CHAPTER EIGHT

AUTISM AND SCHIZOPHRENIA

It is time to move on to look at some new diseases. The focus of this chapter is on autism and schizophrenia.

Autism is a brain disorder that begins in early childhood and persists throughout adulthood. It affects communication and social interaction. People with severe cases may have very poor speech, exhibit temper tantrums and be unable to manage their own toileting. Asperger's syndrome is a relatively mild but common form of autism and many individuals can still operate at a high level. The incidence of autism is debated by experts, with most but not all seeming to agree that the rate has increased greatly in recent decades and that it may be about one child in every 150.

According to the World Health Organisation (WHO) website, schizophrenia is a severe disorder that typically begins in late adolescence or early adulthood. It is characterised by profound disruptions in thinking, affecting language, perception and sense of self. It often includes psychotic experiences such as hearing voices or delusions. It can impair function through the loss of livelihood or the disruption of studies. According to the WHO, there are 24 million suffers of schizophrenia.

Predominantly, this next part of the story involves a totally new set of scientists working in three different countries. The three groups have been led by Professor Robert Cade and Dr Zhongjie Sun from the University of Florida, Paul Shattock from the Autism Research Unit at University of Sunderland, and Dr Kalle Reichelt from the Pediatrics Research Institute at the University of Oslo, Norway. All three groups have interacted with each other and their work is intertwined. Much of it has been published in the journal of *Nutritional Neuroscience*. Other papers have been published in the journals *Brain Dysfunction*, *Autism* and *Peptides*.

First, a brief digression about Professor Robert Cade, who is a nutritional biochemist, now retired, from the University of Florida. One of his best known pieces of work was to design the sports drink Gatorade back in 1965. The Gators were (and are) the University of Florida's football team, and the story goes that they became legendary for their strong second-half performances after drinking the electrolyte-and-energy-replacement drinks concocted by Robert Cade and his wife Mary. Robert's job was to get the appropriate electrolytes and energy balance into the drink; Mary's was to get it to taste acceptable. The royalties from the subsequent commercialisation of this product have been used to finance some of the work on nutritional links to autism that Professor Cade and colleagues have subsequently undertaken. So consumers of Gatorade products can take comfort in the fact that they have contributed to financing some very important work on autism.

Another brief digression. According to a 1998 article in *New Scientist*, Paul Shattock's interest in autism research was originally stimulated by his own experiences as the father of an autistic child.[1] There are several great stories (and I will recount another one in Chapter 9) where a parent's personal experiences in dealing with a particular disease has led to a life-long dedication to finding scientific answers.

The key concept underpinning the work of Reichelt, Shattock and Cade, together with co-workers such as Zhongjie Sun and Ann-Mari Knivsberg, is that many of the symptoms of neurological conditions, i.e. poor mental health, are related to what we eat and how we metabolise that food. Specifically, the symptoms of autism and schizophrenia show some remarkable similarities to the known symptoms caused by opioids which can be formed from the digestion of certain foods, in particular those containing gluten and casein. The particular genetic makeup of an individual, combined with diverse but possibly unrecognised environmental events to which that individual is exposed, determines whether or not that person is susceptible to these conditions. These scientists have been able to show that many autistic children have high levels of BCM7 and other casomorphins derived from BCM7 in their blood and urine. They have also been able to report remarkable success with diets that are free of casein and gluten, in reducing both the level of BCM7 in the urine and the level of autistic symptoms.

The idea that mental health is affected by what we eat has taken a long time to gain acceptance in some medical circles. It has therefore been a difficult journey for Cade, Shattock, Reichelt, Sun, Knivsberg and colleagues. To some extent they were probably ahead of their time, and their contributions to science will be fully recognised only with hindsight.

