Adverse effects. For reference to life-threatening eosinophilic pleuropericarditis in a patient receiving biotin and pantothenic acid see p.1959.

Deficiency states. Biotin has been used to treat deficiency of biotinidase or holocarboxylase synthetase, enzymes responsible for the recycling and incorporation of biotin. In the UK, the *BNFC* suggests the following doses:

- for isolated carboxylase defects, biotin may be given to neonates in a dose of 5 mg once daily by mouth or slow intravenous injection, adjusted according to response; older patients may be given 10 mg daily. The usual maintenance dose ranges from 10 to 50 mg daily, though up to 100 mg daily may be needed
- for defects of biotin metabolism, 10 mg once daily may be given by mouth or slow intravenous injection, adjusted according to response. Usual maintenance doses are 5 to 20 mg daily but higher doses may be needed

References.

1. Baumgartner ER, Suormala T. Multiple carboxylase deficiency: inherited and acquired disorders of biotin metabolism. *Int J Vitam Nutr Res* 1997; **67:** 377–84.
2. Tsao CY, Kien CL. Complete biotinidase deficiency presenting as reversible progressive ataxia and sensorineural deafness. *J Child Neurol* 2002; **17:** 146.
3. Wolf B. Biotinidase deficiency: new directions and practical concerns. *Curr Treat Options Neurol* 2003; **5:** 321–8.
4. Seymons K, *et al.* Dermatologic signs of biotin deficiency leading to the diagnosis of multiple carboxylase deficiency. *Pediatr Dermatol* 2004; **21:** 231–5.
5. Grünewald S, *et al.* Biotinidase deficiency: a treatable leukoencephalopathy. *Neuropediatrics* 2004; **35:** 211–16.
6. Puertas Bordallo D, *et al.* Neuropatía óptica por déficit de biotinidasa. *Arch Soc Esp Oftalmol* 2004; **79:** 393–6.
7. Hoffman TL, *et al.* Biotinidase deficiency: the importance of adequate follow-up for an inconclusive newborn screening result. *Eur J Pediatr* 2005; **164:** 298–301.
8. Wilson CJ, *et al.* Severe holocarboxylase synthetase deficiency with incomplete biotin responsiveness resulting in antenatal insult in Samoan neonates. *J Pediatr* 2005; **147:** 115–18.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p.1925) has been set for biotin although it was considered that an intake of between 10 and 200 micrograms daily was both safe and adequate.[1] Similarly in the USA an adequate intake of 30 micrograms daily has been set for adults.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aminosam; Panabiotin; ***Austria:*** Bio-H-Tin; Curatin; Medobiotin; Merzbiotin; ***Canad.:*** D Biotin†; ***Chile:*** Hvit; ***Fin.:*** Biotisan; ***Ger.:*** Bio-H-Tin; Biokur†; Biotin-Asmedic; Deacura; Gabunat; Medobiotin†; Natubiotin; Natuderm†; Rombellin†; ***Hung.:*** Bio-H-Tin; ***Ital.:*** Biodermatin; Diathynil; Nebiotin; ***Spain:*** Medebiotin; ***Switz.:*** Bio-H-Tin; Rombellin; ***USA:*** Appearex; Hard Nails.

Multi-ingredient: ***Arg.:*** Folimax B; Megaplus; Tersoderm Anticaspa†; ***Fr.:*** Zeniac LP†; Zeniac†; ***Ger.:*** Carotin; ***Indon.:*** Alicron; ***Spain:*** Doctodermis; Lacerdermol.

Calcium Ferrous Citrate

Ferrous Calcium Citrate. Dicalcium iron(2+) bis(2-hydroxypropane-1,2,3-tricarboxylate).

$C_{12}H_{10}Ca_2FeO_{14}$ = 514.2.
CAS — 53684-61-0.

Profile

Calcium ferrous citrate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)
Israel: Ferrocal.

Multi-ingredient: ***India:*** Raricap; Raricap L.

Calcium Fluoride

Fluoruro cálcico.

CaF_2 = 78.07.
CAS — 7789-75-5.

Pharmacopoeias. In *Ger.*

Profile

Calcium fluoride is used as a fluoride supplement (see Sodium Fluoride, p.1962) for the prevention of dental caries. Calcium fluoride is also used as a source of calcium.

Homoeopathy. Calcium fluoride has been used in homoeopathic medicines under the following names: Calcarea Fluorica; Calc. Fluor; Calcium Fluoratum; Cal. fl.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Calcifluor†.

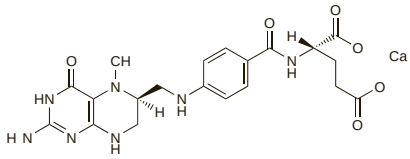
Multi-ingredient: ***Cz.:*** Bifluorid†; ***Denm.:*** Bifluorid; ***India:*** Calcinol; ***Ital.:*** Bifluorid†; ***Pol.:*** Bifluorid; ***Swed.:*** Bifluorid.

Calcium Mefolinate

Calcii Mefolinas; Calcio Mefolinato; Calcium L-Methylfolate; Calcium (6S)-5-Methyltetrahydrofolate.

Кальция L-Метилфолат

$C_{20}H_{23}CaN_7O_6$ = 497.5.
CAS — 26560-38-3.



