TAURINE NUTRITION

K. C. HAYES

Foster Biomedical Research Laboratory, Brandeis University, Waltham, Massachusetts 02254, USA

CONTENTS

INTRODUCTION

Interest in taurine has expanded rapidly in the past 15 years since its first association with clinical disease, evidenced as blindness in cats (Rabin *et al.* 1973; Hayes *et al.* 1975*a*), and the observed depression in plasma taurine concentration in infants fed on formula diets lacking taurine (Gaull *et al.* 1977). Since that time numerous authors have reviewed various aspects of taurine metabolism and biochemistry (Chesney, 1985; Wright *et al.* 1986) and nutrition (Hayes & Sturman, 1981; Hayes, 1985; Gaull, 1986; Chesney, 1988), as well as function in central nervous system (CNS) development (Mandel & Pasantes-Morales, 1978; Rassin, 1981; Sturman, 1986). The present review focuses on the comparative nutritional pathophysiology and metabolism of this unique amino acid with an emphasis on whole-body balance and depletion. In this context taurine is scrutinized as a possible essential nutrient for humans. To address this point requires an appreciation of tissue demands (based on putative functions and turnover of taurine) balanced against the available supply (both in terms of diet and biosynthesis). This balance has been most effectively examined in animal models where the relevant information has been generated under controlled conditions. Comparison with human findings are revealing in certain instances, less so in others.

STRUCTURE AND BIOSYNTHESIS

Taurine is a white, crystalline, tasteless compound (molecular weight 125). It is unique for a number of reasons, not the least of which is its high concentration in a wide range of cells and tissues, even while it always remains a free amino acid in these cells. Unlike most amino acids, a sulphonyl group replaces the carboxyl group and the amino group resides on the β-C rather than the α-C, i.e. it is a β-sulphonic amino acid $H_2N-CH_2-CH_2-SO_2H$ which, at physiological pH, occurs as a true zwitterion, $^{(+)}H_2N-CH_2-CH_2-SO_3^{(-)}$.

Taurine was first isolated more than 150 years ago from ox (*Taurus*) bile, where it is found in conjugation with bile acids through an amide linkage. Particularly-high concentrations (2–30 mM) are found in the cytoplasm of excitable tissues, such as certain parts of the brain, retina, skeletal and cardiac muscles, platelets and white blood cells. These concentrations represent a 20 to 400-fold concentration increase over the typical plasma concentration of 50–200 μM and reflect the cell-mediated active transport against a concentration gradient that is characteristic of this amino acid.

Taurine biosynthesis derives from the trans-sulphuration pathway originating with methionine (Jacobsen & Smith, 1968). As depicted in Fig. 1, the pool of available cysteine is important since glutathione and general protein synthesis compete with taurine at this juncture. Also note that both folic acid and vitamin B_{12} (indirectly via the transmethylation pathway involving regeneration of methionine) and vitamin B_6 (directly at three points in trans-sulphuration) have the potential to have an impact on taurine biosynthesis. Vitamin B_6 deficiency can depress taurine synthesis and tissue stores in the rat (Sturman & Cohen, 1971) and monkey (Stephan *et al.* 1984), but generally only if less than 10 % of the normal dietary vitamin B_6 allowance is fed. During moderate vitamin B_6 restriction, urine and faecal taurine decline in rats, but taurine in plasma and most tissues is not affected, indicating that taurine synthesis is only minimally impaired. In monkeys fed on a diet lacking pyridoxine and taurine, the taurine concentration in plasma, liver, urine, and muscle was depressed by 50–80 %, but brain, heart and retina were not affected. These findings indicate that only extreme pyridoxine deficiency has an appreciable impact on taurine synthesis and status.

Synthesis appears to be the primary responsibility of the liver and CNS. The rate-limiting step in taurine biosynthesis is the decarboxylation of cysteine sulphinic acid by cysteine sulphinate decarboxylase (*EC* 4.1.1.29) (CSA decarboxylase), an enzyme whose activity varies considerably between species and tissues, and probably with age in most species (Sturman & Hayes, 1980; Worden & Stipanuk, 1985). This variability is thought to determine whether taurine qualifies as a dietary essential for a given species under a given set of environmental and physiological circumstances.

GENERAL FUNCTION

It is not apparent that a single mechanism of action can account for all the functions of taurine (Huxtable & Sebring, 1986). However, the bulk of its activity might be explained by taurine exerting control over ionic flux, a mechanism which has been used to explain taurine function in several circumstances (Pasantes-Morales & Cruz, 1983; Wright *et al.* 1986). For example, by regulating calcium flux across the cell plasma membrane or release from intracellular microsomal pools, control might be exerted over excitable tissues in terms of electrical excitation and contractility. Since cytoplasmic Ca^{++} acts as the second messenger in a broad array of cell functions (Exton, 1985), including prostaglandin metabolism, cell division, osmotic balance and contractility, the impact of taurine could be considerable. Whether such regulation represents the specific interaction of taurine with
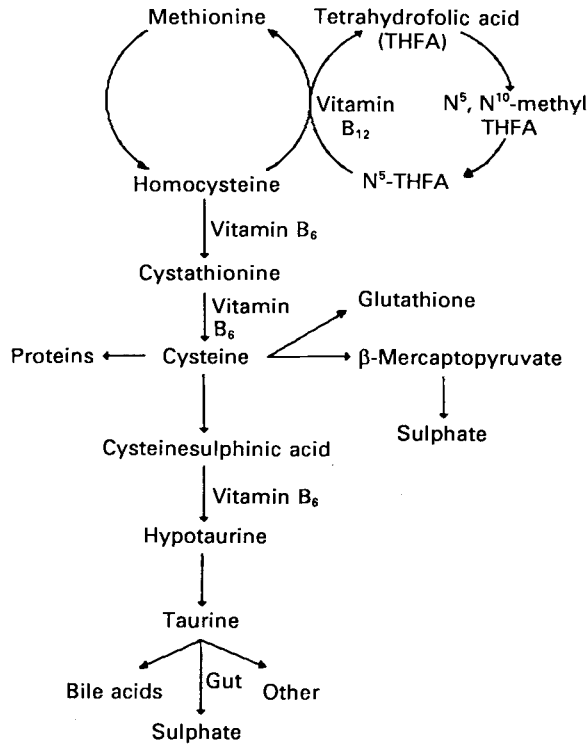
Fig. 1. Taurine biosynthesis.

membrane phospholipid(s), or membrane-associated protein(s), or cytoplasmic molecule(s) is unknown. The end result is that taurine seems to maintain cytoplasmic Ca^{++} within a narrow range during metabolically induced fluctuations in this ion.

A related hypothesis (van Gelder, 1983) envisions a model with taurine modulating Ca^{++} mobilization during depolarization, to stabilize membranes and control the excitation threshold. In the model Ca^{++} concentration and excitation are influenced by pH, bicarbonate generation, and a taurine–zinc complex regulating carbon dioxide (pH) and ammonia in the generation of glutamate. In van Gelder's (1983) model taurine would serve as a neurodepressant by controlling the synthesis of glutamate which then acts as a neurotransmitter. The same combination of events would also impact cell osmoregulation (van Gelder & Barbeau, 1985).

