CHAPTER TWO

MILK AND CASOMORPHINS

Most readers of this book will not be scientists. And for those who have studied science, it was probably at high school and long-since forgotten. However, in many spheres of life some knowledge of science is very helpful. If nothing else, it helps stop con-artists and rip-off merchants from pulling the wool over our eyes. Or to use another agricultural term, it is helpful in sorting the wheat from the chaff.

In this chapter I want to provide just enough science so that lay people can understand the basic scientific issues that underpin the A2 milk hypothesis. You should not need any existing science knowledge for this chapter to make sense. Indeed it is not necessary to remember all of the facts presented here. But for those with inquisitive minds who want to test the scientific logic of what I say in later chapters, it is in this chapter that the foundations are laid.

Bovine milk (milk from cattle) is about 87% water and 13% 'solids' – fat, protein, lactose (milk sugar) and minerals (Diagram 1). However, there are some differences between individual cows and breeds. For example Holstein/Friesian[1] cows produce milk that is about 12% solids, whereas Jersey milk is about 15% solids.

The protein is of two general types, casein and whey. The casein proteins are the ones that precipitate out in acids, whereas the whey proteins stay in solution. When Little Miss Muffet was eating her curds and whey, the curds contained the casein proteins that had precipitated out as solids. The whey proteins were still in solution as a liquid. So even the term 'solids' is a bit confusing. What we really mean by solids is the non-water part of the milk. If all the water is evaporated off then the solids are what we have left.

The casein proteins can be further divided into three types, these being alpha-, beta- and kappa-casein. In a litre of bovine milk there are
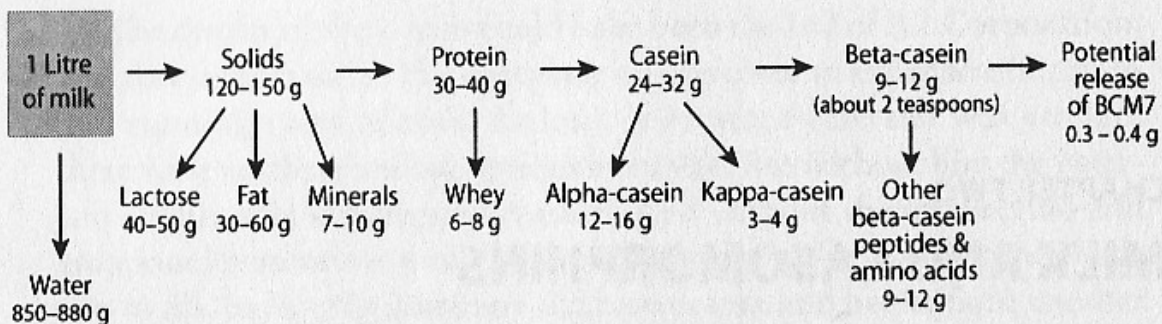
Diagram 1. Contents of a litre of milk.

9–12 grams (about two teaspoons) of beta-casein, again depending on the breed of cow. It is these beta-casein proteins that we are interested in.

All proteins are composed of amino acids. A key characteristic of an amino acid is that it contains at least one atom of nitrogen. Just like fats and carbohydrates (including sugars), amino acids also contain carbon, hydrogen and oxygen. But it is the nitrogen and its binding to hydrogen and carbon atoms that sets amino acids apart. Amino acids are a fundamental building block of life.

According to most textbooks there are 20 amino acids that are found in human tissues. Eight of these are typically classed as essential dietary components, although for infants and possibly old people there can be 10 that need to be ingested. The remainder can be made internally from other amino acids.

When we eat foods containing protein our body breaks down the protein with the help of digestive enzymes produced in our stomach and intestines, first into protein fragments called peptides, and then into individual amino acids. This process is called hydrolysis (*hydro* = water, *lysis* = breaking down), because molecules of water are broken down by reacting with the proteins and peptides. The amino acids that form are then absorbed into the bloodstream. But not all peptides get broken down into amino acids and absorbed. Some are excreted in faeces, and some manage to get through the gut wall into the bloodstream while still in peptide form.

