analogues of 5'-methylthioadenosine on cellular metabolism: Inactivation of S-adenosylhomocysteine hydrolase by 5'-isobutylthioadenosine. *Biochem. J.* 210:429–35
161. Raina, A., Pajula, R.-L., Eloranta, T. 1976. A rapid assay method for spermidine and spermine synthases: Distribution of polyamine-synthesizing enzymes and methionine adenosyltransferase in rat tissues. *FEBS Lett.* 67:252–55
162. Recasens, M., Benezra, R., Basset, P., Mandel, P. 1980. Cysteine sulfinate aminotransferase and aspartate aminotransferase isoenzymes of rat brain: Purification, characterization, and further evidence for identity. *Biochemistry* 19: 4583–89
163. Sakai, T., Hori, C., Kano, K., Oka, T. 1979. Purification and characterization of S-adenosyl-L-methionine decarboxylase from mouse mammary gland and liver. *Biochemistry* 18:5541–48
164. Samejima, K., Yamanoha, B. 1982. Purification of spermidine synthase from rat ventral prostate by affinity chromatography on immobilized S-adenosyl (5')-3-thiopropylamine. *Arch. Biochem. Biophys.* 216:213–22
165. Scandurra, R., Federici, G., Dupré, S., Cavallini, D. 1978. Taurine and isethionic acid production in mammals. *Bull. Mol. Biol. Med.* 3:141–47
166. Schlenk, F. 1983. Methylthioadenosine. *Adv. Enzymol.* 54:195–265
167. Schneider, J. F., Westley, J. 1969. Metabolic interrelations of sulfur in proteins, thiosulfate, and cystine. *J. Biol. Chem.* 244:5735–44
168. Schrader, J., Schütz, W., Bardenheuer, H. 1981. Role of S-adenosylhomocysteine hydrolase in adenosine metabolism in mammalian heart. *Biochem. J.* 196: 65–70