Until recently these scientists did not realise that BCM7 was released only from A1 beta-casein and not from A2 beta-casein. This is understandable because, as neuroscientists, they did not read the literature on dairy genetics and the ways in which some cows differ from others. So their advice has been, at least until recently, that autistics should consider a diet free of milk. However, there are now at least three different groups of biochemists (including Fonterra's own scientists) who have found that BCM7 is released because of a biochemical feature of A1 beta-casein that is different to A2 beta-casein. So the argument in favour of A2 milk for autistic children comes from linking these separate strands of research.

To the best of my knowledge there have been no trials specifically investigating A2 milk and autism apart from an abandoned trial by Fonterra (and about which I will say more later in this chapter). Instead, research has been focusing directly on the milk devil, BCM7, and similar peptides derived from gluten. However, many parents of autistic children, particularly in Australia where A2 milk has become widely available, are saying that their children's autistic symptoms diminish when their milk intake is restricted to A2. In Britain it is not possible to get certified A2 milk but some parents have been using Guernsey milk, which is very low in A1 beta-casein.

There is also some epidemiological evidence that provides interesting support. Intriguingly, this evidence comes from a patent application by Fonterra, in which they claimed that deaths from mental-health problems were much higher in countries that had high intakes of A1 beta-casein. Subsequently Fonterra abandoned the patent application. This in itself is intriguing and provides a story that I will outline later in this chapter.

The first person to suggest that autism might be linked to opioids was the scientist J.A. Panksepp in a paper published in 1979 in the journal *Trends in Neuroscience*. Then in 1981 Kalle Reichelt and colleagues proposed that these opioids were coming from the incomplete breakdown of certain foods, in particular those containing gluten and casein. Subsequently, the evidence has slowly accumulated that many autistic people do indeed have large quantities of opioids in their blood and urine. There is also evidence that a high proportion of children with autism suffer from increased permeability of the gut wall, and this is a key to explaining what is going on.

Measuring what opioids do in the human body is complex. The method that Reichelt and Shattock use is called High Performance Liquid Chromatography (HPLC), and has gradually been refined but still needs considerable skill. Shattock says that he has now examined more than 1500 autism sufferers and that there are some very clear but complex patterns evident from the chromatography.

At this point a reminder of what a peptide is may be helpful. It is simply a protein fragment. Whereas a protein is made up of many amino acids linked together, a peptide is a much shorter chain of amino acids. Peptides are the first-stage products of protein digestion. The next stage is for them to be broken down into individual amino acids. In most people it is not possible for significant amounts of peptides to get through the gut wall into the bloodstream. But for other people with so-called 'leaky guts' these peptides can get through the gut wall.

A key point in relation to autism and schizophrenia is that the gliadomorphin from gluten and the BCM7 from milk seem to 'hunt together'. Readers may recall from Chapter 7 that they have a very similar structure. With coeliac disease (which will be discussed in Chapter 9) it is clear that gluten and its derivatives play the lead role. Any role played by BCM7 is subsidiary. However, in the case of heart disease it would seem that the milk devil, BCM7, acts independently of any involvement by gluten. And in the case of Type 1 diabetes, although it seems that the milk devil plays the prime role, it would be foolish to totally discount the potential importance of gluten. In autism and schizophrenia it seems that metaphorically speaking, the gluten and the casein stand shoulder to shoulder in their attack.

One of the more important papers linking gluten and casein to autism and schizophrenia was published by Robert Cade and seven co-authors in *Nutritional Neuroscience* in 2000, and titled 'Autism and Schizophrenia: Intestinal Disorders'. Their starting point was Dohan's hypothesis from way back in 1966: that schizophrenia is linked to gluten consumption from wheat, barley, oats and rye. That hypothesis stemmed from the observation that schizophrenia was very rare and mild in societies where these grains were not used, but very common and severe in countries where they made up a large part of the diet. The hypothesis was later extended to include milk.