NOTE. Metafolin is a trade name that has been used for calcium mefolinate.

Profile

Calcium mefolinate is the calcium salt of 5-methyltetrahydrofolate, the biologically active metabolite of folic acid (p.1940). It is used as a food supplement and also has similar uses to folic acid.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Biofolic; Furoic; Prefolic; ***USA:*** Deplin.

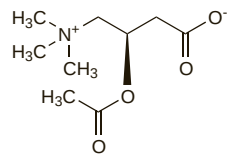
Multi-ingredient: ***USA:*** Cerefolin; Metanx.

Carnitine Derivatives

Acetylcarnitine Hydrochloride

Acetilcarnitina, hidrocloruro de; Acetyl-L-carnitine Chloride; Levacecarnine Hydrochloride; Levocarnitinum acetilum hydrochloricum; ST-200. (3-Carboxy-2-hydroxypropyl)trimethylammonium acetate (ester) chloride.

$C_9H_{17}NO_4$,HCl = 239.7.
CAS — 5080-50-2.
ATC — N06BX12.
ATC Vet — QN06BX12.



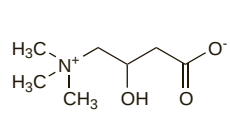
(acetyl-L-carnitine)

Carnitine *(rINN)*

Carnitina; Carnitinum; Karnitin; ST-198; Vitamin B_T. (3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt; 3-Hydroxy-4-trimethylammoniobutyrate.

Карнитин

$C_7H_{15}NO_3$ = 161.2.
CAS — 461-06-3.

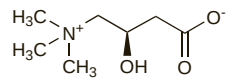


Levocarnitine *(BAN, USAN, rINN)*

L-Carnitine; L-Karnitin; Levocarnitina; Lévocarnitine; Levocarnitinum; Levokarnitiini; Levokarnitin; Levokarnitinas. (*R*)-(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt; (*R*)-3-Hydroxy-4-trimethylammoniobutyrate.

Левокарнитин

$C_7H_{15}NO_3$ = 161.2.
CAS — 541-15-1.
ATC — A16AA01.
ATC Vet — QA16AA01.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Levocarnitine). A white or almost white, hygroscopic, crystalline powder or colourless crystals. Freely soluble in water; soluble in warm alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 6.5 to 8.5. Store in airtight containers.

USP 31 (Levocarnitine). White, hygroscopic, crystals or crystalline powder. Freely soluble in water and in hot alcohol; practically insoluble in acetone, in ether, and in benzene. pH of a 5% solution in water is between 5.5 and 9.5. Store in airtight containers.

Levocarnitine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de levocarnitina; Lévocarnitine, Chlorhydrate de; Levocarnitini Hydrochloridum. (*R*)-3-Hydroxy-4-trimethylammoniobutyrate hydrochloride.

Левокарнитина Гидрохлорид

$C_7H_{15}NO_3$,HCl = 197.7.
CAS — 6645-46-1.

Levocarnitine Propionate *(rINNM)*

L-Carnitine propionate; Lévocarnitine, Propionate de; Levocarnitini Propionas; Propionato de levocarnitina; Propionylcarnitine; L-Propionylcarnitine; Propionyl-L-carnitine; ST-261.

Левокарнитина Пропионат

$C_{10}H_{19}NO_4$ = 217.3.
CAS — 20064-19-1.

Levocarnitine Propionate Hydrochloride *(USAN)*

Propionyl-L-carnitine Hydrochloride; STI-261. (2*R*)-3-Carboxy-*N*,*N*,*N*-trimethyl-2-(propanoyloxy)propan-1-aminium chloride.

$C_{10}H_{20}ClNO_4$ = 253.7.
CAS — 119793-66-7.

Adverse Effects and Precautions

Gastrointestinal disturbances such as nausea, vomiting, diarrhoea, and abdominal cramps have been reported after the use of levocarnitine. Body odour has also been noticed in some patients, possibly due to the formation of the metabolite trimethylamine (see Fish Odour Syndrome, p.1923). Decreasing the dosage may reduce or eliminate these effects; oral levocarnitine should be consumed slowly to decrease gastrointestinal disturbances. Seizures have been reported.

Patients with severe renal impairment should not be given high oral doses of levocarnitine for long periods, because of the accumulation of the metabolites trimethylamine and trimethylamine-*N*-oxide. This is said not to occur to the same extent after intravenous dosage. Diabetic patients given carnitine while receiving insulin or hypoglycaemic drugs should be monitored for hypoglycaemia.

Renal impairment. Of 30 patients given DL-carnitine intravenously after dialysis sessions 3 developed myasthenia-like symptoms but when these 3 were given only levocarnitine the symptoms did not occur.[1] It was considered that in anuric uraemic patients the D-isomer was not excreted adequately and that accumulation had blocked neuromuscular transmission. It was therefore suggested that levocarnitine, rather than the DL-form, should be used. (High and prolonged oral doses of levocarnitine should, however, be avoided—see above.)

