

EDITORIAL

Clinical and
Experimental
Allergy

Unpasteurized milk: health or hazard?

M. R. Perkin

Division of Community Health Sciences at St George's, University of London, London, UK

Humans have been consuming animal milk for thousands of years, with evidence of consumption in the British Isles during the Neolithic period [1]. Before the industrial revolution, the majority of the population in the United Kingdom worked in agriculture and cow's milk formed an integral part of the normal diet. Cow's milk has therefore been an allergen to which humans have been exposed for millennia.

The literature identifying that farming children have a reduced prevalence of allergic disorders compared with other rural children is now substantial. It is clear that a diversity of putative protective factors are involved: exposure to barns and stables, early contact with farm animals and working on a farm during pregnancy. The paper by Waser et al. [2] adds to the small but growing body of evidence that consumption of unpasteurized milk is another factor mediating a protective effect on allergic disorders. Unpasteurized milk consumption shares with the broader farming literature a heterogeneity in the effects that have been observed. Riedler found an independent protective effect of early unpasteurized milk consumption on asthma, current wheeze, hayfever, current rhinitis symptoms and atopic sensitization [3]. The latter was noteworthy as the definition of a positive response was the same as Waser (≥ 3.5 kU/L) and the panel of inhalant allergens included house dust and storage mites, cat dander, grass and birch pollen and cow epithelium. An additive effect was seen from the combination of early milk consumption and early stable exposure. The paper by Radon, cited by Waser, was particularly interested in the issue of *H. pylori* and *T. gondii* infection and was based on adults rather than children [4]. This paper did not find an independent protective effect of unpasteurized milk consumption on atopy; it was only the

combination of unpasteurized milk consumption and regular visits to animal houses before the age of 7 years that was protective [odds ratio (OR)_{adj} 0.35%, 95% confidence interval (CI) 0.17–0.74] and the combination of unpasteurized milk consumption and IgG against *H. pylori* (OR_{adj} 0.38%, 95% CI 0.15–0.98). Barnes' study in Crete shared a similarity with the current paper in that both rural and urban children were included [5]. The results of Barnes' study are difficult to interpret in that farm animal contact and unpasteurized milk consumption had protective effects on atopy for urban but not rural children. However, in the regression analysis, unpasteurized milk consumption, farm animal contact and being a rural child all had independent protective effects on atopy.

The New Zealand study quoted by Waser was small (293 children) but found a very significant reduction in eczema (OR_{adj} 0.2%, 95% CI 0.1–0.8) and a similar effect, but not statistically significant, for current allergic rhinitis (OR_{adj} 0.3%, 95% CI 0.1–1.1) [6]. No significant effect was found for atopy (OR_{adj} 0.6%, 95% CI 0.2–1.9).

Our study found protective effects of unpasteurized consumption on current eczema and seasonal allergic rhinitis symptoms, but most significantly for atopy (OR_{adj} 0.24%, 95% CI 0.10–0.53) [7]. Consistent with Waser, the protective effect was observed across farming groups and therefore cannot be explained by it being a proxy for another farm-based exposure.

With regard to specific allergens, the results of Waser are confusing. One would have hypothesized that the effect of unpasteurized milk consumption would be broadly similar for sensitization to a range of different aeroallergens. In contrast, Waser found no effect for Phadiatop, storage mites and cat dander, a reduction in sensitization for pollen and horse dander and a borderline increase in sensitization for house dust mite (HDM). Our results were remarkably consistent for any aeroallergen, HDM and grass pollen.

There are two issues to resolve: what is it about unpasteurized milk consumption that confers a protective effect and why is the effect heterogeneous depending on

Correspondence:

Dr M. R. Perkin, Division of Community Health Sciences at St George's, University of London, Room 6.18, 6th floor Hunter Wing, Cranmer Terrace, Tooting, London SW17 0RE, UK.

E-mail: m.perkin@sgul.ac.uk

the country and population studied? Answering the former may well assist in being able to answer the latter and it would seem that there are two possibilities discussed in the following two subsections.