Cade and his colleagues then asked the following six questions:

1. Is there an unusually high concentration of peptides in blood and urine of schizophrenic and autistic patients?

2 If [peptides] enter the blood, can they penetrate the blood/brain barrier?
3 What structures do they enter?
4 Could involvement of the brain structures the peptides enter cause the symptoms of autism and schizophrenia?
5 If the peptides are removed or greatly decreased in concentration are the disease symptoms and signs diminished or cured?
6 If a normal animal is given one of the peptides will it produce symptoms similar to those of autism and schizophrenia?

For all six questions there was in fact already published evidence suggesting an affirmative answer, and Cade and his colleagues laid out the sources of this information. But they pointed out that no one team of scientists had previously attempted to join all these questions together. In doing this, they also presented extensive previously unpublished data they had collected from 150 autistic children and 120 schizophrenic adults. They also included data from 76 normal adults and 43 normal children.

The story they found is quite complex (very seldom are there simple answers in medicine) but the answers were also very clear. Normal subjects had three different patterns of peptide excretion, with each individual fitting into one category. The autistic children and schizophrenic adults exhibited the same three patterns, but with much greater levels of peptide excretion. In fact there was no overlap in the ranges, with perfect separation for each pattern type between on the one hand those with autism and schizophrenia, and on the other hand those who were normal controls. So yes, there *was* an unusually high concentration of peptides in the blood and urine of these schizophrenic and autistic patients.

They also found that more than 85% of all autism and schizophrenia sufferers had greatly enhanced IgG antibodies to casein and gluten. IgG antibodies are part of the body's immune system. The greatly enhanced sensitivity of these antibodies to gluten and casein in autism and schizophrenia sufferers strongly suggests that the body is trying to fight something related to these peptides.

Perhaps the most interesting data relate to what happened when autism sufferers were placed on a diet free of any casein and gluten. Of 70 autistic children ingesting a gluten-free casein-free (GFCF) diet, and who were followed for one to eight years, 81% improved significantly within three months on a range of scores such as social isolation, eye contact, mutism, learning skills, hyperactivity, stereotypal activity, panic attacks and self-mutilation. Of the 13 children who did not improve, five continued to excrete high levels of casomorphins and gliadomorphins, suggesting they may not have been following the prescribed diet.

For schizophrenia sufferers the success rate was only 40%. A major problem here was that most of those who did not respond quickly subsequently failed to stick with the diet. And this is one of the key problems with GFCF diets: the response is not immediate and in the first few weeks it may in fact be quite negative owing to opioid withdrawal symptoms. However, for those who do persist and get a positive response, the improvement is ongoing for at least 12 months. It seems that it may take at least that long to get all of the BCM7 off the opiate receptors in the brain. Those who then go off the diet typically regress.

Another important paper published in *Nutritional Neuroscience* the following year (2001) was by the Norwegians Ann-Mari Knivsberg, Kalle Reichelt and M. Nodland. They summarised a series of trials and dietary interventions that they had undertaken with autism sufferers over a period of 12 years. Their data included both groups and individuals. They concluded:

> People with autism are as different from each other as people without development disorders are. Dietary intervention is no cure that can remove all autistic traits in all children with autism. There can be no doubt, though, that the vast majority of the participants described were more harmonious, more social, communicative and capable of using his or her skills in a better way than before the diet was implemented. The reports thus should form a solid basis for further investigations on the effect of dietary intervention in autism.

Ann-Mari Knivsberg and Kalle Reichelt have continued to publish regularly, sometimes with co-authors. In 2002 they published a paper in *Nutritional Neuroscience* titled 'A Randomised, Controlled Study of Dietary Intervention in Autistic Syndromes'.[2] In the abstract they stated that 'A randomly selected diet and control group with 10 children in each group participated. Observations and tests were done before and after a period of one year. The development for the group of children on diet was significantly better than for the controls.'

