phenylalanine remains above 15 mg/100 ml whether or not metabolites are present in the urine. Some clinicians would put this level at 20 mg/100 ml, others at 8 or 10 mg/100 ml. A recent report (Angeli *et al.*, 1974) describes 8 retarded microcephalic infants born to a mother with a serum phenylalanine of 18 mg/100 ml; if this level is harmful to the fetus, where dare we draw the line below which we can say there will be no harm to the neonate? After about 4 months of treatment we advise observing the effects of increasing the phenylalanine in the diet in the manner described by Blaskovics *et al.* At the age of one year we look at the total daily intake of phenylalanine. These two observations help to indicate the need for further strict dieting, or relaxation with a view to stopping treatment.

F. P. HUDSON and C. CLOTHIER
Alder Hey Children's Hospital,
Eaton Road,
Liverpool L12 2AP.

Dr. Blaskovics comments as follows:

Dr. Hudson and Miss Clothier suggest that our proposed classification scheme may be modified when more precise enzymological methods are available. We would hope so, but because of adverse attitudes toward what is now considered 'unethical research', the final enzymological answers for clinical application may not be available for years to come. We may have to rely even more on various kinds of oral challenges to classify patients and our critics may 'allow' us to use natural foods as the least offensive agents to accomplish this.

Dr. Hudson and co-worker indicated that they preferred the classification scheme suggested by Drs. Scriver and Rosenberg because it was simpler, more practical, and it embraced our 5 types. We believe fewer types are less desirable and firmly believe that every effort must be made to refine and subdivide our scheme further. To reduce the number of types because it is simpler would be comparable to returning to fewer types of glycogen storage diseases or maple syrup urine diseases.

They stress the importance of estimating the daily phenylalanine tolerance of patients while receiving dietary treatment. This is acceptable but with qualifications. Before starting standardized testing in our clinic (which we presume is not dissimilar from other clinics), we were complacently satisfied with a patient's dietary prescription when the serum phenylalanine was in an acceptable range. The tolerance could be estimated; however, we found that if less than the maximally tolerated phenylalanine intake was given, in addition to adequate calories and protein, the phenylalanine tolerance varied. For example, some children with types III and IV phenylalaninaemia were considered to have classical PKU because their initial diagnostic phenylalanine levels were quite high (between 20 and 37 mg/100 ml) and because their serum phenylalanine levels *did not* become subnormal while receiving 'usual intakes' for PKU infants and children. Furthermore, the serum phenylalanine levels in types III, IV, and

V phenylalaninaemia will often fluctuate on a constant high phenylalanine intake. Depending upon how one defines PKU (and in most instances it is with an arbitrary fixed serum phenylalanine level and the presence of certain urinary metabolites which can be related to the serum phenylalanine levels), the diagnosis can and often will vary from day to day. Making a diagnosis in relation to the serum phenylalanine levels while the patient receives a 'normal' diet is also fraught with dangers. A normal diet varies considerably from country to country, with age, ethnicity, fads, religion, etc. We believe that the concept of a 'normal diet' has been a hinderance to progress and diagnosis.

Dr. Hudson provides the best evidence for not estimating tolerance but for using a standardized diagnostic challenge. To quote him, 'We estimated the daily phenylalanine intake required by 24 of our patients on a low phenylalanine diet at some point between the ages of 11 and 13 months, and at a time when the serum phenylalanine was at an acceptable level. In 18 cases the intake was between 275 and 450 mg/day (mean 365, 2 SD 120). They are all, to the best of our knowledge, cases of classical phenylketonuria. 5 patients were able to tolerate 500 to 600 mg phenylalanine/day. 4 of these returned to normal diet between the ages of 1 year 3 months and 3 years. On normal diet one patient maintains a serum phenylalanine level of 2-3 mg/100 ml, in the other 3 the range is 7-13 mg/100 ml'.

We do not believe that the difference between 450 mg/day and 500 mg/day is significant, and we find it extremely difficult to classify patients on the basis of a 50 mg/day difference in phenylalanine intake. The serum phenylalanine *off diet* in one patient (2 to 3 mg/100 ml) did not change from the *on diet* level (assumed by us), yet the phenylalanine intake must have doubled if not trebled on a normal diet. The same is probably true for the other 3 patients whose levels rose to 7 to 13 mg/100 ml on a normal diet.