The beta-casein protein that we are interested in here is a folded chain of 209 amino acids. There are at least eight variants of this beta-casein. Initially they were categorised as A, B, C, D, E and F, reflecting the order in which they were identified. Subsequently, the A beta-casein was subdivided into three types, now known as A1, A2 and A3.

In fact it is now known that the most common forms of beta-casein are A1 and A2. The first of these to be identified by scientists was called

A1 beta-casein. A2 beta-casein got that name because it was the second of the A variants to be identified. It was only later that science was able to show that A2 beta-casein was the original one.[2] The only difference between A1 and A2 beta-caseins is the amino acid at position 67 (Diagram 2). In the case of A1 beta-casein the amino acid at position 67 is histidine, whereas with A2 beta-casein it is the amino acid proline.

It may seem surprising, but this tiny difference in the protein structure can have a major effect when the protein is digested. The reason is that
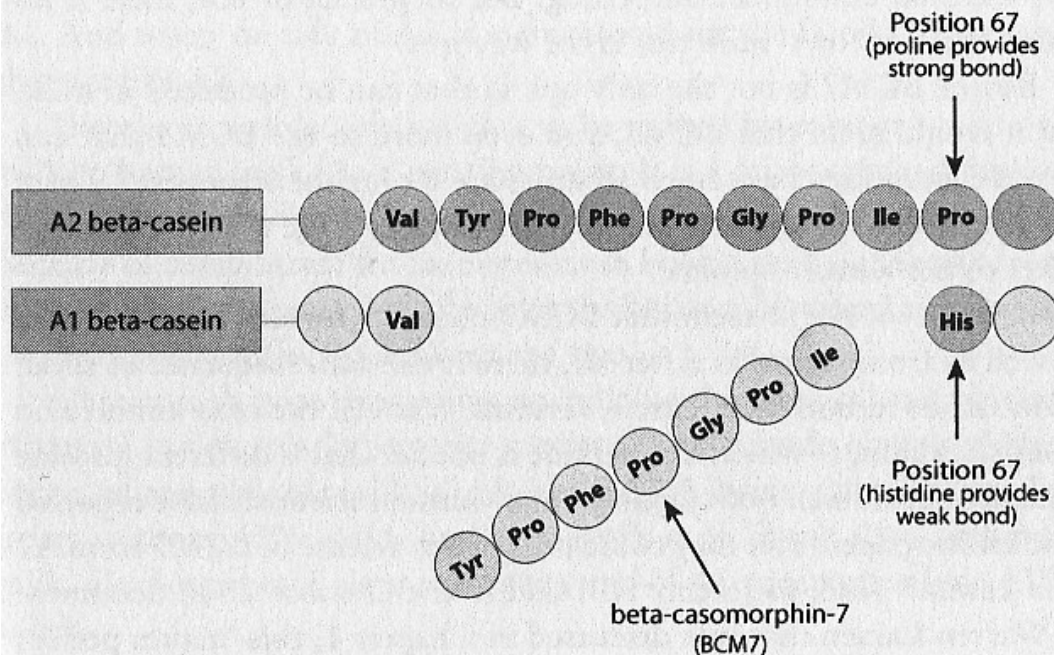
Diagram 2. Release of beta-casomorphin-7.

the proline binds very closely to the amino acid next to it in position 66, which is isoleucine, whereas the histidine linkage with isoleucine is easily broken by digestive enzymes. With A2 beta-casein the proline also binds very tightly with the amino acid in position 68. The outcome of all this is that digestion of A1 beta-casein can produce a peptide of a string of seven amino acids called beta-casomorphin-7 (or BCM7) whereas the evidence is that this does not occur (or at least not to any significant degree) with A2 beta-casein.[3]

The distinguishing characteristics of casomorphins are that they derive from casein and they have opioid (narcotic) properties. Hence the *caso* from casein and the *morphin*, which like 'morphine' derives from Morphus, the Greek god of sleep. The existence of casomorphins and their narcotic properties was first reported in 1979 by German scientists.[4]

The full structure of bovine BCM7 is tyrosine-proline-phenylalanine-proline-glycine-proline-isoleucine. In the shorthand of chemistry this is usually written as Tyr-Pro-Phe-Pro-Gly-Pro-Ile. Fortunately there is no need to remember either the longhand or shorthand version to understand what follows. However, what is important is that the bonds linking the prolines to the other amino acids are particularly strong, and this gives BCM7 great resistance to further breakdown. My biochemist mates tell me that having three proline molecules so close together is very unusual and indeed surprising. But surprising or not, there is no doubt that for cows' milk this is the way it is.