This trial was 'investigator-blind', meaning that although the parents of the children knew the type of diet their child was on, the investigators who were taking the measurements did not know. Currently this appears to be the only trial of the GFCF diet that has involved a control group and has been investigator-blind.[3]

A major challenge with investigating the GFCF diet is to meet the desired scientific standard of 'double blind'. One suggested approach is to have both the trial group and the control group (both of which would comprise autistic children) on a GFCF diet, and then for each group to be given a supplement that was either free of casein and gluten, or rich in these proteins. A variation on this is to use the 'crossover' approach, where halfway through the trial the GFCF group shifts to the casein-and-gluten supplement and vice-versa. Once again, the only people who would know who is getting which supplement would be scientists who are totally independent from the trial except for holding the diet codes. This protocol has recently been tested for a 12-week period (6 weeks plus 6 weeks) on 15 children, 12 of whom completed the test.[4] But to get meaningful results the trial would need much larger numbers of children and to be conducted for much longer, because of the time taken for the opioid peptides to be eliminated from the brain and for measurable impacts on development to show up. As of April 2007 a group from University of Rochester Medical Centre, New York, was recruiting for a similar preliminary trial with 30 children.[6] Yet another group from the University of Pittsburgh has a similar trial planned using 80 children, but for the longer time of three months per treatment.[5] Even then, the Pittsburgh team describe its work as only phase 1. It says that 'Phase 1 data will be used to obtain funding for double-blind trials (phase 2) and the study of neurobiological mechanisms underlying improvement in symptoms (phase 3).' Hopefully, the three month treatment will be long enough to identify any changes that are occurring, but it is still a short time period given the findings of Cade and his colleagues.

So it is going to be a long time before there are any results from GFCF diets that classically trained scientists who demand controls and double-blinding might regard as proof. And there are still likely to be many challenges along the way with children dropping out of these artificial diets. Most drug companies, which are working with products like pills that are logistically much simpler than a whole diet, base their plans on the assumption that it takes at least 10 years to get a new product to market after the first promising results are obtained. So it could well take as long or longer to get conclusive results from the GFCF diets.

In the absence of proof from double-blind diet trials it is inevitable that there should be a focus on individual case studies and anecdotal reports. In fact there are many thousands of people who follow the GFCF diet. American scientists George Christison and Kristin Ivany have noted that in 2005 there were nine discussion groups on yahoo.com alone devoted primarily to this topic, with a combined membership of over 10,000.[7] Also, they say that the website gfcfdiet.com supports 180 'Autism and GFCF Diet' support groups in the USA alone.

Some scientists tend to be very critical of case histories and observational reports on the grounds that they are anecdotal and hence do not have the controls that rigorous scientific research regards as so important. Undoubtedly, some believers will be influenced by wishful thinking and not all such 'evidence' will be valid. Nevertheless, I have chosen to quote from one of them because they provide information about the fabric of decisions that every parent of an autistic child has to make. There are numerous such reports posted on the web, but I have chosen to quote here from the website of Jorgen Klaveness, a Norwegian lawyer. There is something particularly moving about the way that he writes:

> When my son was 18 months old, he started to slip away from us. He was diagnosed with a 'brain disorder', later he got the 'autistic label'. Those of you who have been through the same process know what he went through.
>
> At a certain stage, we stopped wondering if something was wrong with our child, and started looking for what we could do for him. We stopped being afraid that he might be an idiot, and started marvelling at the way the little chap was, in his own way, struggling along with his enormous problem.
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> When he was eight years old, we heard about the GFCF diet. We're lucky to live in Norway, close to one of the foremost research centres in the world, and to Dr Karl Ludvig Reichelt ... After a short trial period, we've never looked back without shuddering at the idea of what would have happened if we hadn't met Dr Reichelt ... We've never got 'back' the son we hoped for initially; he'll never be able to make up for all that he lost during his first eight years. But his entire life has been taken up in a new direction. He's able to learn again. He has learnt to speak. He plays with other children. He's become toilet trained. He has developed a strong sense of humour and a genuine attachment to us. He means something for us and we mean something for him. We're connected ...
>
> I want as many as possible of the world's autistic children to have

> the chance that my son got when he was eight. I also want as many of them as possible to get the chance that he didn't get when he was two.

