

URINARY CONCENTRATION OF METHYLMALONIC AND *p*-HYDROXYPHENYLACETIC ACIDS

Age (mo)	Methylmalonic acid (mg/g creatinine)	<i>p</i> -hydroxyphenylacetic acid (mg/g creatinine)
1	45	330
2	29	193
15	2	23
Normal	< 5	< 40

which was treated medically with no recurrence of apnoea. At 2 months of age the urine organic acids were again abnormal. The child was lost to follow-up and subsequently received sporadic medical care. At about 1 year of age he was found to have Hirschsprung's disease. Urine organic acid measurements before corrective surgery were said to be abnormal. These tests were normal after recovery from surgery.

Methylmalonic aciduria has been reported in many conditions, most often in an inborn error of organic acid metabolism involving deficient activity of methylmalonyl coenzyme A mutase.¹ Our patient had none of these disorders. He had no detectable homocystinuria and did not have a vitamin B₁₂ deficiency. The concentrations of methylmalonic acid excreted by our patient, although abnormal, were not as high as those usually seen in individuals with inborn errors of methylmalonic acid metabolism.² Additionally he never had metabolic acidosis. Enzymatic assay was not done; however, the fact that he had transitory methylmalonic aciduria argues against an inborn error of metabolism.

Our patient most likely generated methylmalonic and *p*-hydroxyphenylacetic acids by bacterial fermentation of intestinal substrates, which was enhanced by obstipation from the Hirschsprung's disease. It is well recognised that organic acids may be produced in the intestine by the action of gut flora. This has been most clearly seen in Oasthouse disease, in which there is methionine malabsorption.³ Subsequent bacterial fermentation of methionine in the gut leads to production of alpha-hydroxybutyric acid which is absorbed into the systemic circulation and excreted in the urine. Similarly, *p*-hydroxyphenylacetic acid can be produced by gut bacterial decarboxylation of tyrosine to tyramine, followed by amine oxidation to the cognate acid. Elevated excretion of urinary *p*-hydroxyphenylacetic acid is frequently observed in absorptive disorders and diseases of the small intestine associated with bacterial overgrowth.⁴ There are also reports of production of D-lactic acid in the gut caused by bacterial action, most frequently seen in blind intestinal loop syndrome.⁵

Our hypothesis is supported by Bain and colleagues' observation and by a report which implicated gastrointestinal bacteria as contributors to the body methylmalonate pool.⁶ The relation of our patient's disorder to that described recently as benign methylmalonic aciduria is not clear, but the possibility that even moderate levels of methylmalonic aciduria may be due to a pathological condition such as Hirschsprung's disease needs to be kept in mind when evaluating patients.

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SIR,—Protein catabolism has been considered to be the major source of propionate in propionic and methylmalonic acidemia but Dr Bain and colleagues suggest that bacterial fermentation in the gut is important. We suggest that large quantities of oral carbohydrate may precipitate some episodes of acute deterioration because of propionate production by fermentation within the gut.

We have studied a 3½-year-old boy with propionic acidemia that had presented in the neonatal period. He was admitted dehydrated with persistent vomiting and improved with intravenous rehydration, at which time his plasma propionate was 30 µmol/l. Oral feeds of a 15% solution of soluble glucose polymer ('Caloreen') were restarted but he deteriorated and became encephalopathic. Oral feeds were discontinued and he was given intravenous 10% glucose with L-carnitine (75 µmol/kg/h). 12 h later we studied his propionate and protein turnover using primed continuous infusions of [D₅] propionate and 1-[¹³C] leucine. The maximum contribution of protein catabolism to propionate production was calculated from the leucine oxidation rate and the relative content of leucine and the amino acid precursors of propionate in protein.

The plasma propionate concentration was very high (3 mmol/l) and in-vivo propionate production was more than 1000 µmol/kg/h. However, the maximum contribution that could be attributed to protein catabolism was 17 µmol/kg/h. The formation of massive amounts of propionate in the gut would account for this discrepancy.

Conventional treatment for children with inherited disorders of propionate metabolism who become unwell is an emergency regimen in which the usual low-protein diet is replaced by one that is protein-free with a high carbohydrate content. This will suppress protein catabolism but some of the concentrated carbohydrate solution may enter the large bowel. This may be fermented by anaerobic gut bacteria to form propionate,¹ which is readily absorbed.² Since three 6-carbon sugars will produce about 1 mol of propionate,³ every gram of carbohydrate could generate 2 mmol of propionate.

Protein catabolism may be inhibited by such a regimen but smaller quantities of carbohydrate together with gut sterilisation may be advisable to reduce propionate production by the gut.

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IS ALZHEIMER'S DISEASE DISTINCT FROM NORMAL AGEING?

SIR,—Dr Brayne and Dr Calloway (June 4, p 1265) argue that there is little evidence that senile dementia of the Alzheimer's type is distinct from the normal ageing process. They conclude this after observing a unimodal frequency distribution of scores of cognitive function on the Blessed dementia scale and the information-memory-concentration scale in 365 women aged 70-79. We have problems with this reasoning.

The scales used are crude and probably subject to measurement error, and this might blur a true bimodality. (This may be one reason why Platt, in the celebrated Pickering-Platt controversy,¹ could find no convincing evidence of bimodality for blood pressure.) Another reason for the failure to observe bimodality may be that Brayne and Calloway measured cognitive impairment and not the specific neuropathological changes of Alzheimer's disease. Therefore, extreme scores on their tests may result from senile

dementia of the Alzheimer's type, but also from vascular dementia, secondary dementia, or depression. It is unlikely that such a mixed bag of diseases with a different aetiology and different determinants will produce a clear bimodal distribution of cognitive function.