One of the more-specific molecular interactions of taurine occurs in neutrophils, where taurine modulates cytoplasmic peroxide generation of hypochlorous acid by coupling with the latter to form chlorotaurine. This process effectively dampens the potential oxidative insult from that system during phagocytic and biocidal activity in the neutrophil (Weiss *et al.* 1982; Wright *et al.* 1986). An extension of this function might include a general antioxidant role for taurine, but this has been refuted by experiments involving lipid peroxidation where taurine fails to exert a protective effect (Wright *et al.* 1986). Nonetheless, taurine supplementation increases the glutathione (GSH) content of platelets (Pronczuk *et al.* 1988).

BIOLOGICAL FUNCTION AS EVIDENCED BY DEFICIENCY

FELINE TAURINE DEFICIENCY

The prime example of the multifaceted biological activity of taurine is revealed through the constantly evolving taurine-deficiency syndrome in cats. Indeed, taurine deficiency has become an important nutritional problem in cats over the past 15 years. Since the original descriptions of clinical blindness and retinal degeneration (Hayes *et al.* 1975*a,b*), the number of deficiency signs has increased substantially to include reproductive failure and growth retardation coupled with CNS dysfunction and deformed spinal skeleton (Sturman *et al.* 1985), cardiomyopathy (Pion *et al.* 1987), platelet hyperaggregability (Pronczuk *et al.* 1988), as well as impaired neutrophil function (Schuller-Levis & Sturman, 1988).

Our understanding of the peculiar susceptibility of feline species to taurine deficiency has progressed, but a full appreciation of the situation is elusive. The consensus is that cats cannot synthesize appreciable amounts of taurine, particularly in the liver. In addition, they seem to require substantial quantities (more than other species) of this sulphur amino acid for metabolic purposes. Since the limiting enzyme for taurine biosynthesis, CSA decarboxylase, is low in cats, any taurine needed in excess of that synthesized must come from the diet (Knopf *et al.* 1978). On the demand side, it soon became apparent that bile acid metabolism in cats was somewhat unique in that essentially all bile acids were conjugated with taurine (Rabin *et al.* 1976). This is unlike most species, such as man, which also conjugate with glycine, or the rabbit, which typically conjugates all its bile acids with glycine. In essence, as available taurine becomes limited in cats, the bile acid pool, and to a lesser extent even the retina, conserves taurine while most tissues deplete their concentration to less than 10% normal. A second consideration is that kittens grow quickly, increasing the relative demand for taurine by virtue of their rapidly expanding muscle mass. A third factor is the significant demand for cysteine used in the synthesis of fur in this species. Yet a fourth possibility that requires further documentation is whether taurine, or possibly the cysteine-containing peptide, GSH, act as primary conjugators in cats to detoxify xenobiotics and other metabolites in preparation for biliary and urinary excretion as demonstrated in the ferret (Emudianughe *et al.* 1983). Reliance on the GSH-detoxification pathway by cats compensates for the limited availability of specific glucuronyl transferases serving this function in other species (Cullison, 1984). If metabolically important, this pathway could substantially increase the feline requirement for cysteine and taurine.

Ordinarily the cat, as the ultimate carnivore, should not encounter a taurine problem because its natural diet of meat and fish contains a high concentration of taurine. However, the plant kingdom is essentially devoid of taurine and is low in sulphur amino acids, so when commercial diets were formulated with cereals and grains, the current crisis evolved. This is particularly striking in cats fed on cereal-based dog food (Aguirre, 1978). Surprisingly the problem has not been resolved since several commercial cat formulas, including canned meat diets fortified with taurine, still fail to maintain normal plasma taurine levels (Pion *et al.* 1987). Much of the taurine in these canned diets appears to be unavailable or, if absorbed, is rapidly metabolized and excreted (Cooke *et al.* 1988). Further research is needed to rectify this predicament.

As indicated earlier the molecular action of taurine is unresolved. However, the various investigations involving the deficiency syndrome in cats provide several clues concerning its function. The retinopathy has been investigated most intensely. The primary defect appears to reside with the structural integrity of the photoreceptor outer segments (Hayes *et al.* 1975*b*) and the underlying structure of the tapetum lucidum (Sturman *et al.* 1981). When retinal taurine concentration is reduced to 50–75% of normal, the structure and function

(as measured by electron microscopy and electroretinogram (ERG)) deteriorate progressively. If not corrected by taurine supplementation, the photoreceptor cells eventually atrophy and disappear causing irreparable blindness. The implication is that taurine stabilizes the structure of the photoreceptors by modulating ionic flux (Ca^{2+}, Na^+, K^+) or osmotic gradients, or both, in the retinal photoreceptors and by stabilizing tapetal cell structure via possible Zn–taurine–cysteine interactions.

Taurine deficiency cardiomyopathy has recently been revealed as a major clinical problem in cats (Pion *et al.* 1987). The myopathy represents a failure in contractility, presumably due to abberant Ca^{2+} balance in the myocardial cell. The cardiomyopathy probably requires lengthy and extreme taurine depletion since moderately severe depletion with purified diets has not resulted in clinical evidence of heart failure in cats maintained for several years in experimental colonies involved in taurine research, even when other signs of deficiency exist and even though the taurine concentration in cardiac muscle has been reduced to $< 10\%$ of normal.

Also concerning the cardiovascular system, it was found recently (Pronczuk *et al.* 1988) that platelets from modestly depleted cats ($< 20\ \mu$M plasma levels) were twice as prone to collagen-induced aggregation as taurine-supplemented cats. In the same study taurine supplementation of normal humans increased the stability of their platelets to collagen-induced aggregation. In addition, platelet production of thromboxane (TX) B_2 was depressed while platelet GSH concentration was increased by taurine. Again, platelet aggregation and TXB_2 production are linked to cytoplasmic Ca metabolism in the platelet and both are modulated by the platelet redox status (GSH content) (Thomas *et al.* 1986). It was not possible to assess whether the higher GSH level associated with taurine supplementation represented increased GSH synthesis due to a sparing effect on cysteine utilization, or decreased catabolism of GSH due to direct taurine inhibition of platelet aggregation. Nonetheless, it serves to focus attention on the taurine–Ca–sulphydryl connection, a relationship relevant to its putative antioxidant potential (Wright *et al.* 1986). The implications for cats may be significant since this species is highly prone to thromboembolism (Tilley & Liu, 1975), episodes of which might be prevented by adequate taurine nutrition.

Growth depression in kittens is another aspect of taurine deficiency that has been well documented (Sturman *et al.* 1985). Kittens born and suckled by depleted queens gain less weight. It was found that deficient kittens that survive have been born 30–50% smaller than control kittens. Severe depletion of the queen during pregnancy often results in fetal death and malformations (Sturman & Messing, 1988). When kittens survive to be suckled, they frequently develop a spastic posterior gait and thoracic kyphosis attributed to dyplasia of the cerebellar granule cell layer. These defects appear to represent a failure in cell division and cell differentiation, again processes known to be modulated by intracellular Ca pools.