Klaveness also wrote about the problems of getting repeated double-blind crossover experiments of the type that are generally accepted as scientific proof:

> That kind of proof isn't likely to appear in the next few years either. The experiment would be costly and very time consuming, and the treatment is relatively simple, cheap, and available without a prescription. Nobody is going to make money out of it, and therefore too little research is likely to go into it.

Perhaps Klaveness was not quite right when he said the treatment was simple. Many people find that sticking to a diet free of gluten and casein is in fact very difficult. Not only is there ongoing temptation to give in, but there are many foods that must be avoided and many hidden sources of gluten and casein. Klaveness himself reports how his child for a long time continued to have an intake of gluten from supposedly gluten-free foods.

A further comment from Klaveness also seems relevant:

> As parents of autistic children, we don't need scientifically tested hawsers. We'll throw our children any piece of string or straw that offers hope. The GFCF diet is such an option. Our experience tells us that it will work for some. We believe that it will work for many. It is likely to work better the earlier you start.

Despite the lack of double-blind trials of a GFCF diet there is of course considerable scientific evidence relating to beta-casomorphins and autism. The associations that Cade, Sun, Reichelt and Shattock have all found between peptides in the urine and autism are hard to dismiss. However, other scientists using other methods have not as yet been able to replicate their results and so the methods remain controversial.[8]

So far in this chapter I have placed considerable focus on gluten and casein in combination. The human trials and dietary interventions that have been reported have in general not tried to separate one from the other. The justification for this has been the assumption that opioid peptides from both gluten and casein are being absorbed into the bloodstream, and then crossing the blood/brain barrier. However, it is now time to look more carefully at what we know about BCM7 independent of any combined effects with peptides from gluten. This work comes from animal trials.

Zhongjie Sun and Robert Cade undertook some very informative work where they injected BCM7 into rats. In one such trial, published in the journal *Autism* in 1999, they used BCM7 to investigate to which parts of the brain, if any, the BCM7 became attached. To measure the outcomes they had to euthanise the rats and dissect the brains. The answer they obtained was that the BCM7 became attached to areas of the brain that had 'been shown to be altered either functionally or anatomically in patients with schizophrenia, and most have been shown to be functionally abnormal in autism.' They concluded that BCM7 could cross the blood/brain barrier, activate opioid receptors and affect brain regions similar to those affected by schizophrenia and autism.

In another trial, also published in *Autism* in 1999, Sun and Cade injected normal rats with BCM7 to investigate their subsequent behaviour. Cade and his co-authors referred to this work in their *Nutritional Neuroscience* paper of 2000:

> Fifty seven seconds later the rats began running frantically, knashing their teeth and foaming at the mouth. They then became hostile and defensive, attacking their normal cage mate if it came near. Pain sensitivity was greatly decreased, a finding occurring frequently in many patients with autism and schizophrenia. They also paid no attention when a bell was rung over their cage while normal rats invariably looked up for the source of the sound. This is of interest because mothers of children with autism frequently think their child is deaf.

Sun and Cade reported in the journal *Peptides* in 2003 that in normal rats, gliadorphin (GD7), the major opioid in gluten, affected only three regions of the brain, while BCM7 affected 45. Also, they demonstrated that the mechanism by which GD7 gained access to brain cells was by 'diffusion through circumventricular organs', while BCM7 passed the blood/brain barrier by 'carrier facilitation'.

In other words, the GD7 can only get into a few bits of the brain by sneaking through the bushes whereas BCM7 drives straight up the highway and goes wherever it wants to. Also, they noted that BCM7 caused 'bizarre behavior changes' whereas GD7 caused no behavioural change.