Bovine BCM7 is not the only opioid that can be produced in milk. But it would seem that BCM7, and even more so the BCM5 that can in some situations be formed from it, are by far the strongest.[5] There are also opioid antagonists in milk that can to a large extent negate the effect of the weaker opioids.

In theory it might seem that BCM7 could be formed from A2 milk as well as from A1 milk. After all, there is the same sequence of seven amino acids in both beta-casein variants. It is just the next amino acid along the chain, to which this peptide is bound, that is different (proline instead of histidine). Both Japanese and German scientists have reported in scientific papers that they could not get any release of BCM7 from A2 beta-casein.[6] And, as Jeremy Hill said in the October 2000 document to Warren Larsen that was discussed in Chapter 1, this 'makes perfect mechanistic sense'. This is because the bonds linking this proline to the adjacent amino acids are very strong.

New Zealand Dairy Research Institute scientists (subsequently part of Fonterra Innovation) reported, as part of their 2001 patent application linking A1 milk to autism and related mental diseases, that they too had investigated whether any BCM7 could be released from A2 milk.[7] They reported very small amounts of BCM7 but thought this was likely to be due to some low-level contamination with A1 milk. They concluded that 'if BCM7 was released from the hydrolysis of A2 casein, the rate of reaction was many orders of magnitude less than for A1 casein.'

So it seems that at least on this point there is not much controversy. Scientists essentially agree on where BCM7 does and does not come from, though it would be dangerous to say unequivocally that it is impossible for BCM7 to be released in tiny amounts from A2 milk. This is because digestion is a thermodynamic process and there are random elements

to it. But if it does sometimes occur then the amount is very small. In contrast, the amount released from A1 milk can be very large.

So far I have only described the A1 and A2 beta-caseins. But there are also at least six minor variants of beta-casein called A3, B, C, D, E and F. Variants B, C and F all have histidine at position 67 and therefore can be expected to break down just like A1. In contrast, variants A3, D and E all have proline at position 67 and therefore behave the same as A2 in relation to BCM7 release. So when we talk about A1 beta-casein this is really shorthand for the family of variants that act the same as A1. And when we talk of A2 it is shorthand for the family of variants that act like A2.

There are considerable insights to be gained by comparing bovine milk to human milk. As a starting point, it is a fairly safe assumption that if there are problems associated with bovine milk then they will be because of components that are present in bovine milk but absent from human milk, or alternatively because the balance between components is substantially different between the two.

All mammals raise their young on milk but the chemical and physical structure varies greatly between species. To take some obvious differences, whereas bovine milk is only about 13% solids, the milk of polar bears is about 43% solids and grey seal's milk about 68%. Human milk, like bovine milk, is at the watery end of the spectrum: about 13% solids.

Accordingly, the important differences between human and bovine milk relate not to the overall solids content (which is similar for both) but to their constituents. Human milk is higher in lactose, similar in fat, but much lower in protein than bovine milk. It is also considerably lower in minerals such as calcium, sodium and potassium.[8]

I am going to focus here on the protein differences between human and bovine milk. This is not only because the BCM7 story is about proteins (there is absolutely no way that BCM7 could be released from fats, lactose or minerals), but also because most allergies to milk, particularly in children, are associated with its proteins. Many adult humans, particularly those of non-European ancestry, are also intolerant of lactose because they lack the digestive enzyme lactase. But that is another story, albeit a story that may well be relevant to A2 milk, and which I will take up in Chapter 9.

