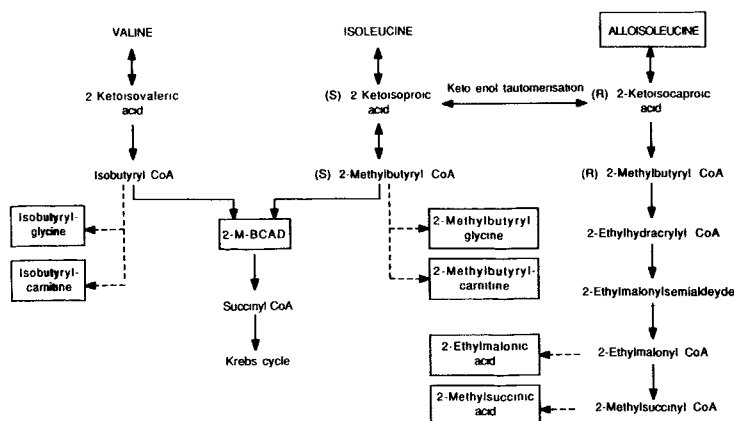




Predicted formation in vivo of ethylmalonic acid from isoleucine.

Intermediates that accumulate in patients shown in boxes (alloisoleucine after isoleucine oral loading test). 2-M-BHAD = 2-methyl branched chain acyl-CoA dehydrogenase.

orthostatic acrocyanosis with striking distal swelling, chronic diarrhoea, and diffuse petechiae. Acrocyanosis and distal swelling rapidly occurred upon standing and disappeared in the supine position. Peripheral neuropathy and dysautonomia were excluded by normal conduction velocity studies, response to pain, lacrimation, and histamine skin test. Extensive investigations excluded the possibility that chronic diarrhoea was due to food intolerance (gluten, cow's milk proteins, lactose), bacterial or parasitic infections, or inflammatory bowel disease. Platelet counts and coagulation studies were repeatedly normal. One patient died unexpectedly at home at the age of 2 years, and the other two are severely mentally retarded. Riboflavine and carnitine were attempted in two patients with no apparent effect.

Magnetic resonance imaging revealed hyperintensity of the cerebellar white matter and bilateral hyperintensity of caudate and lenticular nuclei in all three cases. These findings seem specific and are not seen with other metabolic diseases affecting the central nervous system.⁴

All patients had persistent lactic acidosis (3.3–6.0 mmol/l) with recurrent metabolic decompensation (with normal blood glucose and ammonia). Urinary excretion of ethylmalonic acid was very high at 62–933 mmol/mol creatinine (range in age-matched controls 0.4–17); isobutyrylglycine was also raised (79–159 mmol/mol creatinine; urinary control 0.01–8.6); and there was a 2–5-fold increased excretion of methylsuccinic acid, n-butyrylglycine, isovalerylglycine, and 2-methylbutyrylglycine, as determined by stable isotope dilution analysis.² Hexanoyl, suberyl, and 3-phenylpropionyl glycine levels were not increased. Glutaric acid and C₆–C₁₀ dicarboxylic acids were not increased, even during metabolic decompensation. Isobutyrylcarnitine⁵ was the most abundant carnitine ester in urine. Butyryl, isovaleryl, and 2-methylbutyryl carnitine were present in the plasma of all three patients.

In one patient, activities of short, medium, and long chain acyl-CoA dehydrogenase were normal in cultured skin fibroblasts, as determined by fluorimetry. By the same method, activity of cells grown in riboflavine-depleted medium was comparable to control cell lines. In the same patient, oxidation of 1-[¹⁴C]-palmitate, 1-[¹⁴C]-octanoate, and 1-[¹⁴C]-butyrate were normal. Oxidation rate of 9,10(n)-[³H]-myristate in whole cells was also normal (courtesy of Dr W. J. Rhead, University of Iowa).

The normal straight-chain fatty acid oxidation in vitro and the pronounced excretion of ethylmalonic acid and isobutyryl and 2-methylbutyryl conjugates raise the possibility of a defect of 2-methyl branched-chain acyl-CoA dehydrogenase.⁶ A block at this level could induce activation of the isoleucine R-pathway, resulting in the formation of alloisoleucine and R-2-methylbutyryl-CoA⁷ (figure). On the assumption that this substrate can be oxidised in vivo by an alternative acyl-CoA dehydrogenase, such as short-chain acyl-CoA dehydrogenase,⁶ this pathway would provide a link between isobutyryl and 2-methylbutyryl conjugates and ethylmalonic acid excretion. This view is supported by the increase

in excretion of 2-ethyl-hydracrylic acid, the immediate precursor of ethylmalonate semialdehyde in the R-pathway of isoleucine, and by the finding, in one patient, of a 22% increase in ethylmalonate excretion 3 h after an oral dose of isoleucine (60 mg/kg). Alloisoleucine was also detectable in plasma after the load.

This new clinical and biochemical phenotype, so far limited to Italian patients, could lead to the recognition of a new inborn error of metabolism. 2-methyl branched-chain acyl-CoA dehydrogenase may be the enzyme affected.

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Allergenic peanut oil in milk formulas

SIR,—Professor Moneret-Vautrin and colleagues' findings (Nov 2, p 1149) may explain why I have noted peanut sensitivity more frequently in recent years in bottle-fed infants and young children, in the total absence of any history of ingestion of any food known to contain peanut. The previous investigations they cite¹ seem such excellent evidence that peanut oil is not allergenic that the possible role of oil in infant formulae may have been overlooked. Two bottle-fed infants with eczema both cleared on changing to a soya formula, but both had very severe skin reactions to peanut. Both mothers, who had met when attending the same antenatal clinic, had cravings for peanut during pregnancy, but were not sensitised themselves. Perhaps their children were sensitised in utero, and traces of peanut allergen in the milk formula, rather than cow's milk, was the cause of the eczema.

The authors are to be commended for their positive approach and for persuading parents to permit challenge testing to confirm the diagnosis. Such an approach would be highly improbable in the UK, where most dermatologists do not even do skin prick tests. Suppressing topical steroids would be used without investigation, since departments of broad-based allergy and clinical immunology are few and far between in this country. The possibility of fatal anaphylaxis from unsuspected peanut allergy suggests that peanut oil should be banned in infant formulae.

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