Unpasteurized milk contains something beneficial that is absent or present in a smaller quantity in store-bought milk

Pasteurization

Pasteurization is the process of heating food to achieve a significant reduction in any microbiota present. It does not aim to achieve sterilization of the food. First undertaken by Louis Pasteur and Claude Bernard on 20 April 1862, its use for milk was suggested by Franz von Soxhlet in 1886. The technique used most commonly in the United Kingdom is high-temperature short-time pasteurization which involves heating the milk for a short period (heating to approximately 75 °C for up to 30 s).

Waser speculates about the difference in the levels or composition of pathogenic and non-pathogenic microbes in farm milk compared with store milk. Fortunately, there are excellent data from a 'National Study on the Microbiological Quality and Heat Processing of Cows' Milk' undertaken by the UK Ministry of Agriculture, Fisheries and Food, which subsequently metamorphosed into the Joint Food Safety and Standards Group (JFSSG) and finally the Food Standards Agency (FSA) [8]. All 754 approved dairy establishments in the United Kingdom that heat treated milk at the time of the survey (1999–2000) were invited to take part and 258 dairies agreed to participate. Those that participated were representative of all dairies in the United Kingdom in terms of size and location. The number of sampling visits a dairy

received was determined by its throughput in litres of milk processed per annum, the maximum being four visits for the largest dairies (>100 million L/annum). The intended tests were for total viable count, coliforms, coagulase-positive *Staphylococcus*, *E. coli*, *E. coli* O157, *Listeria* spp., *Listeria monocytogenes*, *Salmonella* spp. and *Campylobacter* spp. The results comparing raw with pasteurized milk are shown in Table 1. Unpasteurized milk contained significantly more bacteria ($P < 0.0001$) for all four groups in the table. In addition, non-pathogenic *Listeria* spp. were found in 37% (223) of the raw milk samples and 0.4% (5) of the pasteurized samples.

Waser discusses the importance of the gut flora in murine models for establishing a healthy functioning immune system. Could it be that either the increased quantity and/or the increased diversity of bacteria found in the unpasteurized milk is mediating the protective effect?

Endotoxin

Endotoxins are structural components of bacteria that can induce immunological reactions particularly after bacterial lysis. The prototypical example of endotoxin is lipopolysaccharide (LPS) found in the outer membrane of various Gram-negative bacteria [9]. Endotoxin has been postulated as one of the mechanisms by which the reduced prevalence of allergy among farming children may be being conferred [10].

While attention to date has focused on exposure to endotoxin as an aeroallergen, the amount of LPS in raw milk compared with pasteurized milk has been assessed. Suhren et al. analysed the LPS content of milk and milk products using the Limulus test. A number of experiments were conducted, one of which was to compare the LPS

Table 1. Difference in microbiological quality of samples of raw and pasteurized milk in a national survey of UK dairies

	Log ₁₀ count/mL of milk							Total samples % (<i>n</i>)
	<1.00	1.00–1.99	2.00–2.99	3.00–3.99	4.00–4.99	5.00–5.99	≥6.00	
	% (<i>n</i>)	% (<i>n</i>)	% (<i>n</i>)	% (<i>n</i>)	% (<i>n</i>)	% (<i>n</i>)	% (<i>n</i>)	
Total viable count (TVC)*								
Raw	0.2 (1)	0.5 (3)	4.1 (25)	38.9 (237)	39.3 (240)	13.3 (81)	3.8 (23)	100 (610)
Pasteurized	0.7 (10)	3.9 (55)	45.2 (639)	42.2 (596)	5.9 (84)	2.1 (29)	0 (0)	100 (1413)
Coliforms*								
Raw	13.9 (85)	29.8 (182)	37.5 (229)	14.1 (86)	3.8 (23)	0.8 (5)	0 (0)	100 (610)
Pasteurized	90.3 (1276)	6.9 (97)	2.5 (35)	0.4 (5)	0 (0)	0 (0)	0 (0)	100 (1413)
<i>Escherichia coli</i> *								
Raw	48.2 (294)	33.8 (206)	15.1 (92)	2.3 (14)	0.7 (4)	0 (0)	0 (0)	100 (610)
Pasteurized	99.9 (1411)	0.1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	100 (1413)
Coagulase-positive staphylococci*								
Raw	81.5 (497)	8.0 (49)	7.4 (45)	3.0 (18)	0.2 (1)	0 (0)	0 (0)	100 (610)
Pasteurized	99.9 (1411)	0.1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	100 (1413)

* χ^2 test $P < 0.0001$ raw vs. pasteurized milk.

content of eight samples of milk taken from a dairy plant before and after pasteurization (71–74 °C for 30 s) [11]. The LPS content of pasteurized milk was 0.52 times (0.32–0.85) lower than before heat treatment. Thus, could enteral exposure to this increased quantity of LPS mediate the protective effect?