The protein level of human milk is about 1.6% in the first few days

following birth and then drops to about 0.9%.[9] In comparison, bovine milk is typically 3–4%, depending on both the breed and individual differences. The specific balance between the proteins is also quite different. In bovine milk about 80% of the proteins are casein proteins whereas in humans the major proteins are whey proteins.[10]

Although beta-casein is the most important of the human casein proteins it is different to the beta-casein produced by cows. The human beta-casein is a shorter protein chain and so the analogous positions in relation to the bovine BCM7 are from 51 to 57 instead of 60 to 66. However, all human beta-casein is of the A2 type rather than the A1 type, in that the adjacent amino acid at the next position (58 in humans and 67 in cows) is proline. This acts as a major barrier to the production of BCM7 in humans.

There is also another extremely important qualification that needs to be made. BCM7 from human milk is not the same as bovine BCM7. In chemical terms it has the structure Tyr-Pro-Phe-Val-Glu-Pro-Ile. In other words, although still meeting the definition of a casomorphin, it has two amino acids that are different from bovine BCM7. A proline and a glycine have been replaced by a valine and a glutamine.

Does this all really matter? Well, yes it does, for two reasons. The first is that the opioid properties of human BCM7 are about ten times weaker than the bovine form. I will return to that later. The second reason is that human milk also releases much less BCM7. Fonterra scientists (led by Jeremy Hill) in association with a Massey University scientist have tested human milk from 15 volunteers to see if they could get a release of BCM7 from it. They stated in a poster paper to the International Dairy Federation Conference in 2003 that on average they got about 2.5 micrograms of BCM7 per millilitre.[11] This is less than 1% of the BCM7 that could be released from the same amount of A1 milk (although they did not make this comparison). So overall, when it comes to the relative opioid effect, human milk has less than one-thousandth the potential potency of A1 cows' milk.

The 'big picture' from this is that human milk is most like A2. It is intriguing that there is this small BCM7 release, and it links with another stream of research that suggests that psychosis in new mothers is linked to their being poisoned either by their own or bovine milk. But that is another story, and beyond the scope of this book.[12]

To get back to the implications for the A2 hypothesis, Jeremy Hill's team have made two claims. The first was that 'these results show that it

is likely that some BCM7 is released during the digestion of human milk in the gastrointestinal system.' I have no argument with that, except for the need to make it clear that this is human BCM7 – different to bovine BCM7 – and that it is a very small amount.

The second conclusion was that 'The proposal by McLachlan (2001) that it is the release of BCM7 from beta-casein A1 that makes the consumption of milk containing this variant a risk to human health looks to be unfounded in light of the likelihood that human milks also release an equivalent peptide upon digestion.' I believe this requires a huge leap of logic, given that we have just seen that human milk releases a different casomorphin and in much smaller quantities. Quite simply, Hill's conclusion is totally unsupported by the evidence.

Such a conclusion is highly unlikely to ever be acceptable in a refereed paper, but it is the sort of thing authors can write in a non-refereed poster paper. At this particular conference the attendees were senior staff of dairy companies from all around the world. The vast majority of them would have looked at the conclusions and accepted them at face value. The paper would have reinforced a widespread assumption (which at that stage I myself shared) that the A2 arguments were shonky and misguided. And it would have made the work of A2 Corporation, which was desperately seeking commercial partners from the dairy marketing world, just that little bit harder.

Whether these results will ever appear in the scientific press is unclear. In March 2004 I wrote to the Massey University co-author Dr Alison Darragh (who subsequently became a Fonterra employee) saying that I had seen a comment in an industry magazine, attributed to Jeremy Hill, that the paper was at press. Darragh replied, 'We have published it in abstract form at a conference, and I am currently writing the paper. I will keep your email on file and forward a copy to you when it is published.'

So far I have heard nothing despite a reminder email to Dr Darragh in early 2007, sent to her Fonterra address. I also asked Jeremy Hill himself in March 2007. He said he would follow it up with Alison Darragh as to what had happened, but I have heard nothing. Also, there is no evidence of publication in the international databases, which is a sure sign there is nothing in the peer-reviewed medical literature. But my guess is that if the work does get published (which it should be), the anti-A2 conclusions will be omitted (because the faulty logic would be picked up by the reviewers). However, the damage has already been done. And arguably the industry article saying that the paper was 'at press' (implying that it

had been accepted following refereeing by scientific peers) was less than accurate. All that had been written was an abstract.