1. Bazzato G, *et al.* Myasthenia-like syndrome after but not - carnitine. *Lancet* 1981; **i:** 1209.

Pharmacokinetics

Oral doses of levocarnitine are absorbed slowly and incompletely from the small intestine. Bioavailability has been reported to be only about 10 to 15%, with peak plasma concentrations attained about 3 to 4 hours after an oral dose. Plasma concentrations after oral doses represent the sum of endogenous and exogenous material. Levocarnitine does not appear to bind to plasma proteins. It is mainly eliminated by the kidneys, undergoing extensive tubular reabsorption. After intravenous doses, levocarnitine appears to undergo minimal metabolism. Levocarnitine given orally may undergo degradation in the gastrointestinal tract, leading to the

formation of metabolites such as trimethylamine-*N*-oxide and γ-butyrobetaine, recovered in the urine and faeces, respectively.

◊ References.

1. Evans AM, Fornasini G. Pharmacokinetics of L-carnitine. *Clin Pharmacokinet* 2003; **42:** 941–67.
2. Bain MA, *et al.* Disposition and metabolite kinetics of oral L-carnitine in humans. *J Clin Pharmacol* 2006; **46:** 1163–70.
3. Fornasini G, *et al.* A pharmacokinetic model for L-carnitine in patients receiving haemodialysis. *Br J Clin Pharmacol* 2007; **64:** 335–45.

Uses and Administration

Carnitine is an amino acid derivative that is an essential cofactor of fatty acid metabolism.

Carnitine is used in the treatment of primary carnitine deficiency and in carnitine deficiency secondary to a variety of defects of intermediary metabolism or other conditions such as haemodialysis. Both the L- and the DL-isomers have been used, but it is believed that only levocarnitine is effective and in addition, that DL-carnitine supplementation can lead to carnitine deficiency.

In the UK, depending on the condition, up to 200 mg/kg daily of levocarnitine is given orally, in 2 to 4 divided doses. Rarely, higher doses of up to 400 mg/kg daily may be needed. In the USA, lower doses of about 2 to 3 g daily are recommended for adults; the dose given for infants and children is 50 to 100 mg/kg daily in divided doses, to a maximum of 3 g daily.

When given intravenously, up to 100 mg/kg daily is given in 3 to 4 divided doses by slow intravenous injection over 2 to 3 minutes. Higher intravenous doses have been given, but are associated with an increased incidence of adverse effects.

In patients with carnitine deficiency secondary to haemodialysis, the recommended dose of levocarnitine is 10 to 20 mg/kg intravenously after each dialysis session, adjusted according to plasma-carnitine concentrations. An oral maintenance dose of 1 g daily may be considered (but see Adverse Effects and Precautions, above).

Levocarnitine is under investigation for the treatment of zidovudine-induced mitochondrial myopathy. Carnitine derivatives have been used to treat conditions including cardiovascular disease, peripheral arterial disease, cerebrovascular insufficiency, peripheral neuropathies, and neurological disorders, see below.

Carnitine chloride, carnitine hydrochloride, carnitine orotate, and bicarnitine chloride have also been used.

Carnitine supplementation. Carnitine occurs as distinct L- and D-isomers although naturally-occurring carnitine is almost exclusively the L-isomer.[1] Carnitine is an essential co-factor of fatty acid metabolism in the heart, liver, and skeletal muscle.[1,2] It is normally synthesised in the liver, brain, and kidneys in sufficient quantities to meet human requirements but dietary sources such as meat and dairy products also provide carnitine.[1-4] In plasma and tissues carnitine is present in the free form and as acylated esters of which acetylcarnitine is the most abundant.

Although DL-carnitine is the form often present in over-the-counter preparations and dietary supplements, levocarnitine should be preferred, as the two isomers differ in their actions. Levocarnitine acts as a substrate for carnitine acetyltransferase while D-carnitine acts as a competitive inhibitor; also, levocarnitine-induced stimulation of palmitate oxidation is competitively inhibited by D-palmitoylcarnitine. Such differences are believed to account for findings of benefit only with the L-isomer, or unwanted effects when D-carnitine or DL-carnitine was used.[1,5]

Primary **carnitine deficiency** is a disorder of the membrane transport of carnitine and patients have presented with hypoglycaemia and encephalopathy, skeletal myopathy, and cardiomyopathy. Therapy with carnitine in these primary deficiency states is considered to have a rational basis.[2,4-6] Secondary carnitine deficiency occurs in many inherited metabolic disorders, especially in the organic acidurias and disorders of beta-oxidation. The value of carnitine for these conditions is controversial.[2,4,6-8]

Carnitine deficiency may also arise during the long-term use of **drugs** such as valproic acid,[5,9-11] pivampicillin,[12,13] or pivmecillinam,[12] which are conjugated with carnitine. Whether carnitine supplementation can prevent or reverse this type of deficiency is unclear: although treatment with carnitine raised plasma-carnitine concentrations, it had no more effect than placebo on the well-being of children receiving valproic acid therapy in one study,[14] but others have found levocarnitine supplementation of value in attenuating valproate-induced hyperammonaemia after a protein-rich meal,[15] and some paediatric neurologists consider supplementation justified in selected children with epilepsy,[16,17] including those with, or at risk of, valproate-induced hepatotoxicity and hyperammonaemic encephalopathy. There is some suggestion that carbamazepine and phenobarbital can also decrease carnitine concentrations.[10,11] Therapy with cisplatin[18] or ifosfamide[19] has been reported to cause increased urinary excretion of carnitine.

