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LETTER TO THE EDITOR

A critique of Truswell's A2 milk review

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Truswell's recent review of the A1/A2 milk hypothesis in this journal (Truswell, 2005) is very clear in its conclusion that 'there is no convincing or even probable evidence that the A1 β-casein of cow milk has any adverse effects in humans'. The basis on which this conclusion is reached needs scrutiny.

There are seven strands off evidence relevant to the A1/A2 hypothesis: epidemiology, milk chemistry, pharmacology, animal experiments, human trials, clinical observations, and consumer experiences. It is the totality of these seven strands that makes the A2 hypothesis so intriguing.

Epidemiology

There are two key peer-reviewed papers referred to by Truswell (McLachlan, 2001; Laugesen and Elliott, 2003). Both provide remarkably strong evidence for an association at the inter-country level between intake of A1 β-casein and the incidence of type 1 diabetes and ischaemic heart disease. However, Truswell also draws on three other papers as part of his counter argument against the epidemiology. What Truswell does not advise readers is that these other papers were all conference papers and published as such. Two were poster papers presented at an international dairy industry conference and then published as poster papers of approximately one page (Crawford *et al.*, 2003; Hill *et al.*, 2003). The third was a conference paper presented to the New Zealand Society of Animal Production (Hill *et al.*, 2002). All were authored by Fonterra scientists. Fonterra is New Zealand's largest dairy company, marketing more than 95% of New Zealand's dairy production according to the Fonterra website (www.fonterra.com), and also responsible for marketing approximately 40% of the world's internationally traded dairy products. At the time these papers were published, Fonterra was involved in court proceedings against A2 Corporation in relation to issues surrounding A1 β-casein as a health risk factor.

All three of these counter papers used dairy protein intake rather than A1 β-casein intake as the independent variable, yet it can be shown from the data presented by Laugesen and Elliott (2003) that only slightly more than half of the inter-country variance in A1 β-casein intake can be explained by total intake of dairy protein. Accordingly, it is a major fallacy to use total dairy protein as a proxy for A1 β-casein. A second major issue is that it is not possible to replicate the analyses by the Fonterra scientists because of insufficient information provided in their papers. In particular, the countries included in their analyses are not stated. A third issue is that when I attempted in 2004 to undertake a comparable analysis to Hill *et al*. (2002), and in particular to test the effect of increasing the range of countries beyond those included by Laugesen and Elliott (2003), I was thwarted because the essential WHO databases had been withdrawn because of stated data anomalies. Such anomalies could in themselves easily explain why Hill *et al*. (2002) obtained low correlations for the most recent years, despite themselves confirming high correlations for earlier years. It is almost inevitable that poor data will mask relationships.

The strength of the Laugesen and Elliott analyses comes from the strict criteria used for selecting countries for the analyses so as to minimise confounding errors (for diabetes being part of the WHO DiaMond or EURODIAB surveys, and for IHD being 'healthcare-affluent' countries with more than $US1000 per capita total health expenditure based on purchasing power parities), the meticulous reporting of data sources, and the remarkable strength of the statistical associations ($P<0.001$). Truswell argues against the small number of countries used (data was available for 19 countries for diabetes and 20 for IHD) and also argues that for some of the countries the data 'do not follow the average regression line'. This latter point is of course true, for unless there was perfect correlation there must by definition be individual countries that lie not only off the regression line but also outside the standard error for the regression coefficient. It is of course for the purpose of assessing the importance of apparent outliers and sample size issues that statistical analyses are undertaken, with significance levels being a function of these factors.

Milk chemistry and pharmacology

Truswell acknowledges that β-casomorphin-7 (BCM-7) is released by digestion of A1 beta-casein and that BCM-7 has opioid and cytomodulatory properties. Yet he also states that 'there is no convincing or even probable evidence that the A1 β-casein of cow milk has any adverse effect in humans'. This is puzzling as there are a number of studies that have measured BCM-7 in human blood and urine and have linked this to the symptoms of autism and schizophrenia (Cade *et al.*, 2000; Knivsberg *et al.*, 2001; Reichelt and Knivsberg,

2003) The evidence that BCM-7 is released from A1 β-casein but not A2 beta casein comes from Hartwig *et al*. (1997), Jinsmaa and Yoshikawa (1999) and also from a New Zealand Dairy Board patent application (PCT/WO 02/19832 A1). There have also been animal studies showing the effects of injected BCM-7 (Sun and Cade, 1999; Sun *et al*., 1999). The fact that BCM-7 is not just an opioid but an exceptionally powerful opioid was identified by Koch *et al*. (1985).