We can gain some further insights about A1 beta-casein versus A2 beta-casein by looking at the situation with other mammals that are closely related to cattle. What we find is that goats' milk contains A2 beta-casein and no A1 beta-casein. In most, but probably not all sheep, the milk contains only A2 beta-casein.[13] Yaks produce only A2 beta-casein. And so do all *Bos indicus* cattle, which are the native cattle of Asia.

Putting all of this evidence together allows us to say with high confidence that the A2 beta-casein was the original beta-casein, and that in genetic and historical terms the A1 beta-casein is a 'Johny-come-lately'. The most likely time of the mutation of the gene responsible, which is known to be on the sixth chromosome, is between 5000 and 10,000 years ago, at a time when cattle were being taken north into Europe and long before most of the modern European breeds developed.

I am often asked why the A1 variant (or allele) has become so common. Does this mean that the A1 beta-casein has advantages that led to its being selected for, so that it became widely spread throughout European cattle? The answer is probably 'no', since no-one has been able to suggest a likely advantage of A1 beta-casein. The answer is more likely to be found in what animal-breeding scientists call the 'founder effect'.

The founder effect is about the very large impact of the genetic profile of the individual animal from which a breed is founded. For example, a particular bull may have had a superior temperament as a result of a genetic difference that had nothing to do with whether it was A1 or A2. This bull would then have been selected to mate with a range of cows, and the progeny that inherited the same characteristic would then be used to mate with other animals, eventually creating a new breed. If that original bull happened by chance to also be carrying the A1 allele then the animal breeders would unwittingly have been selecting this allele at the same time, so it would become widespread and common throughout the new breed.

The founder effect also answers the other question I am often asked, which is why does the incidence of the A1 allele vary so much between the different modern breeds? Modern breeds have developed within only the last 2000 years, and in many cases over a much shorter period. If, say, the original black-and-white animal happened to have the A1 allele,

then the black-and-white breeds would have a high incidence of that allele (and they do). Similarly, if the mutation that led to yellow cattle first occurred in an individual carrying the A2 allele, then it would be expected that the yellow breeds would probably be high carriers of the A2 allele (and they are).

The message from this is that the A1 beta-casein that we find in the milk of so many of our modern cows is essentially an anomaly. The 'original' milk was clearly A2 milk, and the A1 milk that so many of our modern cows produce is probably just an aberration.

But there are other interesting possibilities. For example, we don't know very much about how calves metabolise BCM7. A common effect of opioids is to make animals more placid. Did farmers actively select the more placid calves, and was this placidity caused by drinking opioid-laced milk?

Processed products

So far, when talking about the release of BCM7 from cows' milk, I have been talking about fresh milk. What happens when the milk is processed, producing pasteurised milk, cheese, yoghurt, butter, ice cream and dairy desserts? For some of those products we have some answers, but there remain plenty of unknowns.

First, let's look at pasteurisation – heating milk to kill bacteria. There is a range of pasteurisation methods, ranging from the old Holder method of heating it to about 63°C for about 30 minutes, to the ultra-high-temperature (UHT) method where the milk is heated to 145°C for just a few seconds. There are also intermediate methods such as heating to 90°C for about 15 seconds. In parts of Europe much of the milk is UHT. One of the advantages is that it can be kept unrefrigerated for months as long as it remains sealed. Not everyone likes UHT milk and some people say it tastes different. In the USA, Australia and New Zealand most milk is pasteurised using one of the intermediate methods.

All pasteurisation methods, and indeed any treatment of milk at more than about 48°C, have the potential to break down or denature the protein. Once the key temperature of about 48°C is reached then it is probably the time that it remains heated, rather than further increases in temperature, that becomes critical, although both time and temperature are undoubtedly relevant. As the protein structure breaks down it is unclear which peptides will be released, but in Chapter 3 I will discuss

some circumstantial evidence that when milk is pasteurised by the Holder method, more BCM7 may be released upon subsequent digestion than occurs with the intermediate temperature methods.