There is also some evidence[5,20] that carnitine supplements may be of benefit to low birth-weight preterm **infants**, but a double-blind study[21] failed to confirm this effect. A systematic review concluded that there are insufficient data to support the use of carnitine supplementation for the treatment of apnoea of prematurity, despite a plausible rationale for such treatment.[22] While some evidence of benefit exists for carnitine supplementation of neonates receiving parenteral nutrition,[5] a systematic review found no evidence of effect on weight gain, fat utilisation, or ketogenesis.[23]

Low concentrations of carnitine have also been reported to occur in a variety of other conditions (see below).

1. Li Wan Po A. Carnitine: a scientifically exciting molecule. *Pharm J* 1990; **245:** 388–9.
2. Anonymous. Carnitine deficiency. *Lancet* 1990; **335:** 631–3.
3. Anonymous. L-carnitine. *Med Lett Drugs Ther* 2004; **46:** 95–6.
4. Scaglia F, Longo N. Primary and secondary alterations of neonatal carnitine metabolism. *Semin Perinatol* 1999; **23:** 152–61.
5. Goa KL, Brogden RN. L-Carnitine: a preliminary review of its pharmacokinetics, and its therapeutic use in ischaemic cardiac disease and primary and secondary carnitine deficiencies in relationship to its role in fatty acid metabolism. *Drugs* 1987; **34:** 1–24.
6. Evangeliou A, Vlassopoulos D. Carnitine metabolism and deficit when supplementation is necessary? *Curr Pharm Biotechnol* 2003; **4:** 211–9.
7. Rinaldo P, *et al.* Effect of treatment with glycine and -carnitine in medium-chain acyl-coenzyme A dehydrogenase deficiency. *J Pediatr* 1993; **122:** 580–4.
8. Winter SC. Treatment of carnitine deficiency. *J Inherit Metab Dis* 2003; **26:** 171–80.
9. Raskind JY, El-Chaar GM. The role of carnitine supplementation during valproic acid therapy. *Ann Pharmacother* 2000; **34:** 630–8.
10. Verrotti A, *et al.* Carnitine deficiency and hyperammonemia in children receiving valproic acid with and without other anticonvulsant drugs. *Int J Clin Lab Res* 1999; **29:** 36–40.
11. Castro-Gago M, *et al.* Serum carnitine levels in epileptic children before and during treatment with valproic acid, carbamazepine, and phenobarbital. *J Child Neurol* 1998; **13:** 546–9.
12. Holme E, *et al.* Carnitine deficiency induced by pivampicillin and pivmecillinam therapy. *Lancet* 1989; **ii:** 469–73.
13. Melegh B. Carnitine supplementation in pivampicillin treatment. *Lancet* 1989; **ii:** 1096.
14. Freeman JM, *et al.* Does carnitine administration improve the symptoms attributed to anticonvulsant medications?: a double-blinded, crossover study. *Pediatrics* 1994; **93:** 893–5.
15. Gidal BE, *et al.* Diet- and valproate-induced transient hyperammonemia: effect of -carnitine. *Pediatr Neurol* 1997; **16:** 301–5.
16. De Vivo DC, *et al.* -carnitine supplementation in childhood epilepsy: current perspectives. *Epilepsia* 1998; **39:** 1216–25.
17. Lheureux PER, *et al.* Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence? *Crit Care* 2005; **9:** 431–40.
18. Heuberger W, *et al.* Increased urinary excretion of carnitine in patients treated with cisplatin. *Eur J Clin Pharmacol* 1998; **54:** 503–8.
19. Marthaler NP, *et al.* Increased urinary losses of carnitine during ifosfamide chemotherapy. *Cancer Chemother Pharmacol* 1999; **44:** 170–2.
20. Shortland GJ, Walter JH. L-carnitine. *Lancet* 1990; **335:** 1215.
21. Shortland GJ, *et al.* Randomised controlled trial of L-carnitine as a nutritional supplement in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1998; **78:** F185–F188.
22. Kumar M, *et al.* Carnitine supplementation for preterm infants with recurrent apnea. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 08/11/05).
23. Cairns PA, Stalker DJ. Carnitine supplementation of parenterally fed neonates. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 08/11/05).

CARDIOVASCULAR DISEASE. There is some evidence that carnitine supplementation may exert a cardioprotective role. Benefit in patients with *cardiomyopathies*,[1-3] reduction of infarct size in patients with *myocardial infarction*,[4] and increased exercise performance in patients with *angina*[5] or *intermittent claudication*,[6-8] have all been described in patients given carnitine. While variable effects on cholesterol and triglyceride plasma concentrations have been described,[5] studies in diabetic[9] and hyperlipoproteinaemic[10] patients have reported reductions in plasma lipoprotein(a) concentrations. However, carnitine supplementation in patients with chronic *heart failure* failed to increase exercise capacity,[11] and its value outside of actual deficiency is still considered uncertain.[5]

