cardiomyopathy, failure to thrive, metabolic acidosis, hypoglycaemia, and raised transaminase activities, and ammonia concentrations. Treatment is intended to restore free carnitine levels to 20 µmol/l or greater, and average daily doses range from 100 to 600 mg/kg (in one child with glutaricaciduria type II). Side-effects were infrequent (7%), mild, and mainly gastrointestinal.

Complete medical records are available for 39 patients with inborn errors of metabolism, and response to carnitine was graded as follows:

Clinical feature	*No affected*	*No improved*
Muscle strength/stamina	35	21 *(60%)*
Motor milestones	35	19 *(54%)*
Infection frequency	18	7 *(39%)*
Failure to thrive	15	7 *(47%)*
Mental status	27	13 *(48%)*

The clinical picture during carnitine therapy was judged to have improved because of carnitine in 25 cases (64%), and treatment was judged to have been life-saving in 5 cases.

1 patient was a 9-month-old with methylmalonyl-CoA mutase 0 enzyme deficiency who had severe neutropenia, chronic otitis and sinusitis, persistent metabolic acidosis, and profound failure to thrive. Carnitine therapy at 350 mg/kg daily coincided with a sharp increase in weight gain, resolution of neutropenia, decreased acidosis, and improvement in infection frequency and severity. The patient is now 7 years old and is meeting developmental milestones. Another patient presented with acidosis, failure to thrive, coma, hypoglycaemia, and respiratory arrest at 6 weeks of age. Diagnosed with glutaricaciduria type II the patient is now 3 years of age and enjoying normal growth and development while on L-carnitine 600 mg/kg daily as an oral solution. In both cases the metabolic error would normally be lethal.

The failure of others to see a response to L-carnitine in the treatment of organicacidurias is probably due to the need for higher doses to maintain functional levels of plasma and tissue free carnitine. Anecdotal though these studies and cases are, as clinicians treating metabolic diseases we have come to respect the detoxifying powers of L-carnitine. For patients with lethal metabolic disorders to exceed by far their predicted life span and to attain developmental milestones is a significant and reportable observation.

Medical Genetics/Metabolism,
Valley Children's Hospital,
Fresno, California 93703, USA
SUSAN C. WINTER
ELINOR M. ZORN

Metabolic Research and Analysis,
Fresno, California
W. HUGH VANCE

1. Roe CR, Millington DS, Maltby DA, et al. L-carnitine therapy in isovaleric acidemia. *J Clin Invest* 1984; 74: 2290–95.
2. Winter SC, Szabo-Aczel S, Curry CJR, et al. Plasma carnitine deficiency: clinical observations in 51 pediatric patients. *Am J Dis Child* 1987; 141: 660–65.
3. Roe CR, Bohan TP. L-carnitine therapy in propionicacidaemia. *Lancet* 1982; i: 1411.
4. Seecombe DW, Snyder F, Parsons HG. L-carnitine for methylmalonicaciduria. *Lancet* 1982; ii: 1401.
5. Roe CR, Millington DS, Maltby DA. L-carnitine enhances the excretion of propionyl coenzyme A as propionyl carnitine in propionic acidemia. *J Clin Invest* 1984; 73: 1785–88.
6. Wolff JA, Thuy LP, Haas R, et al. Carnitine reduces fasting ketogenesis in patients with disorders of propionate metabolism. *Lancet* 1986; i: 289.

SIR,—Your March 17 editorial draws attention to the biochemical and clinical importance of L-carnitine. However, the detoxification function and clinical value of carnitine therapy require further comment.

The normal and apparently minor detoxification function may be very important in the regulation of acetyl-CoA/CoA ratios; it is critically important in abnormal conditions, including diabetic ketoacidosis, defects in mitochondrial ß-oxidation, and other disorders of organic acid metabolism in which acyl-CoA accumulates, and it provides the rationale for the therapeutic use of L-carnitine in these conditions.[1,2] In such patients overt carnitine deficiency may not occur, and total carnitine concentrations may be above normal. However, the often greatly increased ratio of acylcarnitine to free carnitine leads to depletion of free carnitine especially in mitochondria. These patients have a secondary carnitine insufficiency—ie, insufficient L-carnitine for their increased metabolic needs, especially during episodes of acute metabolic decompensation. Some have found this concept difficult to appreciate but it is now gaining wider acceptance.[3-5]