The impaired immune function in taurine-deficient cats is under investigation (Schuller-Levis & Sturman, 1988). Total white cells are reduced and neutrophils, like platelets, are readily depleted of taurine and demonstrate depressed biocidal function. We have observed a high incidence of conjunctivitis and a peculiar suppurative arthritis in peripheral joints of neonates born to deficient queens, possibly related to impaired resistance to infection.

Thus, the expression of this unique feline deficiency is widespread, affecting many organ systems. Since taurine is present in most cells and presumably impacts Ca metabolism in these cells, the breadth of the deficiency should not be surprising. In fact, careful scrutiny of other systems, e.g. olfactory, adrenal, kidney, gonads, or bile (hepatic function), where taurine is known to concentrate, should extend the list of potential defects in this feline syndrome.

DEFICIENCY IN OTHER ANIMAL SPECIES

Certain aspects of the cat syndrome have been recorded in monkeys. The first indication that primates were susceptible to taurine-responsive perturbations of physiological import came with the report of depressed growth rates in infant cebus and cynomolgus monkeys fed on taurine-free, soya-bean protein formulas from birth to 5 months of age (Hayes *et al.* 1980). Plasma, urine, and several tissues had taurine values substantially below that of supplemented monkeys, and daily weight gain was significantly reduced. Subsequently, infant rhesus monkeys fed for 2 years with a casein-based, taurine-free diet had lower plasma taurine values than controls (50 v. 100 μM) and a transiently abnormal ERG (after 10 months), with residual cone disruption observed by electron microscopy after 2 years (Sturman *et al.* 1984). No growth problem was noted. Since the reported plasma taurine concentrations were within what might be considered a normal range, the retinal degeneration seems an enigma. Adult cebus monkeys (Stephan *et al.* 1984) and squirrel monkeys (Stephan, Sturman & Hayes, unpublished results) fed on a taurine-free diet did not deplete plasma or tissue taurine pools unless synthesis was compromised by vitamin B_6 deficiency.

HUMAN DEPLETION AND DEFICIENCY

Although the limitation or absence of dietary taurine traditionally has not been thought to induce clinical disease in humans, this perception has recently been modified somewhat. Most recently taurine supplementation of children with cystic fibrosis improved their fat absorption and led to increased growth, both in terms of weight gain and bone growth (Darling *et al.* 1985). One group of preterm infants also experienced minimal improvement in fat absorption when fed on a milk formula containing 400 μM-taurine (Galeano *et al.* 1987). A rationale for the taurine effect lies in the tendency for taurine-conjugated bile acids to be absorbed lower in the small bowel (mostly in the ileum) than glycine conjugates, thereby increasing the solubilization, digestion, and absorption of fat along the entire small intestine. In children with cystic fibrosis it would seem important to determine whether a potential secondary effect of taurine, i.e. sparing cysteine or increasing the available sulphate pool, or both, was benefiting these children, since limiting dietary sulphate reduces bone formation in rats (Michels & Smith, 1965), and the increased mucus production in cystic fibrosis might greatly increase sulphate utilization. This could increase a requirement for dietary sulphate or the need to generate sulphate from oxidation of cysteine and taurine, the latter occurring only by bacterial conversion in the gut (Sturman & Hayes, 1980).

The absence of taurine from human infant formulas, fed either to full-term or preterm infants, results in decreased plasma and urinary taurine (Gaull *et al.* 1977; Jarvenpaa *et al.* 1982). However, the severity of depletion in plasma taurine of these infants (35 μM) was much less than that in cats (from 10 μM to undetectable). Nonetheless, with the exception of the effects on growth in children with cystic fibrosis, taurine supplementation of infant formulas at 250–300 μM generally has failed to influence fat absorption or growth, serum cholesterol, blood urea–nitrogen, serum proteins, acid-base balance, or bile metabolism (Raiha *et al.* 1976; Jarvenpaa *et al.* 1982; Jarvenpaa, 1983; Jarvenpaa *et al.* 1983; Rassin *et al.* 1983; Tyson *et al.* 1985), which would suggest that the dietary requirement for taurine in humans (i.e. its consideration as an essential nutrient) is minimal for most physiological circumstances. Alternatively, as is the case with canned cat foods, a much higher taurine load (> 400 μM) may be required in processed formulas to elicit a response in infants.

The most substantial taurine depletion in humans has been observed during partial or total parenteral nutrition (TPN) in children and adults (Geggel *et al.* 1985; Vinton *et al.* 1986). Under these circumstances, plasma taurine in children dropped below 30 μM (cf.

55–70 μM for controls) and a retinal defect was detected by ERG that was normalized by taurine infusion. It has been noted that no cysteine was added to the original TPN solution (Vandewoude & De Leeuw, 1985), which may have a bearing on taurine synthesis if we can extrapolate from the cat findings (see below). Thus, to date the only physiological measure of taurine depletion reported in humans, when plasma taurine was less than 30 μM, is a delayed implicit time in the retinal b-wave, the dysfunction originally noted in taurine-deficient cats (Rabin *et al.* 1973).

PHYSIOLOGICAL ASPECTS OF THE TAURINE REQUIREMENT

SYNTHESIS VERSUS TURNOVER AND EXCRETION

In the absence of dietary taurine, the basis for depletion rests on the balance between synthesis and utilization, including excretion. In the context of synthesis, the question of cysteine availability becomes a factor, since it represents the bottle-neck in substrate competition on the pathway to taurine synthesis (Fig. 1). Thus, if cysteine is limiting due to immaturity of the trans-sulphuration pathway, increased cysteine utilization for protein synthesis (e.g. during fur formation), increased conversion to GSH, or oxidation to sulphate, taurine synthesis could be compromised. Studies in cats indicate that simply adding methionine (10 g/kg) or cystine (8 g/kg) to a 360 g casein/kg diet had minimal effect on plasma taurine status (2–5 μM), whereas both amino acids substantially improved retinal taurine concentrations and partially alleviated the ERG abnormalities (Berson *et al.* 1976). O'Donnell *et al.* (1981) similarly noted that plasma taurine concentrations in depleted cats ($< 10 \mu$M) were minimally affected by supplements of sulphur amino acids, but not by varying the range or quality of dietary protein consumed (170–700 g soya bean or casein/kg). Recently Laidlaw *et al.* (1987) added 50 g cystine/kg to a 430 g casein/kg diet and restored the plasma and white-blood-cell taurine in cats to approximately 50 % normal.