1. Winter SC, Buist NRM. Cardiomyopathy in childhood, mitochondrial dysfunction, and the role of L-carnitine. *Am Heart J* 2000; **39** (suppl): S63–S69.
2. Helton E, *et al.* Metabolic aspects of myocardial disease and a role for -carnitine in the treatment of childhood cardiomyopathy. *Pediatrics* 2000; **105:** 1260–70. Correction. *ibid.*; **106:** 623.
3. Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. *Am Heart J* 2000; **139** (suppl): S120–S123.
4. Pauly DF, Pepine CJ. The role of carnitine in myocardial dysfunction. *Am J Kidney Dis* 2003; **41** (suppl): S35–S43.
5. Arsenian MA. Carnitine and its derivatives in cardiovascular disease. *Prog Cardiovasc Dis* 1997; **40:** 265–86.
6. Hiatt WR, *et al.* Propionyl-L-carnitine improves exercise performance and functional status in patients with claudication. *Am J Med* 2001; **110:** 616–22.
7. Brevetti G, *et al.* European multicenter study on propionyl-L-carnitine in intermittent claudication. *J Am Coll Cardiol* 1999; **34:** 1618–24.
8. Wiseman LR, Brogden RN. Propionyl-L-carnitine. *Drugs Aging* 1998; **12:** 243–8.
9. Derosa G, *et al.* The effect of -carnitine on plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus. *Clin Ther* 2003; **25:** 1429–39.
10. Sirtori CR, *et al.* L-carnitine reduces plasma lipoprotein(a) levels in patients with hyper Lp(a). *Nutr Metab Cardiovasc Dis* 2000; **10:** 247–51.
11. The Investigators of the Study on Propionyl- -Carnitine in Chronic Heart Failure. Study on propionyl- -carnitine in chronic heart failure. *Eur Heart J* 1999; **20:** 70–6.

EXERCISE PERFORMANCE. Improved exercise performance in patients with angina or peripheral vascular disease has been described in patients given carnitine supplementation (see above). However, evidence of benefit from the use of carnitine in healthy subjects in an attempt to improve athletic performance is lacking.[1,2]

1. Tonda ME, Hart LL. N,N dimethylglycine and -carnitine as performance enhancers in athletes. *Ann Pharmacother* 1992; **26:** 935–7.
2. Brass EP. Supplemental carnitine and exercise. *Am J Clin Nutr* 2000; **72** (suppl): 618S–623S.

FATIGUE. Placebo-controlled studies in elderly subjects found that levocarnitine supplementation significantly reduced physical and mental fatigue,[1,2] while an open study in patients with chronic fatigue syndrome reported improvement in mental fatigue with acetylcarnitine, and general fatigue improvement with propionylcarnitine.[3] In a crossover study with amantadine, patients with chronic fatigue syndrome given levocarnitine for 8 weeks showed improvement in 12 out of 18 parameters measuring fatigue; patients who were most ill at the start of the study improved the most.[4] There is also some suggestion that levocarnitine supplementation may be of benefit in alleviating fatigue induced by antineoplastic chemotherapy,[5] or interferon.[6] For reports of carnitine use for fatigue in multiple sclerosis patients, see Neurological Disorders, below.

1. Pistone G, *et al.* Levocarnitine administration in elderly subjects with rapid muscle fatigue: effect on body composition, lipid profile and fatigue. *Drugs Aging* 2003; **20:** 761–7.
2. Malaguarnera M, *et al.* L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. *Am J Clin Nutr* 2007; **86:** 1738–44.
3. Vermeulen RCW, Scholte HR. Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. *Psychosom Med* 2004; **66:** 276–82.
4. Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of chronic fatigue syndrome. *Neuropsychobiology* 1997; **35:** 16–23.
5. Graziano F, *et al.* Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic cancer patients. *Br J Cancer* 2002; **86:** 1854–7.
6. Neri S, *et al.* L-carnitine decreases severity and type of fatigue induced by interferon-α in the treatment of patients with hepatitis C. *Neuropsychobiology* 2003; **47:** 94–7.

HAEMODIALYSIS. Carnitine homoeostasis is altered in renal failure[1] and a functional deficiency may develop in patients on dialysis.[2] This dialysis-related carnitine disorder manifests notably as anaemia, intradialytic hypotension, cardiomyopathy, and muscle weakness and fatigability. Treatment with intravenous levocarnitine 20 mg/kg after each dialysis session has been recommended. Clinical response should be evaluated at 3-monthly intervals, and treatment stopped if no improvement is seen within 9 to 12 months.[2] A systematic review suggested a beneficial effect of levocarnitine for the management of anaemia in haemodialysis patients.[3] Since carnitine supplementation has been associated with a reduction[4,5] in the incidence of haemodialysis-induced cramps (p.1671) it has been suggested that these cramps might be due in part to carnitine deficiency.

1. Matera M, *et al.* History of -carnitine: implications for renal disease. *J Ren Nutr* 2003; **13:** 2–14.
2. Eknoyan G, *et al.* Practice recommendations for the use of L-carnitine in dialysis-related carnitine disorder: National Kidney Foundation Carnitine Consensus Conference. *Am J Kidney Dis* 2003; **41:** 868–76.
3. Hurot J-M, *et al.* Effects of -carnitine supplementation in maintenance hemodialysis patients: a systematic review. *J Am Soc Nephrol* 2002; **13:** 708–14.
4. Ahmad S, *et al.* Multicenter trial of L-carnitine in maintenance hemodialysis patients II: clinical and biochemical effects. *Kidney Int* 1990; **38:** 912–18.
5. Sakurauchi Y, *et al.* Effects of L-carnitine supplementation on muscular symptoms in hemodialyzed patients. *Am J Kidney Dis* 1998; **32:** 258–64.

