

HYPOTHESIS

Did malaria select for primary adult lactase deficiency?

B Anderson, C Vullo

β galactosidase is the intestinal enzyme that catalyses the digestion of lactose in milk. It is thought to be controlled by an autosomal gene with a dominant lactase persistence allele, and a recessive lactase restriction allele which is responsible for 'primary adult lactase deficiency'.¹⁻⁶ At birth lactase activity is high in almost all mammals but it declines to low levels after weaning in most of the animal kingdom and slowly declines between two and six years in most humans.⁵⁻⁹

It has only been realised in the last 20 years that there is this high frequency of low lactase activity (60-100%) in most of the adult world population^{6 10} - found in most native populations of tropical and subtropical zones such as Africa, east and south Asia, the Pacific, Australia, and the Mediterranean countries, and in American Indians and Eskimos who migrated from east Asia 40 000 years ago. In all these peoples there is a history of drinking little or no unfermented milk.

In contrast, lactase activity remains high in most adults in northwest Europe, and in nomads coming from the African and Asian deserts.⁶ These people have in common a long history of milk drinking. This suggested the geographic evolutionary hypothesis of Simoons to explain the world distribution.^{8 10 11}

Simoons' hypothesis proposes that because most adult humans and mammalian animals have low lactase activity, lactase persistence after infancy must be the 'unusual' condition and lactase restriction the earliest phenotype; and that with otherwise marginal nutrition a mutant lactase persistence phenotype in adulthood would have given a survival advantage to milk drinkers. It is suggested therefore that in the past 10 000 years a natural selection for the lactase persistence phenotype took place in parts of the world where milk drinking had become a habit, such as in northwest Europe and the deserts.

There have been several other hypotheses^{5 6 8 10 12-16} all of which presuppose that the earliest phenotype was low lactase activity, but Kretchmer¹⁷ pointed out that this was a 'prejudice rather than a proven fact'. Evidence is against enzyme induction by lactose¹¹ and the most commonly accepted hypothesis is that of Simoons, though there have been some queries.^{6 15 18-20} In particular, Nei and Saitou²⁰ consider that the lactase persistence phenotype is much older than was suggested, as its presence in virtually all

races today suggests that it existed before the separation of the important three major races - more than 100 000 years ago and long before milk drinking existed. High lactase activity would have permitted the adoption of the milk drinking habit although in turn it could then have given an advantage for survival.

The suggested antiquity of the lactase persistence phenotype has encouraged us to suggest that another explanation for the very high frequency of primary adult lactase deficiency in the world today might be a selection by malaria commencing very early in prehistoric times for a mutant lactase restriction phenotype. Bruce-Chwatt^{21 22} states that it is generally agreed that the host-parasite relationship originated in tropical Africa at the dawn of humanity; that in the neolithic revolution 10 000 years ago the infection was well established in Mesopotamia, India, China, and the Nile Valley, and on the Mediterranean shores; and that from these five main foci it spread through the tropical and subtropical world. In about the 15th century malaria appeared in northern Europe for a few centuries but it seems that it was not usually the falciparum strain causing fatal malaria.

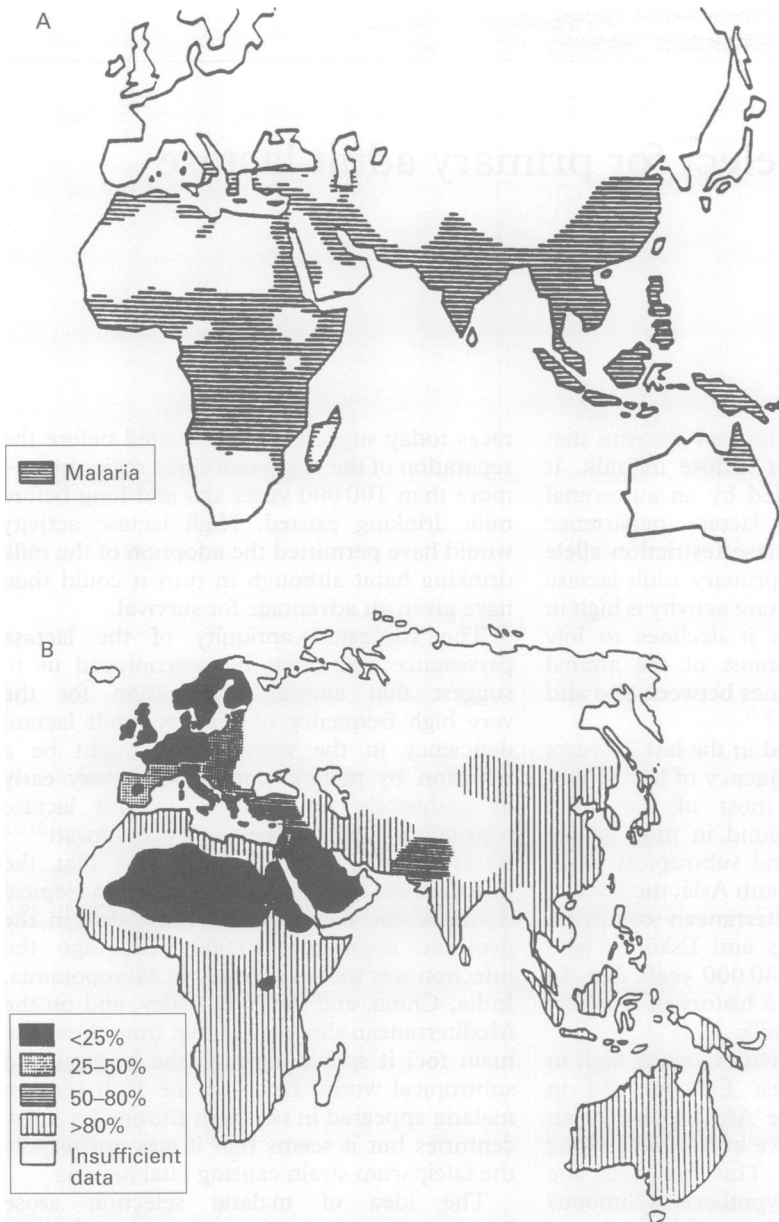
The idea of malaria selection arose because the areas where lactase deficiency predominates compare closely with those where falciparum malaria was always endemic (Figure)^{21 22}; and where thalassaemia, G6PD deficiency, and sickle cell disease are believed to have been selected for by malaria.²³ The absence of malaria in the African and Arabian deserts could explain why in these people high lactase activity predominates.