It is also important to appreciate that detoxification occurs at the mitochondrial level: while we agree that quantitatively in some conditions acylcarnitine excretion is low during L-carnitine supplementation in comparison with overall flux this may be misleading. Acylcarnitine concentrations increase substantially in patients on supplemental L-carnitine and this is highly significant at the mitochondrial level where detoxification is occurring. The restoration of mitochondrial homoeostasis via oral or intravenous L-carnitine results in a rapid and sustained clinical response.[6,7] Contradicting your editorial view, treatment with L-carnitine also provides long-term benefit on the recurrent metabolic decompensation and on general wellbeing.[7-10] We agree that chronic administration of L-carnitine to patients with disorders of β-oxidation and other non-ketotic hypoglycaemic conditions could be detrimental by priming the defective pathway. However, L-carnitine has also proved valuable in these conditions in the management of acute decompensation by removal of accumulating acyl moieties as acylcarnitines (eg, octanoylcarnitine).[6,8] Indeed, several patients originally described as having "systemic carnitine deficiency" and who responded to L-carnitine have been subsequently shown to have disorders of fatty acid oxidation. Overt carnitine deficiency, whether caused by inherited defects in L-carnitine transport or of dietary origin, does cause severe clinical disease, including hypoglycaemia and cardiomyopathy, that responds to carnitine.

Anyone working with children with severe metabolic disease will appreciate that controlled trials are very difficult in this area. More research is certainly required on the clinical value and on the biosynthesis, physiology, and function of L-carnitine, a compound that started life as vitamin B_t of questionable value. Your editorial is welcome in stimulating such interest.

R. A. CHALMERS
M. D. BAIN
T. E. STACEY
C. DE SOUSA

Department of Child Health,
St George's Hospital Medical School,
London SW17 0RE, UK

1. Roe CR, Hoppel CL, Stacey TE, Chalmers RA, Tracey BM, Millington DS. Metabolic response to carnitine in methylmalonic aciduria. *Arch Dis Child* 1983; 58: 916–20.
2. Chalmers RA, Roe CR, Stacey TE, Hoppel CL. Urinary excretion of l-carnitine and acylcarnitines by patients with disorders of organic acid metabolism: evidence for secondary insufficiency of l-carnitine. *Pediatr Res* 1984; 18: 1325–28.
3. Bieber LL. Carnitine. *Annu Rev Biochem* 1988; 57: 261–83.
4. Siliprandi N, Sartorelli L, Ciman M, Di Lisa F. Carnitine: metabolism and clinical chemistry. *Clin Chim Acta* 1989; 183: 3–12.
5. Winter SC, Szabo-Aczel S, Curry CJR, Hutchinson HT, Hogue R, Shug A. Plasma carnitine deficiency: clinical observations in 51 pediatric patients. *Am J Dis Child* 1987; 141: 660–65.
6. Chalmers RA, Stacey TE, Tracey BM, et al. L-carnitine insufficiency in disorders of organic acid metabolism: response to L-carnitine by patients with methylmalonic aciduria and 3-hydroxy-3-methylglutaric aciduria. *J Inher Metab Dis* 1984; 7 (suppl 2): 109–10.
7. Roe CR, Millington DS, Maltby DA, Kahler SG, Bohan TP. L-carnitine therapy in isovaleric acidemia. *J Clin Invest* 1984; 74: 2290–95.
8. Roe CR, Millington DS, Kahler SG, Kudo N, Norwood DL. Carnitine homeostasis in the organic acidemias. In: Tanaka K, Coates PM, eds. Fatty acid oxidation: clinical, biochemical and molecular aspects. New York: Alan R. Liss, 1990: 383–402.
9. de Sousa C, Chalmers RA, Stacey TE, Tracey BM, Weaver CM, Bradley D. The response to L-carnitine and glycine therapy in isovaleric acidaemia. *Eur J Paediatr* 1986; 144: 451–56.
10. Bain MD, Bartlett S, Jones M, Chalmers RA. L-carnitine provides long term benefit in methylmalonic aciduria and isovalenic acidaemia. 60th British Paediatric Association Annual Meeting. London: BPA, 1988 (abstr G41).