HIV INFECTION. Carnitine deficiency has been reported in HIV-infected patients. Causes may include malabsorption or increased excretion due to a wasting syndrome commonly found in these patients, or toxicity from antiretroviral drugs causing metabolic changes or altered lipid metabolism in the patient.[1] Small, mostly uncontrolled studies have suggested benefit from supplementation with levocarnitine or acetylcar-

nitine in relieving complications of HIV infection and adverse effects of antiretroviral drugs,[2] notably toxic neuropathy.[3,4]

1. Vilaseca MA, *et al.* Low serum carnitine in HIV-infected children on antiretroviral treatment. *Eur J Clin Nutr* 2003; **57:** 1317–22.
2. Ilias I, *et al.* -Carnitine and acetyl- -carnitine in the treatment of complications associated with HIV infection and antiretroviral therapy. *Mitochondrion* 2004; **4:** 163–8.
3. Herzmann C, *et al.* Long-term effect of acetyl-L-carnitine for antiretroviral toxic neuropathy. *HIV Clin Trials* 2005; **6:** 344–50.
4. Osio M, *et al.* Acetyl-l-carnitine in the treatment of painful antiretroviral toxic neuropathy in human immunodeficiency virus patients: an open label study. *J Peripher Nerv Syst* 2006; **11:** 72–6.

MALE INFERTILITY. Increases in sperm motility have been reported in some infertile men treated with carnitine,[1-3] although clinical benefit needs to be further evaluated.[4]

1. Lenzi A, *et al.* Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial. *Fertil Steril* 2003; **79:** 292–300.
2. Lenzi A, *et al.* A placebo-controlled double-blind randomized trial of the use of combined -carnitine and -acetyl-carnitine treatment in men with asthenozoospermia. *Fertil Steril* 2004; **81:** 1578–84.
3. Vicari E, Calogero AE. Effects of treatment with carnitines in infertile patients with prostato-vesiculo-epididymitis. *Hum Reprod* 2001; **16:** 2338–42.
4. Agarwal A. Carnitines and male infertility. *Reprod Biomed Online* 2004; **8:** 376–84.

NEUROLOGICAL DISORDERS. A meta-analysis of 21 studies concluded that acetylcarnitine improved mild cognitive impairment and prevented deterioration in patients with mild *Alzheimer's disease*.[1] However, a systematic review of 11 of these trials concluded that, although some evidence of benefit on clinical global impression exists, use of acetylcarnitine could not be routinely recommended in the treatment of Alzheimer's disease.[2]

Although no differences were found in serum carnitine concentrations in *multiple sclerosis* patients with or without disabling fatigue,[3] there is some suggestion of benefit with acetylcarnitine treatment for those patients with fatigue.[4] Carnitine has been reported to be of benefit in other cases of fatigue (see above).

In *Rett syndrome*, a severe neurodevelopmental disorder, supplementation with levocarnitine led to improvements in sleep efficiency, energy levels, and communication skills.[5] Parental and medical assessment of patient well-being improved in another study;[6] girls with classical Rett syndrome also improved in motor behaviour as assessed medically.

1. Montgomery SA, *et al.* Meta-analysis of double-blind randomized controlled clinical trials of acetyl- -carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol* 2003; **18:** 61–71.
2. Hudson S, Tabet N. Acetyl-l-carnitine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 08/11/05).
3. Fukazawa T, *et al.* Serum carnitine and disabling fatigue in multiple sclerosis. *Psychiatry Clin Neurosci* 1996; **50:** 323–5.
4. Tomassini V, *et al.* Comparison of the effects of acetyl -carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. *J Neurol Sci* 2004; **218:** 103–8.
5. Ellaway CJ, *et al.* Medium-term open label trial of L-carnitine in Rett syndrome. *Brain Dev* 2001; **23** (suppl): S85–S89.
6. Ellaway C, *et al.* Rett syndrome: randomized controlled trial of -carnitine. *J Child Neurol* 1999; **14:** 162–7.

Preparations

USP 31: Levocarnitine Injection; Levocarnitine Oral Solution; Levocarnitine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Albicar; Fertilix; Neurex; Neuroactil; ***Braz.:*** Levocarnin†; ***Canad.:*** Carnitor; ***Chile:*** Actigeron; Carnicor; ***Fr.:*** Levocarnil; ***Ger.:*** Biocarn; L-Carn; Nefrocarnit; ***Gr.:*** Aveptol; Bitobionil; Carnidose; Carnil; Corubin; Ensial; Frutenor; Growart; Inestom; Intelecta; Koptilan; Levalastine; Levamin; Levars; Levocarnil; Levosan; Lisefor; Listover; Lofostin; Maledrol; Merlit; Mevamyst; Minartine; Minoa; Oskana; Phacovit; Soludamin; Superamin; Tonovit; Trian; Trinalin; ***Hong Kong:*** Carnitene; Carnitor; ***India:*** Carnitor; L-Tine†; ***Ital.:*** Branigen; Branitil; Cardiobil†; Cardiogen†; Carnitene; Carnitolo; Carnitop†; Carnovis†; Carnum†; Carrier†; Dromos; Elleci; Eucar; Eucarnil; Farnitin; Karrer†; Kernit; Lefcar; Levocarvit; Medocarnitin; Megavis; Metina†; Miocardin; Miocor; Miotonal; Neo Cardiol; Nicetile; Normobren; Transfert†; Zibren; ***Mex.:*** Cardispan; Provicar; ***Neth.:*** Nefrocarnit; ***Philipp.:*** Carnicor; ***Pol.:*** Carnivit; ***Port.:*** Cartine; Disocor; Lacetilina; ***Rus.:*** Carniten (Карнитен); Elcar (Элькар); ***Spain:*** Carnicor; Secabiol; ***Turk.:*** Carnitene; ***UK:*** Carnitor; ***USA:*** Carnitor; VitaCarn; ***Venez.:*** Carnisin; Kativil; Lixi; Provicar.