An interesting, yet over-looked aspect of this effect of dietary protein on taurine status is found in studies on cats and preterm infants. In kittens, replacing dietary casein with lactalbumin (neither contains appreciable taurine) reversed the retinal degeneration in the one study which examined this point (Hayes *et al.* 1975 *b*). In preterm infants (Gaull *et al.* 1977) a whey-based (whey–casein (60:40, w/w)) formula, containing 30 g protein/kg as fed, resulted in normal plasma taurine values (60 μM), whereas a similar casein-based regimen (whey–casein (18:82, w/w)) caused plasma taurine to fall below normal (35 μM). Thus, lactalbumin (whey) either facilitated taurine synthesis or spared taurine utilization in both species. These findings also question the 'immaturity' of the trans-sulphuration enzymes in healthy preterm infants, at least in terms of taurine biosynthesis from cysteine, when extra high-quality protein increases the available cystine. The reason for the lactalbumin effect is unknown, but presumably reflects the 3-fold higher cystine concentration in lactalbumin than in casein. In current cat studies (Pronczuk *et al.* 1988) as little as 250 g casein/kg supplemented with arginine, cystine, methionine and threonine is associated with an improved taurine balance (10–20 μM), i.e. lessens the degree of depletion compared with the previous 430 g casein/kg diet without amino acid supplements (plasma taurine $< 5 \mu$M).

Possible explanations for an improved taurine status associated with a lower intake of high-quality protein include facilitated taurine synthesis, a reduced taurine requirement for bile acid, xenobiotic, or other metabolic conjugations and functions, or enhanced kidney tubular re-absorption facilitating taurine conservation, none of which have been assessed adequately as yet. The possibility exists that improving protein quality and

reducing the total protein load (from 430 to 250 g/kg) somehow relieves the demand for taurine utilization, e.g. associated with decreased urea cycle activity. In support of this concept, it is noteworthy that the previously mentioned protein-enriched (30 g/kg) casein-based (whey–casein, 18:82 w/w)) infant formula elevated the serum ammonia concentration while decreasing plasma and urinary taurine in preterm infants (Raiha et al. 1975), and that cats are exceptionally susceptible to diet-induced hyperammonaemia when arginine is limiting (Morris & Rogers, 1978). Whether hyperammonaemia or urea cycle metabolism influences taurine biosynthesis or utilization is unknown, but it is conceivable that taurine may function in the removal of excess ammonia and thus be utilized at an accelerated rate during sustained ureagenesis. It may be relevant that glutamyltaurine has been isolated in significant amounts from synaptosomes (Marnela et al. 1985) and that glutamate ordinarily serves as substrate for arginine synthesis in the urea cycle, but not in cats and probably not in infants (Morris & Rogers, 1978). Thus, if glutamyltaurine synthesis is high in cats, it could increase taurine utilization while decreasing glutamate availability for urea cycle metabolites.

LIVER AND GUT METABOLISM

The enterohepatic circulation (EHC) and associated metabolism may influence the taurine requirement, both from supply side (hepatic synthesis) and utilization (bile acid conjugation and excretion) points of view. For example, patients receiving TPN (i.e. with reduced gut function and bile acid cycling due to interrupted EHC) have decreased taurine in plasma, urine, platelets, and white blood cells (Vinton et al. 1986), even though their requirement for bile acid conjugation should theoretically decline as the percentage of energy from TPN increases. By contrast, vegetarians with no dietary source of taurine (but presumably experiencing a normal taurine demand for bile acid conjugation and normal EHC) have low-normal plasma taurine concentrations (47–70 μM) and decreased urinary taurine excretion (Rana & Sanders, 1986; Laidlaw et al. 1988), implying that whole-body taurine synthesis (including hepatic synthesis) and conservation are essentially adequate for their physiological needs, assuming that a plasma taurine > 30 μM is adequate. On the other hand, it has been suggested that bacterial overgrowth of the small intestine in humans (which interferes with enterohepatic metabolism) leads to taurine depletion (Sheikh, 1981). The implication is that oral food intake, normal bile flow, or EHC recycling are linked to endogenous taurine synthesis or otherwise enhance taurine conservation by sequestering taurine in the bile acid pool. An interesting possibility is that normal digestion and absorption, including gastrointestinal hormones, such as insulin, glucagon or cholecystokinin, directly or indirectly enhance hepatic taurine biosynthesis. As mentioned earlier, the availability of sulphate, provided either directly in TPN solutions or indirectly from oxidation of sulphur amino acids, could affect taurine metabolism since dietary sulphate depresses taurine biosynthesis in rats (Whittle & Smith, 1974). Bacterial overgrowth might also tend to increase taurine oxidation to sulphate, decreasing taurine enterohepatic recycling and increasing sulphate absorption and feedback inhibition of taurine biosynthesis.

Taurine supplementation of guinea-pigs (Kibe et al. 1980) or hamsters (Bellentani et al. 1987) in vivo or added directly in vitro to hepatocytes (Stephan et al. 1987) can stimulate bile acid synthesis. Apparently this is independent of taurine conjugation since the Hep G2 cell does not conjugate its bile acids. Simply increasing the cysteine concentration of the media appreciably also doubled the taurine concentration and increased bile acid synthesis. Here again it appears that sufficiently elevating cysteine, also apparent by adding cystine to cat diets, can drive taurine biosythesis. As was the case with circulating plasma values

in infants (Cooper *et al.* 1984), adults (Vinton *et al.* 1986) and in cats (Berson *et al.* 1976), the tissue culture findings suggest that even if the media or plasma concentrations of cysteine and methionine are 'normal', one cannot assume that the hepatocyte pools of these sulphur amino acids are maximally primed for taurine synthesis.

These taurine–liver–bile relationships are undoubtedly complex as evidenced by an interesting dicotomy in bile metabolism revealed in the cebus–cynomolgus monkey comparison previously mentioned (Stephan *et al.* 1981). Even though the degree of taurine depletion appeared similar in both monkey species, only the cebus continued to conjugate all its bile acids with taurine in a fashion similar to cats, while the cynomolgus shifted substantially to glycine conjugation, a pattern found in humans, hamsters, and guinea-pigs among others. Surprisingly during this shift to glycine by cynomolgus, the cheno-deoxycholate pool was spared, i.e. maintained its taurine conjugation while the cholate pool became increasingly conjugated with glycine. On the other hand, as indicated previously, taurine supplementation in humans and guinea-pigs increases cheno turnover and decreases its pool size. Interestingly, rabbit bile acids are essentially all cholate conjugated with glycine. The implications are that cheno and cholate are synthesized from separate pools of cholesterol and that the resulting bile acids have disparate unequal access to taurine for conjugation, with cheno synthesis and turnover being driven by taurine. Since species differ appreciably in their cheno:cholate ratio, this may reflect differences in taurine availability (synthesis) and utilization.

In the previously described monkey studies taurine depletion did not alter bile acid synthesis, but cebus did have 2·5 times the synthesis rate of cynomolgus. In addition, whereas cebus demonstrated minimal hepatic CSA decarboxylase activity, cynomolgus had none (i.e. no apparent hepatic taurine synthesis), and the cynomolgus bile acid profile was 1 cholate: 2 cheno as opposed to 3 cholate: 1 cheno for cebus. Thus, a high rate of bile acid synthesis (cebus, rat, cat) seems to be associated with a high degree of taurine conjugation. A corollary to this has already been mentioned, i.e. bile acid synthesis can be stimulated by taurine in certain species.