When making ice cream, milk is commonly heated not just to pasteurise it, but because it becomes much easier to mix with the other ingredients. Hence, according to the textbooks it is common to hold the milk at 70°C for at least 15 minutes. I don't know whether all ice-cream makers do this, but two have confirmed to me that they do. What effect this has on the release of BCM7 is unknown, but there is anecdotal evidence that some people can tolerate ice cream made from A2 milk whereas they get severe diarrhoea with ordinary ice cream. So there is a fair chance that BCM7 may be released from ice cream made from 'ordinary' milk. Whether or not the heat treatment process is important is unclear.

The Fonterra Research Centre (now Fonterra Innovation) has done some interesting work looking at the release of BCM7 in a range of cheeses made from 'ordinary' milk (containing both A1 and A2 beta-casein). Its researchers have shown that the amount released varies greatly, depending on the type of cheese. In mozzarella they found no detectable BCM7; in cheddar they found very small amounts, and in blue vein somewhat more. By my calculations this means that the yield of BCM7 in blue vein was about 1% of the amount that would be formed if all the beta-casein had broken down to release BCM7, whereas in cheddar it was about 0.05%. But this is only the BCM7 released during the cheesemaking process. There is still the question of what additional BCM7 is released during digestion, in the stomach and intestines. The Fonterra data indicate that only 7% of the beta-casein remains intact in blue-vein cheese, so there may not be much more BCM7 that can be released (unless it is in an intermediate form between beta-casein and BCM7). But in contrast, with cheddar 63% of the beta-casein is still intact, and for mozzarella the figure is 69%. What happens when this is digested? Quite simply, we do not know. So how we should interpret all of this information is far from clear.

Anecdotal evidence about intolerance to dairy products suggests that at least some people who cannot tolerate ordinary milk, but can drink A2 milk, can also tolerate moderate amounts of cheese. But the significance of this gets complicated because cheese is also lower in lactose than the milk it is made from. Perhaps more importantly, the epidemiological evidence in Chapters 3 and 5 tends to support the perspective that

cheese derived from ordinary milk is not implicated in diabetes and heart disease. In addition, some of my biochemist friends tell me that there are good scientific reasons why the cheesemaking process *might* make the BCM7 inactive. So I'm fairly relaxed about eating cheese made from ordinary milk, but accept that in doing so I am probably still picking up small quantities of BCM7. But I would probably have a different attitude if I thought I was a leaky gut sufferer (which I will soon discuss) and therefore at particular risk of developing one of the auto-immune diseases.

Clearly the issue of BCM7 and cheese is an area where a lot more research needs to be done. So far Fonterra's research in this area has been published only in poster form, first at the 2003 International Dairy Federation Conference, then in the *Australian Journal of Dairy Technology*.[14] Hopefully, at some stage this will be published as a full scientific paper in a peer-reviewed journal. But I am not holding my breath. And is anyone doing some follow-up work? I may be wrong but I think not. No-one has put their hand up to say they are working on it.

What happens to BCM7 in yoghurt is unknown. I cannot find any information in the scientific literature about this. Perhaps it will be a similar story to cheese. But then perhaps not. Without trials all we have is conjecture.

Both sides in the A2 milk controversy seem to agree that BCM7 is not a particular issue in butter. This is because butter is mainly fat rather than protein. Whereas milk contains fat and protein in a ratio of approximately 1:1, in butter the ratio is about 80:1. So unless someone was eating huge amounts of butter, it would not be the source of much BCM7.

Absorption from the Gut

The next important question is what happens to BCM7 when it is released into the gut. Once again there is no simple answer. In healthy adults it should be difficult for BCM7 to get through the gut wall and into the bloodstream, because the molecule is too large. But it appears there are plenty of exceptions. Almost certainly, it depends on the age, health and genetic makeup of the particular person.

Some people suffer from leaky gut syndrome, whereby BCM7 and other peptides pass very easily into the bloodstream. A more formal term is 'intestinal permeability' although it is the former term that seems to be used more widely. And the term 'gut' is arguably more accurate as it encompasses both the stomach and intestines.