Multi-ingredient: ***Arg.:*** Enlinea†; Garcinol Max; Herbaccion Diet; Metabolic; Reductase; Silueta Plus; Tonekin Plus†; ***Braz.:*** Pepsivit†; ***Chile:*** Grisetin Con Carnitina†; ***Indon.:*** Car-Q; Corsel; Naturica DFM; Procardio; Vitaslim; ***Ital.:*** Biocarnil†; Carfosid; Carpantin†; Co-Carnetina B12; Memorandum; ***Mex.:*** Lipovitasi-Or; Redumed; Slim-D; ***Philipp.:*** Fitrum; Godex; Nutrafit; ***Spain:*** Hepadif; Malandil; Pranzo.

Casein

Kazeina.
CAS — 9000-71-9.

Profile

Casein is a protein found in milk and has been used as a source of protein in preparations for enteral and parenteral nutrition; it may be used in the production of protein hydrolysate injection. Calcium caseinate has also been used.

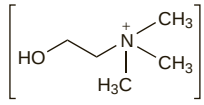
Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Secalbum; ***Canad.:*** Casec†; ***Israel:*** Casec; ***Mex.:*** Calsein; Caseincal†; K-Sein; ***USA:*** Casec.

Multi-ingredient: ***Mex.:*** Calciyodina; ***Switz.:*** Cicafissan; Fissan†; Vitafissan N.

Choline Bitartrate

Bitartarato de Colina; Choline Acid Tartrate; Choline Hydrogen Tartrate; Cholinii Tartras; Colina, bitartrato de. 2-Hydroxyethyltrimethylammonium hydrogen tartrate.
$C_9H_{19}NO_7$ = 253.2.
CAS — 87-67-2.



(choline)

Pharmacopoeias. In *US*.
USP 31 (Choline Bitartrate). A white, hygroscopic, crystalline powder; odourless or with a faint trimethylamine odour. Clear and colourless in solution. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 3.0 and 4.0.

Choline Chloride *(rINN)*

Choline, Chlorure de; Cholini Chloridum; Cholinii Chloridum; Choliny chlorek; Cloruro de colina; Koliinikloridi; Kolinklorid. 2-Hydroxyethyltrimethylammonium chloride.

Холина Хлорид
$C_5H_{14}ClNO$ = 139.6.
CAS — 62-49-7 (choline); 67-48-1 (choline chloride).

Pharmacopoeias. In *Fr.* and *US*.
USP 31 (Choline Chloride). Hygroscopic, colourless or white crystals or crystalline powder, usually having a slight odour of trimethylamine. Clear and colourless in solution. Soluble in water and in alcohol. pH of a 10% solution in water is between 4.0 and 7.0.

Profile

Choline is an acetylcholine precursor. It is involved in lipid metabolism and acts as a methyl donor in various other metabolic processes. Choline has traditionally been considered to be a vitamin B substance although its functions do not justify its classification as a vitamin. Choline can be synthesised in the body. However, its absence in total parenteral nutrition causes hepatic steatosis, and it is also thought to be a requirement in the diet of neonates. Sources of choline, which occurs mostly as lecithin, include egg-yolk and vegetable and animal fat.

Choline is used as a dietary supplement and has been used to treat liver disorders such as fatty liver and cirrhosis. It has been tried in the management of Alzheimer's disease (see Dementia, p.362) but without success. Choline is used as the dihydrogen citrate, and orotate salts as well as the bitartrate and the chloride.

Human requirements. In the USA, an adequate intake (see p.1925) of 550 mg daily in men and 425 mg daily in women has been determined for choline.[1] The tolerable upper intake level for adults is 3.5 g daily.[1]

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: neurotropan†.