Animal studies

Truswell is critical of the use of rabbits in the paper by Tailford *et al*. (2003) on the grounds that rabbits are an unsuitable animal model. However, rabbits are widely used in relation to heart disease trials and for testing of drugs such as the statins. The statistically significant results obtained in the Tailford *et al*. (2003) analyses provide strong evidence that A1 beta protein has medically important implications in an animal model. This does not by itself prove anything in relation to humans, but it is an important piece within the overall jigsaw puzzle.

In contrast, Truswell places great weight on the trials with BB rats and NOD mice reported in Beales *et al*. (2002). What he does not point out is that these trials were funded by the New Zealand Dairy Board (now Fonterra) and that the diets were supplied through the New Zealand Dairy Research Institute (then part of the Dairy Board and now part of Fonterra). What is also not acknowledged is that a confidential but widely circulated memorandum from Jeremy Hill of the New Zealand Dairy Research Institute to the Head of the New Zealand Dairy Board, Warren Larsen, states that 'Another important result from the trial was that a hypoallergenic infant formula (Pregestimil) also produced a high level of diabetes. NZDRI has since shown that Pregestimil contains a high amount of BCM-7. This result is not known outside the NZ dairy industry and forms the basis of a confidential NZDRI report'. The Hill memorandum has been referred to and acknowledged by Warren Larsen on Australian television (Australian Broadcasting Corporation, 2003). The document itself was lodged in the New Zealand High Court by A2 Corporation during court proceedings in 2003, with these proceedings eventually being settled out of court. A commentary on these issues was penned by Cone (2003). However, these and other controversial issues surrounding the diets were not acknowledged in the published paper (Beales *et al*., 2002) of which Hill is a co-author. Reference to the tables reprinted in this journal by Truswell (2005) will immediately show the importance of this information to any interpretation of the Beales *et al*. (2002) results.

Human trials

There have been no human trials measuring the effect of A1 β-casein versus A2 β-casein on either diabetes or heart disease. Given that such trials would need to be very long-term, conducting double-blind trials would be extremely challenging. There have been unpublished short-term trials investigating the effect of A1 and A2 β-casein on serum cholesterol, but these have been inconclusive. There is, however, no *a priori* reason why A1 β-casein, putatively causing LDL oxidation and the laying down of fatty plaque, would necessarily lead to increased serum cholesterol. There have also been human trials investigating the effect of BCM-7 from ingested milk in relation to the symptoms of autism and schizophrenia (Cade *et al*., 2000; Knivsberg *et al*., 2001; Reichelt and Knivsberg, 2003). The evidence strongly indicates that people with impaired intestinal systems ('leaky gut syndrome') are susceptible to absorption of BCM-7 into the blood system, and from there across the blood/brain barrier, leading to symptoms of autism and schizophrenia. Truswell has either ignored or not found this evidence.

Clinical observations and consumer experiences

Discussions on the effect of A1 β-casein on health, including both clinical observations and consumer experience are widely available on the internet. Of course, these observations and experiences do not constitute scientific proof. But scientists must also be careful not to ignore such information. What is clear is that there is a considerable number of people who have an intolerance to 'ordinary milk', who are stating that they can drink A2 milk. Indeed, it would seem to be this experiential evidence that is sustaining the growth of A2 milk consumption in New Zealand and Australia.

Food safety review

Truswell refers in his Abstract to the review of evidence 'by the New Zealand and Australian food standard and food safety authorities'. He is incorrect in saying that this review has not been published as Professor Swinburn's Review was released in August 2004 (Swinburn, 2004). Professor Swinburn focused mainly on the human evidence and did not explore the underlying science. Even with these omissions he was able to conclude in his Lay Report (p2) that 'The A1/A2 hypothesis is both intriguing and potentially very important for population health if it is proved correct. It should be taken seriously and further research is needed'.

He also stated in the Executive Summary to the main report (p5) 'As a matter of individual choice, people may wish to reduce or remove A1 β-casein from their diet (or their children's diet) as a precautionary measure. This may be particularly relevant for those individuals who have or are at risk of the diseases mentioned (type 1 diabetes, coronary heart disease, autism and schizophrenia). However, they should do so knowing that there is substantial uncertainty about the benefits of such an approach.'

In calling for publicly funded research Swinburn commented (p5) that 'the vested commercial interests in the research

and its outcomes add a major complicating factor to the progression of science, the use of the knowledge, and the communications to the public'.

Summary

The conclusions made by Truswell (2005) are fatally flawed on account of selective use of data, data omissions, and errors of fact. The A2 hypothesis remains a very intriguing and important hypothesis. As Swinburn (2004, Lay Report p2) stated: '*it should be taken seriously*'.

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