Nutritional content

Waser quotes data indicating that the nutritional content of cows' milk varies, as one would expect, with the diet the cow has been fed [12]. Grass-fed cattle produced milk with a higher ω -3 fatty acids content. Under the Black–Sharpe [13] dietary fat hypothesis, these ω -3 fatty acids reduce prostaglandin formation by competitive inhibition with ω -6 fatty acids (linoleic acid) and by inhibiting the action of cyclo-oxygenase.

However, unpasteurized milk differs from pasteurized milk in its content of a number of other substances. Paradoxically, in addition to containing a higher microbial load, unpasteurized milk contains antimicrobial substances (lactoferrin, conglutinin, lactoperoxidase and free short-chain volatile fatty acids). The vitamin A and riboflavin content is marginally reduced by pasteurization and whey proteins are denatured by the heating.

Store-bought milk contains something hazardous that is not present or present in a smaller quantity in unpasteurized milk

Nutritional content

A more recent hypothesis put forward to explain the allergy epidemic has been the temporal association with vitamin D supplementation [14]. Wjst argues that the introduction of vitamin D supplementation in newborns coincides with the onset of the increase in allergic disorders. Both breast milk and cows' milk are known to be relatively deficient in vitamin D. In the editorial, Wjst postulates that the reduced prevalence of allergy among farming children may be for one of several reasons. Firstly, farming communities may have a lower use of vitamin D supplements in their children. Secondly, by consuming unpasteurized milk they are not therefore consuming vitamin D-fortified milk. Thirdly, LPS exposure down-regulates vitamin D receptor levels. Finally, LPS-pulsed dendritic cells' IL-12 response can override the blocking effect of calcitriol [14].

Homogenization

The adoption of pasteurization in the milk industry would seem to predate the onset of the allergy epidemic by too significant a period of time for it to be causally related to the epidemic. A closer temporal relationship could be

argued for the homogenization process. Homogenization, undertaken to prevent the cream layer from separating out of the milk, involves the milk being pumped at high pressures through very narrow pipes, breaking up the fat globules. Homogenization of milk causes a reduction of fat globule size and a concurrent increase in the milk fat surface area, which alters the original milk fat globule membrane (MFGM) because the concentration of native MFGM is insufficient to cover the fat surfaces that are formed during homogenization [15]. Adsorption of new material from the milk serum at the oil–water interface occurs to cover this increase in surface area and the new MFGM consists of native MFGM plus adsorbed plasma proteins, with casein as the dominant group [15]. There is, of course, a historical precedent for hypothesizing that the homogenization process might be related to disease. Oster proposed that xanthine oxidase was encapsulated within the reformed MFGM and could therefore avoid digestive enzymes and be absorbed from the gut into the circulatory system. The xanthine oxidase, liberated within the circulation by the action of lipoprotein lipase, could then interact with and destroy plasmalogen, in turn initiating plaque formation [16]. The theory was eventually refuted by the work of Clifford et al. [17]. Clearly, however, in investigating what may underlie the protective association of the consumption of unpasteurized milk, it would seem sensible to consider whether the homogenization process could be inducing changes in cows' milk that might have a deleterious immunological effect.

Summary

Unpasteurized milk consumption arouses strong passions. There is a vociferous 'raw milk' lobby who see it as a panacea for all ills and claim that pasteurization removes the goodness from the milk. Conversely, current medical guidance in the United States and the United Kingdom is strongly prohibitive of consumption, based on the reports of outbreaks of disease from exposure to pathogenic bacteria in unpasteurized milk. This concern would appear to be corroborated by the data from the FSA report on UK dairies: the following species were found in raw milk samples but not pasteurized milk: *L. monocytogenes* 17% (101 samples); *Salmonella* spp. 0.3% (2); *Campylobacter* spp. 0.8% (5); and *E. coli* O157 in 0.2% (1).