Multi-ingredient: ***Arg.:*** Bil 13; GB 100; ***Austral.:*** Gingo A†; Liv-Detox†; ***Austria:*** Orocholin; ***Braz.:*** Alcafelol†; Aminotox†; Anekron; B-Vesil; Betaliver†; Biohepax; Enterofigon; Epativan; Epocler; Extrato Hepatico Composto; Extrato Hepatico Vitaminado†; Hecrosine B12†; Hepacitron†; Hepalin; Hepatobe†; Hepatotris†; Hepatox; Hormo Hepatico†; Jurubileno†; Lisotox; Metiocolin B12; Metiocolin Composto; Necro B-6; Olocynan†; Olohepat†; Panvitrop; Xantina B12†; Xantinon B12; Xantinon Complex; ***Chile:*** Hepabil; ***Cz.:*** Lipovitan†; ***Fr.:*** Citrocholine; Desintex-Choline; Hepacholine†; Hepagrume; ***Ger.:*** Lipovitan†; ***Hong Kong:*** Bilsan; Hepatofalk; ***India:*** Delphicol; Livocip; Mecolin; Sorbiline; Sorliv; ***Indon.:*** Curliv; Curliv Plus; Hepatin; Lipagent; Methicol; Methioson; Naturica DFM; ***S.Afr.:*** Hepavite; Prohep; ***Spain:*** Hepato Fardi†; ***Thai.:*** Liporon; ***UK:*** Lipotropic Factors.

Chondroitin Sulfate–Iron Complex

Chondroitin Sulphate–Iron Complex; Ferropolichondrum; Hierro y sulfato de condroitina, complejo de.
CAS — 54391-57-0.
ATC — B03AB07.
ATC Vet — QB03AB07.

Profile

Chondroitin sulfate-iron complex is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses of up to 900 mg daily, equivalent to up to 90 mg of iron daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Condrofer†; Isairon.

Chromium

Chrom; Chrome; Cromo.
Cr = 51.9961.

Chromium Trichloride

Chromic Chloride; Cromo, tricloruro de.
$CrCl_3,6H_2O$ = 266.4.
CAS — 10025-73-7 (anhydrous chromium trichloride); 10060-12-5 (chromium trichloride hexahydrate).

Pharmacopoeias. In *US*.
USP 31 (Chromic Chloride). Dark green, odourless, slightly deliquescent crystals. Soluble in water and in alcohol; slightly soluble in acetone; practically insoluble in ether. Store in airtight containers.

Chromium Tripicolinate

Chromium Picolinate; Cromo, tripicolinato de.
$C_{18}H_{12}N_3O_6Cr$ = 418.3.

Pharmacopoeias. In *US*.
USP 31 (Chromium Picolinate). Store in airtight containers.

Adverse Effects

Trivalent salts of chromium, such as chromium trichloride, are generally considered to produce few adverse effects. However, hexavalent forms of chromium are notably toxic (see under Chromium Trioxide, p.2281).

Effects on the kidneys. Two cases of renal failure were attributed to ingestion of excessive doses of chromium tripicolinate in women with no history of renal dysfunction.[1,2] Acute renal failure with features of acute tubular necrosis, and requiring haemodialysis, has been reported after ingestion of a chromium picolinate-containing supplement. The amount of chromium in the supplement could not be determined.[3] For mention of decreases in glomerular filtration rate in children receiving chromium-supplemented total parenteral nutrition, see Supplementation, below.

1. Wasser WG, *et al.* Chronic renal failure after ingestion of over-the-counter chromium picolinate. *Ann Intern Med* 1997; **126:** 410.
2. Cerulli J, *et al.* Chromium picolinate toxicity. *Ann Pharmacother* 1998; **32:** 428–31.
3. Wani S, *et al.* Acute tubular necrosis associated with chromium picolinate-containing dietary supplement. *Ann Pharmacother* 2006; **40:** 563–6.

Effects on the skin. There have been rare reports[1,2] of cutaneous reactions to oral chromium tripicolinate, including one of acute generalised exanthematous pustulosis.

1. Young PC, *et al.* Acute generalized exanthematous pustulosis induced by chromium picolinate. *J Am Acad Dermatol* 1999; **41:** 820–3.
2. Fowler JF. Systemic contact dermatitis caused by oral chromium picolinate. *Cutis* 2000; **65:** 116.

Uses and Administration

Chromium is an essential trace element that potentiates insulin action and thus influences carbohydrate, lipid, and protein metabolism. Dietary sources rich in chromium include brewers' yeast, meat, whole grains, and nuts. Chromium trichloride has been given as a chromium supplement in total parenteral nutrition. Chromium tripicolinate is used as a chromium supplement, and is being investigated for improving glycaemic control in patients with diabetes mellitus.

Diabetes mellitus. A review[1] of trivalent chromium in the management of diabetes mellitus (p.431) concluded that it may have an adjunctive role. A meta-analysis[2] found no effect of chromium on glucose or insulin concentrations in non-diabetic subjects; data for diabetic patients were inconclusive. A systematic review[3] found no significant effect with chromium supplementation on lipid or glucose metabolism in non-diabetic subjects, but it may have a modest beneficial effect on glycaemia and dyslipidaemia in those patients with diabetes. Meta-analysis was hampered by the overall poor quality and heterogeneity of available studies,[3] and further research was considered necessary.[1-3]

1. Ryan GJ, *et al.* Chromium as adjunctive treatment for type 2 diabetes. *Ann Pharmacother* 2003; **37:** 876–85.
2. Althuis MD, *et al.* Glucose and insulin responses to dietary chromium supplements: a meta-analysis. *Am J Clin Nutr* 2002; **76:** 148–55.
3. Balk EM, *et al.* Effect of chromium supplementation on glucose metabolism and lipids: a systematic review of randomized controlled trials. *Diabetes Care* 2007; **30:** 2154–63.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p.1925) has been set for chromium although a safe and adequate