169. Schuh, S., Rosenblatt, D. S., Cooper, B. A., Schroeder, M.-L., Bishop, A. J., et al. 1984. Homocystinuria and megaloblastic anemia responsive to vitamin B_{12} therapy: An inborn error of metabolism due to a defect in cobalamin metabolism. *N. Engl. J. Med.* 310:686–90
170. Scott, J. M., Weir, D. G. 1981. The methyl folate trap. *Lancet* 2:337–40
171. Seidenfeld, J., Wilson, J., Williams-Ashman, H. G. 1980. Androgenic regulation of 5'-deoxy-5'-methylthioadenosine concentrations and methylthioadenosine phosphorylase activity in relation to polyamine metabolism of rat prostate. *Biochem. Biophys. Res. Commun.* 95:1861–68
172. Seiler, N., Bolkenius, F. N., Knödgen, B. 1985. The influence of catabolic reactions on polyamine excretion. *Biochem. J.* 225:219–26
173. Seyfried, C. E., Oleinik, O. E., Degen, J. L., Resing, K., Morris, D. R. 1982. Purification, properties and regulation of the level of bovine S-adenosylmethionine decarboxylase during lymphocyte mitogenesis. *Biochim. Biophys. Acta* 716: 169–77
174. Shane, B., Stokstad, E. L. R. 1985. Vitamin B_{12}–folate interrelationships. *Ann. Rev. Nutr.* 5:115–41
175. Shih, V. E., Abroms, I. F., Johnson, J. L., Carney, M., Mandell, R., et al. 1977. Sulfite oxidase deficiency: Biochemical and clinical investigations of a hereditary metabolic disorder in sulfur metabolism. *N. Engl. J. Med.* 297:1022–28
176. Shin, H. K., Linkswiler, H. M. 1974. Tryptophan and methionine metabolism of adult females as affected by vitamin B-6 deficiency. *J. Nutr.* 104:1348–55
177. Shinnar, S., Singer, H. S. 1984. Cobalamin C mutation (methylmalonic aciduria and homocystinuria) in adolescence: A treatable cause of dementia and myelopathy. *N. Engl. J. Med.* 311:451–54
178. Shirahata, A., Pegg, A. E. 1985. Regulation of S-adenosylmethionine decarboxylase activity in rat liver and prostate. *J. Biol. Chem.* 260:9583–88
179. Simpson, R. C., Freedland, R. A. 1975. Relative importance of the two major pathways for the conversion of cysteine to glucose in the perfused rat liver. *J. Nutr.* 105:1440–46
180. Singer, T. P., Kearney, E. B. 1956. Intermediary metabolism of L-cysteinesulfinic acid in animal tissues. *Arch. Biochem. Biophys.* 61:397–409
181. Skarżyński, B., Szczepkowski, T. W., Weber, M. 1959. Thiosulphate metabolism in the animal organism. *Nature* 184:994–95
182. Skiba, W. E., Taylor, M. P., Wells, M. S., Mangum, J. H., Awad, W. M. Jr. 1982. Human hepatic methionine biosynthesis: Purification and characterization of betaine:homocysteine S-methyltransferase. *J. Biol. Chem.* 257:14944–48
183. Skovby, F., Kraus, J. P., Rosenberg, L. E. 1984. Biosynthesis of human cystathionine β-synthase in cultured fibroblasts. *J. Biol. Chem.* 259:583–87
184. Skovby, F., Kraus, J. P., Rosenberg, L. E. 1984. Biosynthesis and proteolytic activation of cystathionine β-synthase in rat liver. *J. Biol. Chem.* 259: 588–93
185. Smolin, L. A., Benevenga, N. J. 1982. Accumulation of homocyst(e)ine in vitamin B-6 deficiency: A model for the study of cystathionine β-synthase deficiency. *J. Nutr.* 112:1264–72
186. Smolin, L. A., Benevenga, N. J., Berlow, S. 1981. The use of betaine for the treatment of homocystinuria. *J. Pediatr.* 99:467–72
187. Sowers, J. E., Stockland, W. L., Meade, R. J. 1972. L-Methionine and L-cystine requirements of the growing rat. *J. Anim. Sci.* 35:782–88
188. Spaeth, D. G., Schneider, D. L. 1976. Turnover of taurine in rat tissues. *J. Nutr.* 104:179–86
189. Spector, R., Coakley, G., Blakely, R. 1980. Methionine recycling in brain: A role for folates and vitamin B_{12}. *J. Neurochem.* 34:132–37
190. Steele, R. D., Barber, T. A., Lalich, J., Benevenga, N. J. 1979. Effects of dietary 3-methylthiopropionate on metabolism, growth and hematopoiesis in the rat. *J. Nutr.* 109:1739–51
191. Steele, R. D., Benevenga, N. J. 1978. Identification of 3-methylthiopropionic acid as an intermediate in mammalian methionine metabolism in vitro. *J. Biol. Chem.* 253:7844–50
192. Steele, R. D., Benevenga, N. J. 1979. The metabolism of 3-methylthiopropionate in rat liver homogenates. *J. Biol. Chem.* 254:8885–90
193. Stipanuk, M. H. 1977. *Interrelationships of methionine and cyst(e)ine metabolism.* PhD thesis. Univ. Wisconsin, Madison
194. Stipanuk, M. H. 1979. Effect of excess dietry methionine on the catabolism of cysteine in rats. *J. Nutr.* 109:2126–39
195. Stipanuk, M. H., Beck, P. W. 1982. Characterization of the enzymic capacity for cysteine desulphydration in liver and kidney of the rat. *Biochem. J.* 206:267–77