Food retailing legislation is making it more difficult to purchase unpasteurized milk with proposals to ban its sale completely under discussion in several countries.

Yet, a paradox remains. Clearly, a dairy farming family's propensity is to ignore governmental advice and utilize this essentially free resource. This paper adds to the weight of evidence that a protective effect is associated with unpasteurized milk consumption. The potential of identifying the underlying mechanism that yields a two-thirds reduction in sensitization must be worth pursuing.

The key issue now is to determine what underlies this protective effect and whether it is possible to separate the protective from the potentially hazardous elements. The EU-funded multi-national GABRIEL study includes a component investigating the content of unpasteurized milk in more detail [18]. Perhaps it may provide the answer.

References

- 1 Milk. <http://en.wikipedia.org/wiki/Milk>. Last accessed 22 February 2007.
- 2 Waser M, Michels KB, Bieli C *et al*. Inverse association of farm milk consumption with asthma and allergy in rural and suburban populations across Europe. *Clinical Exp Allergy* 2007; **37**: 661–70.
- 3 Riedler J, Braun-Fahrlander C, Eder W *et al*. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001; **358**:1129–33.
- 4 Radon K, Windstetter D, Eckart J *et al*. Farming exposure in childhood, exposure to markers of infections and the development of atopy in rural subjects. *Clin Exp Allergy* 2004; **34**:1178–83.
- 5 Barnes M, Cullinan P, Athanasaki P *et al*. Crete: does farming explain urban and rural differences in atopy? *Clin Exp Allergy* 2001; **31**:1822–8.
- 6 Wickens K, Lane JM, Fitzharris P *et al*. Farm residence and exposures and the risk of allergic diseases in New Zealand children. *Allergy* 2002; **57**:1171–9.
- 7 Perkin MR, Strachan DP. Which aspects of the farming lifestyle explain the inverse association with childhood allergy? *J Allergy Clin Immunol* 2006; **117**:1374–81.
- 8 Food Standards Agency. *Report of the national study on the microbiological quality and heat processing of cows' milk*. London, UK: Food Standards Agency, 2003, Retrieved 22 February 2007 from <http://www.foodstandards.gov.uk/multimedia/pdfs/milksurvey.pdf>
- 9 Endotoxin. <http://en.wikipedia.org/wiki/Endotoxin>. Last accessed 22 February 2007.
- 10 Braun-Fahrlander C, Riedler J, Herz U *et al*. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002; **347**:869–77.
- 11 Suhren G, Hesselbarth H, Heeschen W, Südi JI. Evaluation of the lipopolysaccharide (LPS) content as determined by the limulus test in milk and milk products II: raw milk and influences of technological procedures. *Milchwissenschaft* 1986; **41**:156–60.
- 12 Hebeisen DF, Hoeflin F, Reusch HP, Junker E, Lauterburg BH. Increased concentrations of omega-3 fatty acids in milk and platelet rich plasma of grass-fed cows. *Int J Vitamin Nutr Res* 1993; **63**:229–33.
- 13 Black PN, Sharpe S. Dietary fat and asthma: is there a connection? *Eur Respir J* 1997; **10**:6–12.
- 14 Wjst M. The vitamin D slant on allergy. *Pediatr Allergy Immunol* 2006; **17**:477–83.
- 15 Cano-Ruiz ME, Richter RL. Effect of homogenization pressure on the milk fat globule membrane proteins. *J Dairy Sci* 1997; **80**:2732–9.
- 16 Ross DJ, Ptaszynski M, Oster KA. The presence of ectopic xanthine oxidase in atherosclerotic plaques and myocardial tissues. *Proc Soc Exp Biol Med* 1973; **144**:523–6.
- 17 Clifford AJ, Ho CY, Swenerton H. Homogenized bovine milk xanthine oxidase: a critique of the hypothesis relating to plasmalogen depletion and cardiovascular disease. *Am J Clin Nutr* 1983; **38**:327–32.
- 18 GABRIEL Project. <http://www.gabriel-fp6.org/project/index.htm>