Dr. Hudson and co-worker indicate that they increase the phenylalanine in the diet in the manner described by us after about 4 months of treatment. We would like to stress our conviction that an adequate diagnosis cannot be made on the basis of a single challenge. In our clinic and in other centres participating in the Collaborative Study of Children Treated for PKU, approximately 37 of 219 patients (16%) admitted to the study with serum phenylalanine levels >20 mg/100 ml on two occasions 24 hours apart, and with urinary metabolites consistent with PKU, failed to meet these same criteria when challenged later. Most failed to meet these criteria 3 months after the initial diagnosis had been made, but some who met these criteria during the first challenge failed at the one year challenge.

We would also make a plea for a diagnosis based on some form of standardized challenge before dietary discontinuation in all patients so that differences in response to the discontinuation may be appreciated. We believe that there are large numbers of children detected in neonatal screening programmes who have not been adequately diagnosed but will soon be eligible for termination of dietary restriction by virtue of age.

If we hope to gain any knowledge about who may be safely given a normal diet, it is vital that we have at least a 'comparative' diagnosis based upon a standardized study.

We thank Dr. Hudson and Miss Clothier for their comments and also for the opportunity to reply to them.

M. BLASKOVICS

PKU Clinic, Childrens Hospital of Los Angeles,
4650 Sunset Blvd.,
Los Angeles, California 90054.

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Urinary tract infection in children of preschool age

Sir,

The high prevalence of urinary tract infection reported in preschool children in Glasgow (Boothman, Laidlaw, and Richards, 1974) is interesting and also surprising. It contrasts with the lower prevalence found in a slightly larger Leeds survey published in the *Lancet* last year (Davies *et al.*, 1974) and also a London survey (Saxena, Collis, and Laurance, 1975).

The reason for the apparently high prevalence in Glasgow rests mainly on the finding of 6 boys with urinary tract infection out of 81 boys tested in the age range 3-23 months (prevalence 7.4%). We found only one case of definite infection confirmed by suprapubic aspiration, in 334 Leeds boys of similar age (prevalence 0.3%). Was the urinary tract infection of the 6 Glasgow boys confirmed by suprapubic aspiration and culture? If not we suggest the results may be misleading. Have the authors any other explanation for this high prevalence in Glasgow boys? A prevalence of over 7% in boys of 3-24 months would be most surprising. It does not fit in with the known prevalence of urinary tract infection in boys of other ages, ranging from 2.5% in neonates (Littlewood, Kite, and Kite, 1969) to less than 0.05% after the age of 4 years (Kohler, Fritz, and Scherstén, 1972; Kunin, Zacha, and Paquin, 1962).

We agree with Boothman *et al.* that voided urine specimens from children under the age of 1 year contain a large proportion of false significant or doubtful colony counts. In screening over 500 children aged 1-12 months we found that 6.5% had 3 or more consecutive significant or doubtful colony counts. However, this apparently high prevalence of bacteriuria was shown to be false in that suprapubic aspiration showed only one of those 32 children with apparent persistent bacteriuria to have true bladder bacteriuria. It is significant that we found more contamination in boy

infants than girls. Without suprapubic aspiration, urine bacteriology reports in infants are misleading.

S. R. MEADOW, J. M. DAVIES,
G. L. GIBSON, and J. M. LITTLEWOOD
Department of Paediatrics and Child Health,
Seacroft Hospital,
Leeds LS14 6UH.

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The authors reply as follows:

The high incidence of significant bacteriuria in small boys in our study is indeed surprising but there is little to suggest the possibility of false positive cultures except, perhaps, in Case 6 (Table V) (Boothman, Laidlaw, and Richards, 1974). When investigated at the renal clinic, 4 of the 6 boys had positive cultures and these were confirmed in 3 cases by suprapubic aspiration. Reviewing the 2 cases where positive cultures were not obtained at the clinic, it is interesting that one child had serious renal impairment and has since had recurrent infections. This case, together with Case 8 who was admitted with acute symptomatic bacterial pyelonephritis within a fortnight of having one positive and one negative culture, led us to wonder whether some cases of urinary tract infection with intermittent bacteriuria were being missed.

These doubts regarding the possible occurrence of false negative or false positive cultures only serve to highlight the problems which surround the definition, diagnosis, and prognosis of urinary tract infection.

ROSEMARY BOOTHMAN

Social Paediatric and Obstetric Research Unit, Glasgow.

M. LAIDLAW

Glasgow City Laboratory.

I. D. G. RICHARDS

Department of Community Medicine and General Practice, University of Leeds.

Essential fatty acids in cystic fibrosis

Sir,

We have read with interest the report by Elliott and Robinson (*Archives*, 1975) concerning the apparent