Recombinant immunoblot assay for hepatitis C virus antibody as predictor of infectivity

SIR,—As stated by Dr van der Poel and colleagues (Mar 10, p 558), screening of low-risk populations such as blood donors for antibodies to hepatitis C virus (HCV) by the available recombinant ELISA may yield false-positive results. Nor does this assay differentiate past infection from virus carriage and potential infectivity. Blood transfusion services thus find it difficult to decide on policies for discarding suspect blood units and for donor

IMPLICATED AND NON-IMPLICATED DONORS POSITIVE IN ANTI-HCV (ELISA)

Donor	Donor: Blood product	Donor: ELISA*	Donor: RIBA 5-1-1	Donor: RIBA c-100	Recipient: Sero-conversion in ELISA	Recipient: RIBA 5-1-1	Recipient: RIBA c-100
Implicated							
1	WB	7·1	+	+	No	−	−
2	FFP	7·2	+	+	Yes	+	+
3	PC	6·7	+	+	Yes	+	+
4	WB	6·5	+	+	Yes	−	+
5	RBC	7·2	+	+	Yes	+	+
6	WB	1·1	−	−	No	−	−
7	RBC	7·0	+	+	Yes	+	+
Non-implicated							
8	RBC	1·5	−	±	No	ND	
9	FFP	1·8	−	±	No	ND	
10	WB	6·5	−	±	No	ND	
11	RBC	7·2	−	+	No	ND	
12	WB	1·5	−	−	No	ND	
13	RBC	3·7	−	+	No	ND	

*Absorbance/cut-off ratio
WB = whole blood; FFP = fresh frozen plasma; PC = platelet concentrate, RBC = red blood cell concentrate, ND = not done

counselling.[1-3] We have now had the opportunity to use the Chiron recombinant immunoblot assay (RIBA) for detecting HCV antibody. This test is distributed by Ortho Diagnostic Systems (for research use only). This RIBA uses recombinant antigen c-100 expressed in yeast (as does the ELISA) plus a sub-sequence of c-100 (5-1-1) expressed in *Escherichia coli*. Both antigens have been coated in distinct bands on nitrocellulose strips. The result (reactive, borderline, or negative) is read by comparing the colour of an antigen band with positive controls.

We have applied the ELISA and the RIBA to a frozen panel of donor and patient samples from a prospective study in 1987–89 in open heart surgery (unpublished). 685 patients, who received on average 12·3 units of blood products, were followed up for six months postoperatively. 11 patients (1·6%) acquired post-transfusion hepatitis, all being non-A, non-B. 7 had received a product from an anti-HCV (ELISA) positive donor. On the other hand, when 1029 of the donor samples not associated with a hepatitis case were tested 6 were found to be anti-HCV (ELISA) positive. The ELISA and RIBA results on these "implicated" and 6 "non-implicated" donors are shown in the table.

All 6 donor samples that were reactive for antigen bands 5-1-1 and c-100 were associated with hepatitis in the recipient, this being accompanied by seroconversion in 5. No donor specimen that was not linked with hepatitis or seroconversion in the recipient showed reactivity for more than one band. The RIBA may offer help in differentiating infective from non-infective blood donors. Reactivity for both antigens, and 5-1-1 especially, is associated with infectivity.

RIBA kits were kindly provided by Ortho.

Finnish Red Cross
Blood Transfusion Service,
SF-00310 Helsinki, Finland

FREJA EBELING
RUTH NAUKKARINEN
JUHANI LEIKOLA

1. Contreras M, Barbara JAJ. Screening for hepatitis C virus antibody. *Lancet* 1989; ii: 505.
2. Cash JD, McClelland DBL, Urbaniak SJ, Brookes E. Screening for hepatitis C virus antibody. *Lancet* 1989; ii: 505.
3 Flegg PJ. Ethics of screening for hepatitis C virus. *Lancet* 1989; ii: 1221.

Dystrophin function: calcium-related rather than mechanical

SIR,—Dystrophin[1,2] is thought to have a mechanical function, helping to resist stresses associated with muscle contraction.[1,3] A lack of dystrophin in Duchenne muscular dystrophy (DMD) is postulated to predispose to the rupture of the cell membrane and early necrosis of the muscle cell. In our view, however, a mechanical function of dystrophin is not consistent with three important observations:

(1) Dystrophin constitutes only 0·002% of the total protein in skeletal muscle, at a ratio of one molecule for every fifteen muscle nuclei.[4] It is difficult to envisage a satisfactory mechanical role for a molecule present in such low concentration.