The situation is complicated by the fact that the human bile findings generally do not correspond to animal studies since neither premature infants (Watkins *et al.* 1983) nor adults (Hardison & Grundy, 1983) receiving taurine increase bile acid secretion, even though the taurine:glycine ratio increases appreciably. In fact, in adult men the total bile-acid pool size, particularly the cheno pool, was significantly reduced by taurine consumption 3 g/d. When five very premature infants (1400–2100 g) were given a taurine-supplemented (250 μM) formula, their low plasma taurine failed to increase and urinary taurine experienced only a minor increase, but duodenal concentrations of bile acids increased while cholesterol decreased (Okamoto *et al.* 1984). Feeding 400 μM-taurine (breast-milk concentration) to healthy premature infants raised urinary taurine to normal and increased the percentage fat absorption from 87 to 92, especially saturated fatty acids (Galeano *et al.* 1987). Intravenous taurine supplied to premature infants by TPN did not correct cholestasis (Cooke *et al.* 1984), which may mean that an intact, functioning EHC is necessary to elicit taurine stimulation of bile acid synthesis. That infancy and growth rate may not be critical to human taurine balance is suggested by findings indicating that adults receiving TPN also become taurine depleted (Vinton *et al.* 1986), an observation re-emphasizing that a functioning EHC with normal bile acid synthesis may be essential for hepatic taurine synthesis in humans. On the other hand, in contrast to the growing infant cebus, adult cebus monkeys, like human vegetarians, were able to maintain normal plasma (94 μM) and tissue taurine levels when fed on a taurine-free purified diet (Stephan *et al.* 1984.)

KIDNEY AS REGULATOR AND CONSERVATOR

Although the kidney has been emphasized as an important regulator of the plasma taurine concentration, critical evaluation of this regulatory role from a comparative standpoint while considering species differences in the dietary requirement has not been comprehensively addressed. In the healthy kidney taurine is filtered through the glomerulus and partially reabsorbed by the tubular cell (Chesney *et al.* 1983). Nonetheless, kidney reabsorption would appear less important than hepatic synthesis for sustaining whole-body taurine balance. This conclusion derives from the fact that the high plasma concentration of rats and dogs (> 200 μM), as opposed to cats and humans (< 100 μM), is associated with 100-fold higher rates of hepatic synthesis in the former (Hayes & Sturman, 1981), whereas the V_{max} for kidney tubular reabsorption in kittens (Park *et al.* 1988) appears about fivefold greater than in rats (Chesney *et al.* 1983). Thus, even though the cat kidney is working harder to conserve the meagre taurine being synthesized by the cat liver, it still is no match for the greater synthetic ability demonstrated by the rat liver. Clinical findings in kittens also failed to reveal enhanced kidney reabsorption in depleting animals (Rentschler *et al.* 1986). Accordingly, the kidney can be envisioned as a minimally effective dam behind which the plasma and tissue pools of taurine accumulate appreciably only if hepatic synthesis is substantial. An unexplored avenue for assessing the impact of the 'kidney threshold hypothesis' on the plasma and whole-body pools of taurine would be to measure taurine conservation during certain forms of kidney failure which might be expected to cause taurine depletion (proteinuria) or retention (renal shutdown).

This discussion implies that once the kidney-tubular-cell brush border has matured sufficiently for maximal taurine reabsorption to occur (normal term infant?) and synthesis is in progress, dietary taurine should not be required unless aberrant demands on taurine utilization (largely undefined at this time) or interruption in taurine synthesis occur. The fact that children with cystic fibrosis exhibit a growth response to dietary taurine supplements implies that they experience depressed input (synthesis or absorption) or excessive taurine turnover. The supplemented taurine may enter directly into the EHC and function within that pool to enhance fat absorption by virtue of an improved bile acid metabolism. On the other hand, taurine absorption or bile acid recycling may be defective in cystic fibrosis, leading to increased loss of taurine in faeces.

Exploration of the 'kidney threshold hypothesis' by simultaneously assessing synthesis and basal kidney tubular reabsorption would help determine the taurine requirement of an individual or species, from the supply side, i.e. dietary intake plus synthesis. Logically, if an organism has at least some taurine synthesis (essentially all do) and extremely efficient kidney and bile taurine conservation, turnover should be reduced to a point where adequate whole-body supply might be maintained. The cat and pre-term infant fed by TPN seem least capable in this regard (deplete most readily) with full-term human infants and adult humans as intermediate, whereas rats and hamsters appear quite well equipped to maintain a positive balance. The healthy human adult seems capable of adequate balance based on the fact that vegetarians maintain plasma values within the normal range of 45–75 μM, even though dietary intake may be naught and urine concentrations are low.

HUMAN REQUIREMENT

From the information discussed previously concerning the relative lack of taurine deficiency in vegetarians and healthy human infants given casein-rich taurine-free formulas, including premature infants with poor synthesis due to the proposed immaturity of their trans-sulphuration pathway (Gaull, 1982), one would surmise that the dietary taurine

requirement for human adults and infants is minimal. Caution is warranted, however, since the appropriate indices for detecting deficiency (ERG, cardiac contractility, white blood cell and platelet function) have not been sufficiently evaluated in humans over the range of plasma taurine concentrations reported (15–100 μM). Nonetheless, the inference is that overall demand for taurine in humans (mg/kg body-weight per d) is relatively less than in kittens. This could reflect comparative growth rates, not only for muscle mass, which is less than 5% that of kittens, but also for the CNS and retina which undergo much-more-rapid growth and development post-natally in kittens. As discussed earlier, these rapidly expanding pools of taurine in the kitten would increase the relative demand for taurine. It is interesting that in most species the most vulnerable system, i.e. the CNS–retina, usually expresses moderately higher CSA decarboxylase activity than the liver, which displays exceptional taurine synthesis in selected species like the rat and dog, but not the cat (Hayes & Sturman, 1981). The rat and dog also circulate high plasma taurine (> 200 μM).

Urinary taurine excretion has been shown to be reduced in both the pregnant and lactating omnivore and vegan women, in contrast to the pattern for all other amino acids. This was interpreted as a physiological response to the needs of the foetus and sucking infant for this amino acid (Naismith *et al.* 1986). These authors also suggested that taurine is stored in the maternal tissues in early pregnancy for later transfer to the foetus.

INDICES OF TAURINE STATUS

The plasma taurine concentration may prove to be an adequate predictor of taurine status once the relationship between this index, tissue levels, and cell function are fully appreciated. Much research remains to be done, but the indication from cats and humans is that retinal changes are induced when plasma taurine drops below 20–30 μM for a sustained period. Whether plasma levels fluctuate in humans is unknown. Plasma concentrations above 50 μM are presumably adequate. In the cat this concentration can be maintained with 500 μg taurine/kg diet under ideal conditions, but can be as high as 2000 μg/kg for certain canned diets. Ordinarily, adult humans can maintain 40–50 μM plasma taurine without a dietary source.