Earlier in this book I explained how the milk devil BCM7 is released on digestion of A1 beta-casein but not from A2 beta-casein. It is now time to look at what happens in relation to autism and schizophrenia when people consume A2 rather than A1 milk.

Back in 2001 the New Zealand Dairy Research Institute (NZDRI), at that stage still part of the NZ Dairy Board but about to become part of Fonterra, the world's largest international trader of dairy products, applied for a patent concerning A1 beta-casein, autism and schizophrenia.[9] The patent application was titled 'Milk containing beta-casein with proline at position 67 does not aggravate neurological disorders'. In plain language that means A2 milk does not aggravate mental health disorders. The Abstract then says:

> The invention is based on the discovery that the consumption of milk which contains a beta-casein variant which has histidine or any other amino acid not proline at position 67, may on digestion cause the release of an opioid which may induce or aggravate a neurological/mental disorder such as autism or Asperger's syndrome. The invention is supplying milk or milk products that contain beta-casein with proline at position 67 to susceptible individuals.

In other words the NZDRI was claiming that ordinary milk containing A1 beta-casein caused or aggravated mental disorders such as autism, and that susceptible individuals should consume only A2 milk. The five inventors were listed as Robert Crawford, Michael Boland, Carmen Norris, Jeremy Hill and Robin Fenwick. Readers may remember some of these names from earlier chapters of this book. But what a bombshell!

The evidence they produced in support had four parts to it. One was theoretical, in relation to the opioid characteristics of BCM7. This was well known and not controversial, and in itself was not patentable. The second part was that BCM7 was released from A1 beta-casein (and other variants not having proline at position 67) but not from A2. This also was confirmatory rather than new, as it had previously been reported from both German and Japanese laboratories. Whereas the German and Japanese papers were unequivocal on this matter, the NZDRI patent application was not quite so sure, and said:

> The levels of BCM7 measured in hydrolysis of A2 casein were far less than that measured in the hydrolysis of A1 casein. It is difficult to tell, however, due to the presence of small quantities of A1 casein in the A2 casein, whether the BCM7 was formed from the hydrolysis of the A2 casein or to a small amount of A1 casein contaminant, or both. If BCM7 was formed from the hydrolysis of A2 casein, the rate of reaction was many orders of magnitude less than that observed with the hydrolysis of A1 casein.

My bet is that the small release apparent from A2 casein was indeed due to A1 contamination, and that the German and Japanese scientists got it right. It is frustrating that so many of the A2 diets manufactured by NZDRI seem to have been contaminated.

The third part of the evidence was a trial with autistic and non-autistic (control) children aged 6–18 years. Some autistic children were given A2 milk after overnight fasting and then showed low levels of casomorphins in their urine, while others given A1 milk showed up to a 10-fold increase in casomorphins. For normal children (age-matched controls) there was no such increase. This was consistent with results obtained by Cade, Reichelt and Shattock, but it was also new in that this was the first time that A1 and A2 beta-casein had been compared directly.

The fourth part, which was totally new, was the epidemiology. The NZDRI team was able to find 10 developed countries for which there was both satisfactory information on A1 beta-casein intake and data on death rates attributable to mental disorders. The countries were Australia, Canada, Denmark, Finland, Germany, Iceland, New Zealand, Norway, Sweden, and the USA (data from San Diego). The source of death-rate data was the WHO.

The results were staggering! They found that 63% of the between-country variation in deaths from mental conditions can be explained statistically by differences in the intake of A1 beta-casein. The probability of getting a result like this by chance is 0.006 (less than one in 160). In contrast the relationship between A2 beta-casein intake and deaths from mental disease was negative but not statistically significant. This means it would not be valid to claim that A2 is actually protective, but rather that it has no proven influence either way.