In people with a leaky gut it is possible to detect BCM7 in the urine. This condition has been closely associated with the symptoms of autism by Professor Robert Cade and his team from the University of Florida and will be discussed in detail in Chapter 8. There is also very strong circumstantial evidence that people with stomach ulcers or untreated coeliac disease absorb BCM7 through the gut wall. It is also likely that babies can absorb BCM7 the same way; in fact newborn babies need to be able to pass large molecules through the gut wall. Otherwise they would not be able to absorb the colostrum in their mothers' milk. All of this will be discussed in Chapters 8 and 9.

One of Professor Cade's co-workers, Dr Zhongjie Sun, has experimentally injected BCM7 into rats. He and colleagues have published evidence that once in the bloodstream the BCM7 passes very readily across the blood/brain barrier and that it attaches there to opioid receptors.[15] They have also shown that the rats then exhibit behavioural tendencies very similar to those of autism and schizophrenia.[16] They found that the effects could be reversed with administration of naloxone, a well-recognised morphine antagonist. Other scientists have found that BCM7 causes apnoea (breathing dysfunction) in adult rats and newborn rabbits that is analogous to sudden infant death syndrome in humans.[17]

Those of you who sometimes drink the sports drink Gatorade can take some comfort from the thought that you have been a contributor to the work of Professor Cade, Dr Sun and their co-workers. It was Professor Cade who designed the formula for Gatorade, and it is the subsequent royalties (managed by a foundation) that have supported their work into autism and BCM7.

The effects of BCM7 are not restricted to behavioural symptoms. The fact that opioids affect a wide range of immune functions has been known for over a hundred years. This immune effect provides a possible explanation as to why BCM7 appears to be implicated in such a wide range of auto-immune diseases.

However, not all of the effects of BCM7 are necessarily due to its opioid characteristics. The tyrosine molecule on the end of the BCM7, combined with the stability of BCM7, gives the milk devil strong oxidant properties. Indeed BCM7 has been shown *in vitro* (i.e. in a test tube) to be a strong oxidant of low-density lipoprotein (LDL, the 'bad' type of cholesterol).[18] Oxidation of LDL is fundamental to the process whereby fatty plaques are laid down in artery walls, leading in turn

to heart disease.[19] So it seems likely that the effect of BCM7 on heart disease may be twofold, with an opioid-related mechanism (perhaps linked to immune function) and the oxidant properties working like a double-edged sword.

The BCM7 that is released in the gut can affect the digestive system without necessarily being absorbed into the bloodstream. It is well known that casein is sometimes effective in treating diarrhoea, and indeed can lead to constipation. It is also well known that opioids, including BCM7, can reduce the rate of passage through the gut.[20] For example, a common side-effect of codeine, which is an opioid, is constipation. This may explain why babies fed on milk-formula products rather than human milk are susceptible to constipation and in extreme cases can suffer anal fissures.[21] It is also possible, but at this stage unproven, that the slower passage of A1 milk through the digestive system (due to release of BCM7), increases problems of lactose intolerance. The reasoning here would be that lactose intolerance is due to lactose fermentation caused by the absence of the lactase enzyme, and the slower the passage, the more fermentation will occur.

In summary, it is clear is that there is a lot that we know but also much that we don't know about BCM7. We know that BCM7 is produced from A1 beta-casein but not produced, or produced only in very small amounts, from A2 milk. We also know that BCM7 is a very powerful opioid if it gets into the bloodstream. We know that in some people BCM7 can pass from the gut into the bloodstream, and in animals at least, it then readily passes across the blood/brain barrier. We also have strong evidence that BCM7 can compromise the immune system (I will elaborate on this in later chapters). We also know that *in vitro* BCM7 strongly oxidises low-density lipoprotein, and that *in vivo* (i.e. in the body) oxidation of LDL leads to heart disease.