In some respects bile provides a sensitive index of taurine status (Hardison, 1978), even while having a seemingly disparate relationship to other tissue pools. For instance, as certain species become taurine-depleted, they switch to glycine-conjugated bile acids readily (human, cynomolgus monkey) or reluctantly (rat, hamster), while other major glycine conjugators switch to taurine when supplemented with taurine. By contrast, a taurine-free diet can reduce tissue and plasma pools of taurine without appreciably decreasing the percentage of taurine-conjugated bile acids in species like the cat and cebus monkey. The increase in taurine-conjugated bile acids can occur without altering the plasma level, as in hamsters supplemented with taurine compared to those fed on a taurine-free diet (Bellentani *et al.* 1987). This is quite unlike species such as cats and human infants where plasma levels are sensitive to dietary intake, presumably because their plasma taurine contribution from hepatic synthesis is so low. Nonetheless, even in the hamster, taurine supplementation increases bile acid production and pool size as though a local enterohepatic dietary effect of taurine was separated from the greater whole-body metabolic effect. Again, this hypothesis is in need of further investigation.

Urinary taurine depletion is thought to be indicative of low whole-body reserves in those species investigated to date. Since a 24 h urine collection is often impractical, a useful index would be to generate values for the urinary taurine:creatinine ratio so that casual urine samples can be extrapolated to the daily urinary output and used effectively to estimate whole-body balance. Quantitative information on urinary secretion could prove to be a
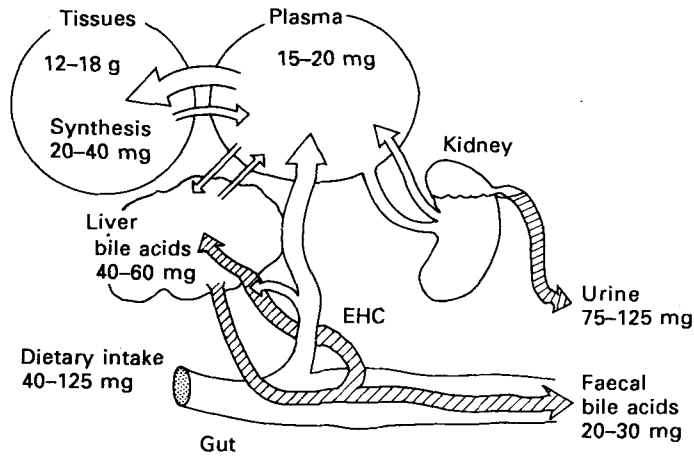
Fig. 2. Taurine distribution and daily balance in omnivorous human beings. EHC, enterohepatic circulation.

sensitive index once the variables that contribute to it, such as kidney threshold and fluctuation in daily intake, are better understood.

TAURINE POOLS

These observations raise the question whether the two systems under discussion (i.e. EHC-bile pool and remaining whole-body pool) are metabolically distinct. In such a model (Fig. 2) the two exit pathways for body taurine (kidney and faecal bile acid conjugates) may not communicate effectively and might best be considered separately for purposes of defining the taurine requirement. Certain information would support such a concept, e.g. kittens depleted of taurine still maintained a bile taurine pool at 88 % of normal, even as they became blind (retinal pool at < 60 %) and the plasma and other tissues were almost totally depleted (< 10 % of normal) (Rabin *et al.* 1976). In addition, plasma taurine in hamsters does not change with dietary supplementation, but bile acid synthesis and secretion are stimulated (Bellentani *et al.* 1987), suggesting a local EHC effect of the taurine supplement. This phenomenon has been noted in humans as well (Hardison, 1978), where hepatic accumulation of taurine due to bile obstruction is not extended to other tissues, and where rapid removal of taurine-conjugated bile acids does not deplete tissue pools.

Local synthesis by certain tissues would impact this model as well. For example, the CNS generally has sufficient taurine synthesis in most species to supply the brain and retina, but has little for export to the plasma. This is presumably why moderate taurine depletion in kittens does not cause CNS dysfunction, other than retinal (and probably olfactory) disturbances. In fact, turnover of taurine by these tissues is slowed many fold and their ability to sequester any available taurine increases substantially when dietary taurine is lacking. Hepatic taurine synthesis is probably the most important determinant of whole-body taurine adequacy, since excess taurine produced by the liver seems to reach the plasma and other tissues in a fashion similar to dietary supplements. However, the bile acid pool in cats appears so efficient in its sequestration of taurine, due to its obligate conjugation with this amino acid, that a serious problem develops in the depleting cat, an animal in which hepatic synthesis is so low that all the taurine synthesized here is used for bile acid conjugation and is unavailable to the plasma and other tissues.

The counterbalance to the taurine supply, of course, is the demand against it. We have dealt with this issue in a general sense already, i.e. the bile demand *v.* that generated by various other tissues; but until we actually understand what regulates the cellular function and turnover of taurine in specific tissues we cannot accurately describe overall demand.

SUMMARY

Taurine function as well as the basis for a dietary taurine requirement are both issues of current interest that are widely investigated. In the preceding discussion concerning the physiology and nutrition of taurine, several hypotheses are suggested for future investigation. At the present time it would appear that under normal physiological circumstances, particularly when the EHC and bile acid synthesis are intact and functioning, humans do not have a dietary requirement for taurine and its biosynthesis in vivo is sufficient to meet functional needs.

REFERENCES

Aguirre, G. D. (1978). Retinal degeneration associated with the feeding of dog foods to cats. *Journal of the American Veterinary Medicine Association* **172**, 791–796.

Bellentani, S., Pecorari, M., Cordoma, P., Marchegiano, P., Manenti, F., Bosisio, E., DeFabiani, E. & Galli, G. (1987). Taurine increases bile acid pool size and reduces bile saturation index in the hamster. *Journal of Lipid Research* **28**, 1021–1027.

Berson, E. L., Hayes, K. C., Rabin, A. R., Schmidt, S. Y. & Watson, G. (1976). Retinal degeneration in cats fed casein. II. Supplementation with methionine, cystine, or taurine. *Investigative Ophthalmology and Visual Science* **15**, 52–58.

Chesney, R. W. (1985). Taurine: its biological role and clinical implications. *Advances in Pediatrics* **32**, 1–42.

Chesney, R. W. (1988). Taurine: is it required for infant nutrition? *Journal of Nutrition* **118**, 6–10.

Chesney, R. W., Gusowski, N. & Friedman, A. L. (1983). Renal adaptation to altered dietary sulfur amino acid intake occurs at luminal brush border membrane. *Kidney International* **24**, 588–594.

Cooke, R. J., Whitington, P. F. & Kelts, D. (1984). Effect of taurine supplementation on hepatic function during short-term parenteral nutrition in the premature infant. *Journal of Pediatric Gastroenterology and Nutrition* **3**, 234–238.

Cooke, J. A., Rogers, Q. R. & Morris, J. G. (1988). Urinary and fecal excretion of taurine by cats fed commercial canned diets. *FASEB Journal* **2**, A1617.

Cooper, A., Betts, J. M., Pereira, G. R. & Ziegler, M. M. (1984). Taurine deficiency in the severe hepatic dysfunction complicating total parenteral nutrition. *Journal of Pediatric Surgery* **19**, 462–466.