(2) Dystrophin is also expressed in nervous tissue. It has been localised immunohistochemically to synaptic regions such as neuromuscular junctions, cornea, and the outer plexiform layer of the retina, taste buds, and neurons in the brain.[5] The presence of dystrophin in the brain may account for the high frequency (about 30%) of mental retardation in DMD.[6,7] A mechanical function of dystrophin in muscle cannot explain this association.

(3) In DMD hypercontraction of muscle precedes breaks in the cell membrane.[8] There is excessive hypercontraction of sarcomeres, especially in the early stages.[9] A mechanical role for dystrophin cannot explain the hypercontraction (or tetanic state) of the sarcomeres.

We suggest that the function of dystrophin is calcium-related rather than mechanical. Dystrophin may be causally related to the hypercontractions seen in the early stages of the disease. Calcium-positive fibres are increased in preclinical cases.[10] There could be a relation with the exposure of more myosin binding sites on actin or failure of the release mechanism or some mild defect in the calcium-pump mechanism. (A major defect of the calcium pump would cause immediate necrosis due to massive activation of calcium-sensitive proteases in the cytosol.[9]) It is unlikely to be related to the function of the sarcoplasmic reticulum or the triadic junction because of the cellular distribution of dystrophin.[1] A strong dystrophin reaction has been observed at the neuromuscular junction rather than on the surface membrane of extrafusal muscle fibres.[5] A calcium-related role for dystrophin could explain its function in nervous tissue.

JOHN S. H. TAY
P. S. LOW
W. L. LEE
P. S. LAI
G. C. GAN

Division of Human Genetics,
Department of Paediatrics,
National University of Singapore,
Singapore 0511

1. Love DR, Davies KE. Duchenne muscular dystrophy: the gene and the protein. *Mol Biol Med* 1989; 6: 7–17
2. Campbell KP, Kahl SD. Association of dystrophin and an integral membrane glycoprotein. *Nature* 1989; 338: 259–62
3. Beam KG. Duchenne muscular dystrophy: localizing the gene product. *Nature* 1988; 333: 798–99.
4. Koenig M, Hoffman EP, Bertelson CJ, Monaco AP, Feener C, Kunkel LM. Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD in normal and affected individuals. *Cell* 1987; 50: 509–17.
5. Miike T, Miyatake M, Zhao J, Yoshioka K, Uchino M. Immunohistochemical dystrophin reaction in synaptic regions. *Brain Devel* 1989; 11: 344–46.
6. Dubowitz V. Mental retardation in Duchenne muscular dystrophy. In: Rowland LP, ed. Pathogenesis of human muscular dystrophies. Amsterdam: Excerpta Medica, 1977: 688–94.
7 Karagan N. Intellectual functioning in Duchenne muscular dystrophy· a review. *Psychol Bull* 1979; 86: 250–59.
8. Mastaglia FL, Kakulas BA. The natural history of human muscle diseases studied by means of serial biopsy. *Proc Aust Assoc Neurol* 1968, 5: 537–43.
9. Kakulas BA. Observations on the pathogenesis of Duchenne muscular dystrophy in the light of recent progress in molecular genetics. *Aust Paediatr J* 1988 (suppl): 4–8.
10. Emery AEH. Duchenne muscular dystrophy. Oxford. Oxford University Press, 1988; 55–57.

Use of 'Nebuhaler' and face-mask in young asthmatic children

SIR,—Inhaled therapy for the treatment of asthma is difficult in children aged under 3 years since their inhalation technique might be faulty and they may dislike closing their mouths over inhaler mouthpieces. To overcome these difficulties the firing of a metered-dose aerosol into a coffee cup, or equipping a large-volume spacer with an anaesthetic mask sealed around the nose and mouth have been proposed.[1,2] I report a cheap, portable, and convenient method of administering inhaled drugs to very young patients.

The system[3] consists of a 750 ml pear-shaped spacer ('Nebuhaler', Astra Pharmaceuticals) fitted with a nebuliser face-mask ('Intersurgical Life-line 1148') with the angled connecting piece removed and the side-holes covered with adhesive tape. The mask can be used by the parent. In small children and infants the mask is used upside down. Because of the shape of the