may be chronically impaired from recurrent infection (even in the absence of overt diarrhoea), it may also prove beneficial when the intestinal flora and architecture are normal. The potential for ORS to improve the absorption or adsorption of other orally administered pharmaceuticals should also be examined.

We thank Prof Jonas Salk for his contribution.

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1 Patriarca PA, Wright PF, Jacob John T. Factors affecting the normal. The potential for ORS to improve the absorption or may be chronically impaired from recurrent infection (even

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Sir—Allen (Jan 14, p 128) claims that in our commentary (Nov 5, p 1242) we failed to take note of the importance of prospective studies of newly diagnosed cases of galactosaemia. We focused on the outcome of retrospective studies because no prospective studies have been published. Allen cites an abstract of his own small uncontrolled retrospective study to support the value of neonatal screening. Unfortunately he cites the world-wide study by Waggoner and colleagues1 that omit the most convincing evidence that early treatment has little effect on long-term outcome—namely, that from sib pairs. The results in the reference we cite and from earlier studies of sibs indicate that the long-term outcome of sibs of known galactosaemia who were usually treated from birth was no different from that of the index case who had been started on treatment much later, many not before 3 months of age. Screened patients might be expected to have fewer neonatal complications, although the timing of the screening test is critical. In the UK, screening tests are done between 6 and 14 days, and a survey1 has shown no difference in neonatal complications in the screened and unscreened groups.

In our final paragraph we emphasize the importance of carefully planned prospective studies of patient outcome. We also mentioned the contribution that a register could make in collecting longitudinal data, and in this respect we are pleased to report that a UK galactosaemia register has now been set up.

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Frequency of familial melanoma and MLM2 gene

Sir—Battistutta and colleagues (Dec 10, p 1607) report that the penetrance of the familial melanoma gene MLM2 is rising, with a decrease in median age of onset of melanoma. They base this conclusion on the finding that subsequent birth cohorts of mutated MLM2 carriers have a higher cumulative risk of melanoma. The study population consisted of 18 kindreds from Queensland, Australia, who were previously linked to the putative MLM2 gene on chromosome 9p. Gene carriers were identified by haplotype analysis. Where data were unavailable for family members, carrier status was imputed while assuming, for example, no new mutations among founders. By age 40, the cumulative risk among carriers was 36%. Among carriers born before 1900 this risk was only 11% whereas carriers born after 1940 had a risk of 64%. The expected age of onset was 45 years in the oldest birth cohort and 21 years in the youngest cohort (Battistutta and co-workers do not explain how they calculated this). They do not say how many carriers were born before 1900 but according to the graph only 5 patients died from melanoma in the oldest cohort. Battistutta and colleagues discuss some potential caveats as alternative explanations for their results. They argue that an earlier diagnosis of more recently affected cases is not likely because the increasing trend in melanoma is largely attributable to invasive lesions. A differential case-ascertainment across cohorts was thought to be unlikely because of the comprehensive search of death certificates and hospital records.

In my opinion Battistutta and colleagues fail to mention the most important possible bias. It is known that hereditary cancers are often diagnosed at an early age. Therefore, in the search for genes (linkage analyses) in hereditary subtypes of common cancers one usually focuses on families with early-onset disease. It is quite possible that the 18 Australian kindreds were selected originally for linkage analyses because of the presence of one or more young melanoma patients. Probably all these young cases belong to the youngest birth cohort because of the availability of hospital and cancer registry records. It is very likely that the relatives of these probands have a smaller risk of melanoma and that they are diagnosed, on average, at older ages than the probands themselves; this pattern is known as regression towards the mean.1 Thus, before it is concluded that the penetrance of the MLM2 gene is increasing it is important to know on which criteria the 18 familial melanoma kindreds were selected.

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1 Bland JM, Altman DG. Regression towards the mean. BMJ 1994; 308: 1499.