Cullison, R. F. (1984). Acetaminophen toxicosis in small animals: Clinical signs, mode of action, and treatment. *Compendium* **6**, 315–321.

Darling, P. B., LePage, G., Leroy, C., Masson, P. & Roy, C. C. (1985). Effect of taurine supplements on fat absorption in cystic fibrosis. *Pediatric Research* **19**, 578–585.

Emudianughe, T. S., Caldwell, J. & Smith, R. L. (1983). The utilization of exogenous taurine for the conjugation of xenobiotic acids in the ferret. *Xenobiotica* **13**, 133–138.

Exton, J. H. (1985). Role of calcium and phosphoinositides in the action of certain hormones and neurotransmitters. *Journal of Clinical Investigation* **75**, 1753–1757.

Galeano, N. F., Darling, P., LePage, G., Leroy, C., Collet, S., Giguere, R. & Roy, C. C. (1987). Taurine supplementation of a premature formula improves fat absorption in preterm infants. *Pediatric Research* **22**, 67–71.

Gaull, G. E. (1982). Taurine in the nutrition of the human infant. *Acta Paediatrica Scandinavica* **296**, Suppl., 38–40.

Gaull, G. E. (1986). Taurine as a conditionally essential nutrient in man. *Journal of the American College of Nutrition* **5**, 121–125.

Gaull, G. E., Rassin, D. K., Raiha, C. R. & Heinonen, K. (1977). Milk protein quantity and quality in low birth weight infants. III. Effects on sulfur amino acids in plasma and urine. *Journal of Pediatrics* **90**, 348–355.

Geggel, H. S., Ament, M. E., Heckenlively, J. R., Martin, D. A. & Kopple, J. D. (1985). Nutritional requirement for taurine in patients receiving long-term parenteral nutrition. *New England Journal of Medicine* **312**, 142–146.

Hardison, W. G. M. (1978). Hepatic taurine concentration and dietary taurine as regulator of bile acid conjugation with taurine. *Gastroenterology* **75**, 71–75.

Hardison, W. G. M. & Grundy, S. M. (1983). Effect of bile acid conjugation pattern on bile acid metabolism in normal humans. *Gastroenterology* **84**, 617–620.

Hayes, K. C. (1985). Taurine requirement in primates. *Nutrition Reviews* **43**, 65–70.

Hayes, K. C., Carey, R. E. & Schmidt, S. Y. (1975*a*). Retinal degeneration associated with taurine deficiency in the cat. *Science* **88**, 949–951.

Hayes, K. C., Rabin, A. R. & Berson, E. L. (1975*b*). An ultrastructural study of nutritionally induced and reversed retinal degeneration in cats. *American Journal of Pathology* **78**, 505–524.

Hayes, K. C., Stephan, Z. F. & Sturman, J. A. (1980). Growth depression in taurine-depleted infant monkeys. *Journal of Nutrition* **110**, 2058–2064.

Hayes, K. C. & Sturman, J. A. (1981). Taurine in nutrition. *Annual Reviews of Nutrition* **1**, 401–425.

Huxtable, R. J. & Sebring, L. A. (1986). Towards a unifying theory of the actions of taurine. *TIPS* December, 481–485.

Jacobsen, J. G. & Smith, L. H. (1968). Biochemistry and physiology of taurine and taurine derivatives. *Physiological Reviews* **48**, 424–511.

Jarvenpaa, A. L. (1983). Feeding the low birth weight infant. IV. Fat absorption as a function of diet and duodenal bile acids. *Pediatrics* **72**, 684–689.

Jarvenpaa, A. L., Raiha, N. C. R., Rassin, D. K. & Gaull, G. E. (1982). Milk protein quantity and quality in the term infant. I. Metabolic responses and effects on growth. *Pediatrics* **70**, 214–220.

Jarvenpaa, A. L., Raiha, N. C. R., Rassin, D. K. & Gaull, G. E. (1983). Feeding the low birth weight infant. I. Taurine and cholesterol supplementation of formula does not affect growth and metabolism. *Pediatrics* **71**, 171–178.

Kibe, A., Wake, C., Kuramoto, T. & Hoshita, T. (1980). Effect of dietary taurine on bile acid metabolism in guinea pigs. *Lipids* **15**, 224–229.

Knopf, K., Sturman, J. A., Armstrong, M. & Hayes, K. C. (1978). Taurine: an essential nutrient for the cat. *Journal of Nutrition* **108**, 773–778.

Laidlaw, S. A., Shultz, T. D., Cecchino, J. T. & Kopple, J. D. (1988). Plasma and urine taurine levels in vegans. *American Journal of Clinical Nutrition* **47**, 660–663.

Laidlaw, S. A., Sturman, J. A. & Kopple, J. D. (1987). Effect of dietary taurine on plasma and blood cell taurine concentrations in cats. *Journal of Nutrition* **117**, 1945–1949.

Mandel, P. & Pasanates-Morales, H. (1978). Taurine in the nervous system. *Reviews in Neuroscience* **3**, 157–193.

Marnela, K. M., Morris, M. R., Panico, M., Timonen, M. & Lahdesmaki, P. (1985). Glutamyltaurine is the predominant synaptic taurine peptide. *Journal of Neurochemistry* **44**, 752–754.

Michels, F. G. & Smith, J. T. (1965). A comparison of the utilization of organic and inorganic sulphur in the rat. *Journal of Nutrition* **87**, 217–220.

Morris, J. G. & Rogers, Q. R. (1978). Ammonia intoxication in the near-adult cat as a result of a dietary deficiency of arginine. *Science* **199**, 431–432.

Naismith, D. J., Rana, S. K. & Emery, P. W. (1986). Metabolism of taurine during reproduction in women. *Human Nutrition–Clinical Nutrition* **40C**, 37–45.

O'Donnell, J. A., Rogers, Q. R. & Morris, J. G. (1981). Effect of diet on plasma taurine in the cat. *Journal of Nutrition* **111**, 1111–1116.

Okamoto, D., Rassin, D. K., Zucker, C. L., Salen, G. S. & Heird, W. C. (1984). Role of taurine in feeding the low birth weight infant. *Journal of Pediatrics* **104**, 936–940.

Park, T., Rogers, Q. R., Morris, J. G. & Chesney, R. W. (1988). Effect of dietary taurine on renal taurine transport by proximal tubule brushborder membrane vesicles in the kitten. *FASEB Journal* **2**, A1617.

Pasantes-Morales, H. & Cruz, C. (1983). Possible mechanisms in the protective action of taurine on photoreceptor structure. In *Sulphur Amino Acids: Biochemical and Clinical Aspects*, pp. 263–276 [K. Kuriyama, R. J. Huxtable and H. Iwata, editors]. New York: Alan R. Liss.

Pion, P. D., Kittleson, M. D., Rogers, Q. R. & Morris, J. G. (1987). Myocardial failure in cats associated with low plasma taurine: A reversible cardiomyopathy. *Science* **237**, 764–768.