Lactase deficiency causes intestinal problems resulting from undigested lactose from milk, which discourages milk drinking,^{10 11 24-26} the richest source of riboflavin. Therefore, with otherwise marginal nutrition a mild riboflavin deficiency might develop. There is increasing evidence in vitro and in vivo, that multiplication of malaria parasites is inhibited in flavin deficient red cells²⁷⁻³⁶ and furthermore, is also inhibited in red cells with a deficiency, induced by nitrosoureas, of the flavin adenine dinucleotide dependent glutathione reductase.^{37 38} Dutta³⁶ believes that the malaria parasite is sensitive to a mild riboflavin deficiency, which is tolerated by the human host. In the three in vivo studies in humans lower red cell parasitaemia related to low riboflavin was shown.^{31 33 34} Flavin

Division of
Paediatrics,
Arcispedale S Anna,
Ferrara, Italy
B Anderson
C Vullo

Correspondence to:
Dr B Anderson, Divisione
Pediatria, Arcispedale S
Anna, Via Savonarola 15,
44100 Ferrara, Italy.

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Geographical distribution in the Old World of (A) *P falciparum* malaria endemic over the centuries and still endemic in most areas and (B) the percentage of low lactase activity in the native populations. These maps are adapted from those contained in references⁵ and ⁶ respectively. This figure is reprinted with permission from McGraw-Hill (ref 6) and World Health Organisation (ref 21).

deficient red cells may not prevent malaria but could lead to less fatality.

There is also evidence that malaria selected for a genetically controlled flavin deficient red cell, probably due to slow red cell metabolism of riboflavin to flavin mononucleotide and flavin adenine dinucleotide which affects the flavin status of red cells but not other tissues.^{30 40} If this accompanied low lactase activity protection against malaria would be even greater.

If selection occurred in adult life it could only have done so if milk drinking existed where now it is virtually absent – the first convincing evidence of milking was in north Africa between 4000 and 3000 BC⁸ though it probably existed earlier.^{10 11} On the other hand, if selection occurred mainly in infancy during late breast feeding and weaning at the time of the decline in lactase activity, it could have commenced independently of the milking habit and as far back as malaria existed.

During the first three months of life an infant is thought to be protected against malaria by passive transfer of maternal antibodies,⁴¹ but it has been known since the time of Horace that older infants are at risk for recurrent severe attacks of malaria.^{41 42} An indication that selection by malaria occurred in infancy could be that lactase activity declines considerably earlier in many of the populations in malarial areas than elsewhere^{5 9 16}; for example, if activity declines in Finns it does so in the late teens whereas it declines between one month and two years in most Thai infants, in whom there is known to be a high incidence of 'weanling diarrhoea'.⁴³ It was suggested that an intolerance seen in Zambia to mother's milk towards the end of breast feeding was caused by the early development of lactase deficiency⁴⁴ and that a progressive lactase deficiency in young mammals controls the time and rate of weaning.⁴⁵

As the lactose content of human milk is high⁵ the decline in lactase activity in infants probably causes excessive intestinal accumulation of undigested lactose. A consequent reduction in breast feeding, without supplementation, could lead to a gradual development of mild riboflavin deficiency and hence protection against severe malaria.

In summary, we propose that the lactase persistence phenotype was the 'wild type' that permitted prolonged breast feeding, and that a mutant lactase restriction phenotype was selected for by malaria, occurring mainly during late breast feeding and weaning and starting as early as Paleolithic times when malaria originated in tropical Africa. The rationale for the selection is that the decline in lactase activity leading to lactose intolerance discouraged breast feeding, a rich source of riboflavin. With inadequate alternate nutrition mild riboflavin deficiency developed, which could be tolerated by the human host but red cell multiplication of malaria parasites was inhibited and severe and fatal malaria prevented. This protection would have been greater if associated with an inherited slow red cell metabolism of riboflavin, also selected for by malaria. Finally, the variable timing of switching off of lactase activity and very early decline found in most malarial areas could have resulted from malaria selecting for a progressively earlier switching off.

We hope that this malaria hypothesis will stimulate studies in different parts of the world into the interrelations between the distribution of lactase deficiency and the history of milk drinking, red cell riboflavin deficiency, and malaria.

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