The NZDRI team re-ran the analysis with Iceland excluded, on the grounds that Iceland had a low incidence of mental disease and presumably looked as though it might be anomalous despite also having milk that is low in A1 beta-casein. But this produced an even higher correlation between A1 intake and mental disease. The NZDRI team also separated out males and females but this provided no new insights, with similar outcomes for both sexes.

So how should we interpret these results? We cannot say with absolute certainty that A1 beta-casein causes deaths from mental illness, because we can never get absolute proof from any correlation. But we can say that the probability of getting a result like this through chance is highly unlikely. It is an amazing result.

These results have never been published in the scientific literature. In fact it wasn't too long before the NZDRI, now part of Fonterra, abandoned the patent application. The reasons subsequently reported in the news media were that they had undertaken follow-up trials with autistic children and were no longer able to obtain the BCM7 peaks in the urine. However, the truth would seem to be not quite that simple.

I did my own little bit of exploration in regard to those subsequent trials and managed to track down one of the scientific investigators involved in them. He was happy to explain the situation to me on the telephone. My file notes from that conversation (in August 2004) state that the trial involved 18 autistics and 18 non-autistics who were age-matched. The trial was a double-blind crossover trial in which participants were fed milk (either 'ordinary', i.e. mixed A1 and A2, or straight A2) and urine samples were collected four hours later. The crossover took place four weeks later. Each sample was then split in two, of which one was analysed at Auckland University and the other at NZDRI in Palmerston North. The analyses showed 'lots of noise in the system, with not only high variance but inconsistent results from split samples'. Whoops! Inconsistent results from split samples meant the analysts in Auckland were getting different results from those in Palmerston North for exactly the same sample. Something was wrong with the testing procedures and so the whole trial had to be abandoned. But that is quite different to saying there were no differences between the autistics and non-autistics.

There are a number of reasons why this trial might have gone astray, but an obvious contributing factor is poor technique in at least one laboratory. As explained in Chapter 7, BCM7 is tricky to analyse for. There may also have been other flaws, including A1 and A2 contamination.

Some other A2 diets supplied by NZDRI around that time are known to have been contaminated with A1 beta-casein, including the samples used for digestion trials of the release of BCM7 in human subjects. Another example of this was presented in Chapter 4. Alternatively, the equipment may not have been properly set up and calibrated in at least one of the labs. But we will never know. The trial was buried and Fonterra abandoned the patent.

But what about the epidemiology? Presumably those results still stand? The scientists couldn't just make up the analyses, and the applicants for the patent would have had to sign documents stating that the application was based on truthful knowledge. The answer is indeed yes, those results do stand. So we cannot simply ignore them and pretend they do not exist. They have not been repudiated.

I have gone back to the WHO databases and undertaken some preliminary correlation analyses, which confirm that statistically significant relationships do exist, although for the year that I investigated (2000) the relationships were not as strong as those found by the NZDRI scientists. The relationship also holds with a larger sample of countries, using the Laugesen and Elliott A1 beta-casein consumption data. But just how we should interpret these results is problematic. For a start, the NZDRI calculations (and my own) were quite crude. If a country has a low birth rate compared to other countries, its overall death rate will be higher simply because old people make up a larger part of the population. (This is why people such as Murray Laugesen and Bob Elliott, and also Corran McLachlan, use age-related rates, such as the death rate in a particular age class.) Did this create a bias? Perhaps. This sort of bias usually creates a meaningless picture (a 'fog') rather than a deceptive one (a 'mirage'). Also, people who suffer from diseases such as schizophrenia do not necessarily die directly from it. So how reliable are these statistics? There is no simple answer to this and related questions. All we can say is that even if we cannot understand and readily explain such results we should be cautious of rejecting them as supposedly due to random factors, given their statistical significance. Ignoring results that we do not like and do not understand is quite common, but it is not good science.

So here we have yet another area of research that needs to be followed up.