All this is like a big jigsaw puzzle, where the overall picture is starting to appear, or indeed, arguably, is already clear. But there are still plenty of small pieces to come. This is not surprising, because scientific puzzles rarely come together in a straightforward way. Prior to Bob Elliott's discussions with Jeremy Hill back in 1993 no-one had even thought of A1 beta-casein as being the culprit. So it is a work in progress. Nevertheless, the big picture seems to be clear: BCM7 really is a little devil. Little in the sense of size, but very big in terms of the mischief it can cause.

I will have more to say about BCM7 as this book progresses. But for the meantime enough has been said, and it is time to start looking at some of the diseases linked to the milk devil.

NOTES

1   Holstein and Friesian are both black and white breeds. They are sometimes regarded as the same breed.

2   See Ng-Kwai-Hang and Grosclaude (2002) in Cattle Genetics section of Bibliography.

3   See Hartwig *et al* (1997) and Jinsmaa and Yoshikawa (1999) in Milk and Casomorphins section of Bibliography.

4   See Henschen *et al* (1979) and Brantl and Teschemacher (1979) in Milk and Casomorphins section of Bibliography.

5   There is a range of milk peptides that have these opioid characteristics. These casomorphins always have a tyrosine molecule as the amino acid at one end, and a particular type of amino acid known as an aromatic amino acid, such as phenylalanine or another tyrosine, in either the third or fourth position on the chain. The presence of proline in position two is crucial for the biological activity of the casomorphin, as it maintains the proper orientation of the tyrosine and phenylalanine side chains. How many other amino acids are hanging on the chain will also have some modifying influence on the bio-active properties of the particular casomorphin.

6   See Hartwig *et al* (1997) and Jinsmaa and Yoshikawa (1999) in Milk and Casomorphins section of Bibliography.

7   See New Zealand Dairy Research Institute (2001) in Autism and Schizophrenia section of Bibliography.

8   It is inevitable, given that human milk is high in lactose, that it is also low in minerals. This is the only way that the milk, while in the mammary glands, can be iso-osmotic with blood.

9   These figures come from the Australian National Health and Medical Research Council's 2003 publication *Dietary Guidelines for Children and Adolescents in Australia*. Other references commonly list the protein level as about 1.1%. However, there are considerable inconsistencies in the published literature on human milk, and it is impossible to rationalise some of the stated figures for total protein, casein percentage, and beta-casein.

10 Most of the proteins in human milk are whey proteins but in general these are not the same whey proteins as in cows' milk. Human milk has no beta-lactoglobulin, which is the major whey protein in bovine milk, and bovine milk has only very small amounts of lactoferrin, a major whey protein in humans. This lactoferrin is believed to be important in human milk as a protective factor because of its anti-bacterial properties.

11 See Norris, Darragh *et al* (2003) in the Milk and Casomorphins section of the Bibliography

12 See Lindstrom *et al* (1990) in the Milk and Casomorphins section of the Bibliography.

13 The NZDRI reported in its subsequently abandoned 2001 patent application relating to autism and schizophrenia that the SWISSPROT database recorded some sheep as having an alanine at position 67. This alanine could be expected to act in the same way as a histidine and hence these sheep could be expected to produce BCM7.

14 See Norris, Coker *et al* (2003) in Milk and Casomorphins section of Bibliography.

15 See Sun, Cade, Fregly and Privette (1999) in Autism and Schizophrenia section of Bibliography.

16 See Sun and Cade (1999) in Autism and Schizophrenia section of Bibliography.

17 See Hedner and Hedner (1987) in Milk and Casomorphins section of Bibliography.

18 See papers by Steinerova *et al* in Heart Disease section of Bibliography. Also the paper by Torreilles and Guerin (1995) – but beware, this is in French.

19 The modern view of heart disease is that inflammation of the arteries and the heart muscle is also a key factor. It is this inflammation, which is itself an immune response, that allows the deposition of fatty plaque to occur. This is because the surface of an inflamed artery is rough and sticky rather than smooth. For a detailed but eminently readable review see the article by Peter Libby in *Scientific American*, May 2002, pp. 47–55.

20 See Becker *et al* (1990) and Defilippi *et al* (1995) in Milk and Casomorphin section of the Bibliography.

21 See Andiran *et al* (2003) in Milk and Casomorphins section of Bibliography.