196. Stipanuk, M. H., Benevenga, N. J. 1977. Effect of cystine on the metabolism of methionine in rats. *J. Nutr.* 107:1455–67
197. Stipanuk, M. H., Drake, M. R., De La Rosa, J. 1985. Pathways of cysteine catabolism in rat hepatocytes. *Fed. Proc.* 44:1591 (Abstr.)
198. Stipanuk, M. H., King, K. M. 1982. Characteristics of the enzymatic capacity for cysteine desulfhydration in cat tissues. *Comp. Biochem. Physiol.* 73B: 595–601
199. Stipanuk, M. H., Rotter, M. A. 1984. Metabolism of cysteine, cysteinesulfinate and cysteinesulfonate in rats fed adequate and excess levels of sulfur-containing amino acids. *J. Nutr.* 114: 1426–37
200. Stockland, W. L., Meade, R. J., Wass, D. F., Sowers, J. E. 1973. Influence of levels of methionine and cystine on the total sulfur amino acids requirements of the growing rat. *J. Anim. Sci.* 36:526–30
201. Sturman, J. A. 1973. Taurine pool sizes in the rat: Effects of vitamin-B_6 deficiency and high taurine diet. *J. Nutr.* 103:1566–80
202. Sturman, J. A., Beratis, N. G., Guarini, L., Gaull, G. E. 1980. Transsulfuration by human long-term lymphoid lines: Normal and cystathionase-deficient cells. *J. Biol. Chem.* 255:4763–65
203. Sturman, J. A., Cohen, P. A., Gaull, G. E. 1970. Metabolism of L-^{35}S-methionine in vitamin B_6 deficiency: Observations on cystathioninuria. *Biochem. Med.* 3:510–23
204. Sturman, J. A., Fellman, J. H. 1983. Methionine metabolism in the rat: Accumulation of hypotaurine after partial hepatectomy. See Ref. 12, pp. 435–47
205. Sturman, J. A., Hepner, G. W., Hofmann, A. F., Thomas, P. J. 1975. Metabolism of [^{35}S]taurine in man. *J. Nutr.* 105:1206–14
206. Sullivan, D. M., Hoffman, J. L. 1983. Fractionation and kinetic properties of rat liver and kidney methionine adenosyltransferase isozymes. *Biochemistry* 22: 1641–45
207. Szczepkowski, T. W., Skarżyński, B., Weber, M. 1961. The metabolic state of thiosulphate. *Nature* 189:1007–8
208. Tabor, C. W., Tabor, H. 1984. Polyamines. *Ann. Rev. Biochem.* 53: 749–90
209. Tallan, H. H. 1979. Methionine adenosyltransferase in man: Evidence for multiple forms. *Biochem. Med.* 21:129–40
210. Tamura, J., Ohkuma, S., Ida, S., Zuo, P. P., Kuriyama, K. 1984. Cysteine uptake and taurine biosynthesis in freshly isolated and primary cultured rat hepatocytes. *Cell Biochem. Funct.* 2:195–200
211. Tateishi, N., Higashi, T., Naruse, A., Hikita, K., Sakamoto, Y. 1981. Relative contributions of sulfur atoms of dietary cysteine and methionine to rat liver glutathione and proteins. *J. Biochem.* 90: 1603–10
212. Tateishi, N., Hirasawa, M., Higashi, T., Sakamoto, Y. 1982. The L-methionine-sparing effect of dietary glutathione in rats. *J. Nutr.* 112:2217–26
213. Tisdale, M. J. 1981. Effect of methionine deprivation on S-adenosylmethionine decarboxylase of tumour cells. *Biochim. Biophys. Acta* 675:366–72
214. Trackman, P. C., Abeles, R. H. 1981. The metabolism of 1-phospho-5-methylthioribose. *Biochem. Biophys. Res. Commun.* 103:1238–44
215. Trackman, P. C., Abeles, R. H. 1983. Methionine synthesis from 5'-S-methylthioadenosine: Resolution of enzyme activities and identification of 1-phospho-5-S-methylthioribulose. *J. Biol. Chem.* 258:6717–20
216. Tsukada, K., Okada, G. 1980. S-adenosylmethionine synthetase isozyme patterns from rat hepatoma induced by *N*-2-fluorenylacetamide. *Biochem. Biophys. Res. Commun.* 94:1078–82
217. Ubuka, T., Umemura, S., Yuasa, S., Kinuta, M., Watanabe, K. 1978. Purification and characterization of mitochondrial cysteine aminotransferase from rat liver. *Physiol. Chem. Phys.* 10:483–500
218. Ubuka, T., Yuasa, S., Ishimoto, Y., Shimomura, M. 1977. Desulfuration of L-cysteine through transamination and transsulfuration in rat liver. *Physiol. Chem. Phys.* 9:241–46
219. Ueland, P. M., Helland, S. 1980. S-Adenosylhomocysteinase from mouse liver: Catalytic properties at cellular enzyme level. *J. Biol. Chem.* 255:7722–27
220. Ueland, P. M., Helland, S. 1983. Binding of adenosine to intracellular S-adenosylhomocysteine hydrolase in isolated rat hepatocytes. *J. Biol. Chem.* 258:747–52
221. Ueland, P. M., Helland, S., Broch, O. J., Schanche, J.-S. 1984. Homocysteine in tissues of the mouse and rat. *J. Biol. Chem.* 259:2360–64
222. Uren, J. R., Ragin, R., Chaykovsky, M. 1978. Modulation of cysteine metabolism in mice: Effects of propargylglycine and L-cyst(e)ine-degrading enzymes. *Biochem. Pharmacol.* 27:2807–14
223. van der Westhuyzen, J., Fernandes-Costa, F., Metz, J. 1982. Cobalamin in-

activation by nitrous oxide produces severe neurological impairment in fruit bats: Protection by methionine and aggravation by folates. *Life Sci.* 31: 2001–10