Even if we accept the unimodal distribution, the fact that a characteristic is distributed unimodally does not necessarily imply that the underlying pathophysiological changes are normal. Atherosclerotic lesions are distributed unimodally and are present in a very large proportion of the adult population. Although the frequency and extent of these lesions rise with age, few people would consider atherogenesis part of the normal ageing process. Would Brayne and Calloway really consider vascular dementia, with its clear link to atherosclerosis, not distinct from normal ageing, because its underlying pathogenetic changes are distributed unimodally in the population?

Brayne and Calloway may be right in suggesting that the underlying disease process in dementia of the Alzheimer's type, characterised neuropathologically by senile plaques and neurofibrillary tangles, may have various determinants. Research into the causes of Alzheimer's disease would benefit particularly from the definition and study of proper contrasts, because this is likely to reveal the largest difference in determinants of the disease. We agree that these determinants may be environmental and genetic—but is this perhaps “a glimpse into the obvious”?

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TOXIC-SHOCK SYNDROME AFTER A MINOR SURGICAL PROCEDURE

SIR,—Mr Frame and Mr Hackett (June 11, p 1330) recommended the use of fresh whole blood or fresh frozen plasma in the management of cases of toxic-shock syndrome (TSS). I have administered pooled gamma-globulin in this syndrome for the same reasons.

Although patients with TSS have lower antibody levels of TSS toxin-1 (TSST-1) than controls, both acutely and on convalescence,¹ it has not been shown that immunoglobulin therapy influences clinical outcome. Asymptomatic colonisation by a potentially toxigenic staphylococcus is associated with the presence of serum antibodies to the toxin,² and indeed patients with these two factors seem resistant to the syndrome. However, whether the antibody itself is the protective mechanism is unclear. The toxin may in part act similarly to concanavalin A as a non-specific T cell mitogen.³ It seems unlikely that the administration of antibody will reverse the immunomodulatory consequences of T8 suppressor/cytotoxic cell activation in established toxæmia.

In surgical practice there will be many cases of TSS not attributable to staphylococci producing TSST-1. Enterotoxin B production will be the most consistent marker of staphylococci from these cases.⁴ In addition, infection by erythrogenic streptococci can produce an identical illness.⁵ There is considerable homology between staphylococcal enterotoxin B and streptococcal pyrogenic exotoxin A; these toxins are distinct from TSST-1.⁶ This may have implications for immunoglobulin therapy.

Most patients presenting with the clinical features of TSS are treated with broad spectrum antimicrobials because the initial features of the illness are similar to endotoxaemia. Both TSST-1 and streptococcal pyrogenic exotoxins cause a considerable increase in host susceptibility to lipopolysaccharide (up to 50 000 times).^{7,8} With the degree of mucosal inflammation that occurs in the condition I wonder whether gram-negative chemotherapy is an advantage or a disadvantage to the patient.

Although Frame and Hackett consider it inappropriate to administer antibiotics in children with burns, as a general rule in

surgical cases in which TSS is suspected I recommend a combination of anti-staphylococcal and anti-streptococcal chemotherapy, pending the results of microbiological investigation. Cases attributable to infection with enterotoxigenic methicillin-resistant *Staphylococcus aureus* have been described.⁹

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MAGNETIC RESONANCE IMAGING AND MAGNETIC EYE IMPLANTS

SIR,—Magnetic resonance imaging (MRI) may be hazardous in patients with magnetic orbital implants. The implant may move or even extrude when subjected to a strong magnetic field. We have seen strong movements of such implants when placed in water and exposed to a field of 1.5T. The magnet will also interfere with the signal and make MRI scans difficult to interpret. Magnetic implants are often inserted after enucleation for choroidal melanoma, so precluding the use of MRI in the investigation of metastases. A patient presented to our unit with neurological symptoms suggestive of metastasis ten years after enucleation for choroidal melanoma and insertion of a magnetic implant. Computerised tomography scanning was negative but MRI could not be done. Acrylic implants should be used instead and we no longer use magnetic implants.

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FACTOR-VIII-RELATED ANTIGEN AND VASCULITIS

SIR,—We read with interest your May 28 editorial (p 1203) on factor-VIII-related antigen (FVIII RAg) and vasculitis. FVIII RAg is a reliable index of vascular damage in the diagnosis, prognosis, and therapy monitoring of systemic vasculitis. However, equivocal FVIII RAg plasma levels have been reported in some of these diseases. For example, patients with scleroderma had high levels of FVIII RAg in one study¹ but normal levels in another.² This discrepancy, which has been explained by the different phase activity of the illness, is not unusual. We have investigated FVIII RAg plasma levels in a group of patients with non-insulin-dependent diabetes mellitus (NIDD) without overt signs of vasculopathy to detect subclinical vascular damage.³ We found both high and normal FVIII RAg plasma levels. Thus, for this group, the significance of FVIII RAg as an index of endothelial damage was low.

We then found⁴ that in those diabetic patients with normal FVIII RAg plasma levels and no sign of vasculopathy, endothelial damage could be detected simply by inducing venostasis, which is known to damage the endothelium. We investigated plasma FVIII RAg levels after venostasis (done at forearm pressure of 10 mm-Hg, above the diastolic pressure for 20 min) in 12 patients. This group