Pronczuk, A., Addesa, A. E., Stephan, Z. F. & Hayes, K. C. (1988). Taurine decreases platelet aggregability in cats and humans. *FASEB Journal* **2**, A1617.

Rabin, A. R., Hayes, K. C. & Berson, E. I.. (1973). Cone and rod responses in nutritionally induced retinal degeneration in the cat. *Investigative Ophthalmology and Visual Science* **12**, 694–704.

Rabin, B., Nicolosi, R. J. & Hayes, K. C. (1976). Dietary influence on bile acid conjugation in the cat. *Journal of Nutrition* **106**, 1241–1246.

Raiha, N. C. R., Heinonen, K., Rassin, D. K. & Gaull, G. E. (1976). Milk protein quality and quantity in low-birth weight infants. 1. Metabolic responses and effects on growth. *Pediatrics* **57**, 659–674.

Rana, S. K. & Sanders, T. A. B. (1986). Taurine concentrations in the diet, plasma, urine and breast milk of vegetarians compared with omnivores. *British Journal of Nutrition* **56**, 17–27.

Rassin, D. K. (1981). The function of taurine in the central nervous system. *Advances in Biochemical Psychopharmacology* **29**, 127–134.

Rassin, D. K., Gaull, G. E., Jarvenpaa, A. L. & Raiha, N. C. R. (1983). Feeding the low birth weight infant: II. Effects of taurine and cholesterol supplementation on amino acids and cholesterol. *Pediatrics* **71**, 179–186.

Rentschler, L. A., Hirschberger, L. L. & Stipanuk, M. H. (1986). Response of the kitten to dietary taurine

depletion: Effects on renal reabsorption, bile acid conjugation and activities of enzymes involved in taurine synthesis. *Comparative Biochemistry and Physiology* **84**B, 319–325.

Schuller-Levis, G. B. & Sturman, J. A. (1988). Immunologic consequences of taurine deficiency in cats. *FASEB Journal* **2**, A1617.

Sheikh, K. (1981). Taurine deficiency and retinal defects associated with small intestinal bacterial overgrowth. *Gastroenterology* **80**, 1363.

Stephan, Z. F., Armstrong, M. J. & Hayes, K. C. (1981). Bile lipid alterations in taurine-depleted monkeys. *American Journal of Clinical Nutrition* **34**, 204–210.

Stephan, Z. F., Lindsey, S. & Hayes, K. C. (1987). Taurine enhances low density lipoprotein binding, internalization, and degradation by cultured Hep G2 cells. *Journal of Biological Chemistry* **262**, 6069–6073.

Stephan, Z. F., Sturman, J. A. & Hayes, K. C. (1984). Vitamin B_6 deficiency decreases lipoprotein ^{3}H-cholesterol incorporation into biliary sterols in cebus monkeys. *Nutrition Research* **4**, 421–435.

Sturman, J. A. (1986). Nutritional taurine and central nervous system development. *Annals of New York Academy of Science* **477**, 196–213.

Sturman, J. A. & Cohen, P. A. (1971). Cystine metabolism in vitamin B_6 deficiency: Evidence of multiple taurine pools. *Biochemistry and Medicine* **5**, 245–268.

Sturman, J. A. & Hayes, K. C. (1980). The biology of taurine in nutrition and development. In *Advances in Nutritional Research*, vol. 3, pp. 231–299 [H. H. Draper, editor]. New York: Plenum.

Sturman, J. A. & Messing, J. M. (1988). Dietary taurine levels and feline pregnancy and outcome. *FASEB Journal* **2**, A1617.

Sturman, J. A., Mortez, R. C., French, J. H. & Wisniewski, H. M. (1985). Taurine deficiency in the developing cat: persistence of the cerebellar external granule cell layer. *Journal of Neuroscience Research* **13**, 405–416.

Sturman, J. A., Wen, G. Y., Wisniewski, H. M. & Hayes, K. C. (1981). Histochemical localization of zinc in the feline tapetum: effect of taurine depletion. *Histochemistry* **72**, 341–350.

Sturman, J. A., Wen, G. Y., Wisniewski, H. M. & Neuringer, M. D. (1984). Retinal degeneration in primates raised on a synthetic human infant formula. *International Journal of Developmental Neuroscience* **2**, 121–129.

Thomas, G., Lucas, F. V., Schumacher, O. P. & Shrinsk, V. (1986). Behavior of intracellular glutathione during placental thromboxane synthesis in diabetics. *Prostaglandins, Leukotrienes and Medicine* **22**, 117–128.

Tilley, L. P. & Liu, S.-K. (1975). Cardiomyopathy and thromboembolism in the cat. *Feline Practice* **5**, 32–41.

Tyson, J., Lasky, R., Flood, D. & Mize, C. (1985). Absence of effect of taurine on growth, electroretinograms (ERG), and auditory evoked responses of very-low-birth weight infants. *Pediatric Research* **19**, 236A.

Vandewoude, M. J. F. & DeLeeuw, I. H. (1985). Taurine requirement with parenteral nutrition. *New England Journal of Medicine* **313**, 120–121.

van Gelder, N. M. (1983). A central mechanism of action for taurine: Osmoregulation, bivalent cations, and excitation threshold. *Neurochemical Research* **8**, 687–699.

van Gelder, N. M. & Barbeau, A. (1985). The osmoregulatory function of taurine and glutamic acid. In *Taurine: Biological Actions and Clinical Perspectives*, pp. 149–163 [S. S. Oja, L. Ahtee, P. Kontro and M. K. Paasonen, editors]. New York: Alan R. Liss.

Vinton, N. E., Laidlaw, S. A., Ament, M. E. & Kopple, J. D. E. (1986). Taurine concentrations in plasma and blood cells of patients undergoing long-term parenteral nutrition. *American Journal of Clinical Nutrition* **44**, 398–406.

Watkins, J. B., Jarvenpaa, A. L., Szczepanik-Van Leeuwen, P., Klein, P. D., Rassin, D. K., Gaull, G. & Rajha, N. C. R. (1983). Feeding the low birth weight infant: V. Effects of taurine, cholesterol and human milk on bile acid kinetics. *Gastroenterology* **85**, 793–800.

Weiss, S. J., Klein, R., Slivka, A. & Wei, M. (1982). Chlorination of taurine by human neutrophils: evidence for hypochlorous acid generation. *Journal of Clinical Investigation* **70**, 598–607.

Whittle, B. & Smith, J. T. (1974). Effect of dietary sulphur on taurine excretion by the rat. *Journal of Nutrition* **104**, 666–670.

Worden, J. A. & Stipanuk, M. H. (1985). A comparison by species, age and sex of cysteinesulfinate decarboxylase activity and taurine concentration in liver and brain of animals. *Comparative Biochemistry and Physiology* **82**B, 233–239.

Wright, C. E., Tallan, H. H., Lin, Y. Y. & Gaull, G. E. (1986). Taurine: biological update. *Annual Reviews of Biochemistry* **55**, 427–453.

Printed in Great Britain