224. van der Westhuyzen, J., Metz, J. 1984. Betaine delays the onset of neurological impairment in nitrous oxide–induced vitamin B-12 deficiency in fruit bats. *J. Nutr.* 114:1106–11
225. Vidal, A. J., Stokstad, E. L. R. 1974. Urinary excretion of 5-methyltetrahydrofolate and liver S-adenosylmethionine levels of rats fed a vitamin B_{12}–deficient diet. *Biochim. Biophys. Acta* 362:245–57

225a. Wagner, C. 1982. Cellular folate binding proteins; function and significance. *Ann. Rev. Nutr.* 2:229–48

225b. Wagner, C. 1985. Folate-binding proteins. *Nutr. Rev.* 43:293–99

226. Wagner, J., Claverie, N., Danzin, C. 1984. A rapid high-performance liquid chromatographic procedure for the simultaneous determination of methionine, ethionine, S-adenosylmethionine, S-adenosylethionine, and the natural polyamines in rat tissues. *Anal. Biochem.* 140:108–16
227. Wainer, A. 1964. The production of sulfate from cysteine without the formation of free cysteinesulfinic acid. *Biochem. Biophys. Res. Commun.* 16:141–44
228. Wilcken, D. E. L., Wilcken, B., Dudman, N. P. B., Tyrrell, P. A. 1983. Homocystinuria: The effects of betaine in the treatment of patients not responsive to pyridoxine. *N. Engl. J. Med.* 309:448–53
229. Wittwer, A. J., Wagner, C. 1981. Identification of the folate-binding proteins of rat liver mitochondria as dimethylglycine dehydrogenase and sarcosine dehydrogenase: Flavoprotein nature and enzymatic properties of the purified proteins. *J. Biol. Chem.* 256:4109–15
230. Xue, G.-P., Snoswell, A. M. 1985. Comparative studies on the methionine synthesis in sheep and rat tissues. *Comp. Biochem. Physiol.* 80B:489–94
231. Yagi, T., Kagamiyama, H., Nozaki, M. 1979. Cysteine sulfinate transamination activity of aspartate aminotransferases. *Biochem. Biophys. Res. Commun.* 90: 447–52
232. Yamaguchi, K., Hosokawa, Y., Kohashi, N., Kori, Y., Sakakibara, S., Ueda, I. 1978. Rat liver cysteine dioxygenase (cysteine oxidase): Further purification, characterization, and analysis of the activation and inactivation. *J. Biochem.* 83:479–91
233. Yamaguchi, K., Sakakibara, S., Asamizu, J., Ueda, I. 1973. Induction and activation of cysteine oxidase of rat liver. II. The measurement of cysteine metabolism in vivo and the activation of in vivo activity of cysteine oxidase. *Biochim. Biophys. Acta* 297:48–59
234. Yamaguchi, K., Shigehisa, S., Sakakibara, S., Hosokawa, Y., Ueda, I. 1975. Cysteine metabolism in vivo of vitamin B_6–deficient rats. *Biochim. Biophys. Acta* 381:1–8
235. Yamanishi, T., Tuboi, S. 1981. The mechanism of the L-cystine cleavage reaction catalyzed by rat liver γ-cystathionase. *J. Biochem.* 89:1913–21
236. Yamanoha, B., Samejima, K. 1980. Inhibition of S-adenosylmethionine decarboxylase from rat liver by synthetic decarboxylated S-adenosylmethionine and its analogs. *Chem. Pharm. Bull.* 28:2232–34
237. Yao, K., Kinuta, M., Akagi, R. 1979. Cat liver cystathionase. *Physiol. Chem. Phys.* 11:257–60