While pondering on these issues I decided to explore the recorded causes of death of people suffering from schizophrenia. The answers were fascinating. There have been quite a few studies done and they all seem to show broadly similar results. Schizophrenia sufferers not only have significantly increased death rates from suicide (which in previously identified schizophrenics are likely to be recorded as due to schizophrenia), but they also have considerably increased death rates from natural causes, especially cardiovascular disease (more than twice the rate).

What is this saying to us? Can it be explained by the lifestyle these people lead? Or is it linked to a leaky gut? If schizophrenics do indeed typically have a leaky gut leading to BCM7 passing through into their bloodstream (and the evidence from Cade, Sun, Reichelt and Shattock seems to be compelling on that) could this explain, in line with the evidence of Chapters 3 and 4, why they would also have increased deaths from cardiovascular disease? There is certainly lots to think about!

New pieces of the jigsaw puzzle continue to be found, although deciding where they fit into the big picture can be problematic. For example, in 2006 Kalle Reichelt and O. Skjeidal reported in the journal *Autism* that IgA antibodies to casein have been found in girls with Rett syndrome.[10] They stated their analyses on 23 sufferers were statistically 'highly significant' in comparison to 53 normal persons used as controls.

Rett syndrome is a serious neuro-developmental disorder caused by a genetic mutation. Reichelt and Skjeidal suggest that their results indicate increased peptide uptake from the intestines by people with this syndrome. The implications of this are that although the fundamental problem is genetic, one of the outcomes may be increased permeability of the intestines (leaky gut) which in turn leads to increased uptake of peptides from gluten and casein. This then causes or exacerbates some of the neurological symptoms. Other studies have shown that gastrointestinal disorders are indeed very common in people with Rett syndrome.

Another piece recently fitted into the puzzle is a 2006 paper in a Norwegian journal by E. Sponheim and colleagues, including Reichelt.[11] They found in a small group of high-functioning autistics that only three out of 17 had abnormal peptides in the urine (compared to no abnormal peptide levels in healthy unrelated controls). This contrasts with the much higher levels of abnormality that Cade, Reichelt and Shattock found for more seriously affected autistics.

The big picture

It is now time to summarise the big picture in relation to autism and schizophrenia. It is apparent that many autistics and schizophrenics excrete abnormally high levels of BCM7 and other similar peptides in their urine. This declines markedly when these people are placed on a gluten-free and casein-free diet. The investigations by teams led by Cade, Reichelt and Shattock in three different countries confirm this.

We also know that BCM7 is released by the digestion of A1 beta-casein, but is either not released at all, or only in tiny amounts, from A2 beta-casein.

Numerous investigations show that eliminating casein and gluten from the diet leads to a marked improvement in the symptoms of autism. Once again Cade, Reichelt and Shattock stand to the fore, together with Reichelt's colleague Ann-Mari Knivsberg. However, none of these medium- to long-term trials has been undertaken using double-blind protocols. Such trials are exceptionally difficult to conduct, but several are being planned. There is one published trial with significant results where the investigators were blind, and several other trials where they were not.

We also know that when BCM7 is injected into rats it causes them to act in a bizarre fashion, with many symptoms that resemble autism. Also, that the BCM7 enters many areas of the brain that are linked to autism, whereas similar peptides from gluten cannot access most of these areas.

We know that many thousands of parents of autistic children use a GFCF diet and believe it has benefits, but we also know that individual case studies such as this are not necessarily reliable.

We also have unsolicited testimonials supplied to A2 Corporation by parents of autistic children who have been given A2 milk. These parents believe their children are better on A2 milk than ordinary milk.[12] Once again, these are only observational case histories that lack controls. However, these results seem plausible, in that we know there is unlikely to be a release of BCM7 from A2 milk.

There are also other pieces to the puzzle, such as the unpublished epidemiological results obtained by Fonterra's scientists, and the published finding of elevated casein antibody levels in Rett syndrome sufferers. Just where these pieces of evidence fit into the overall picture, or whether they do have a place, is yet to be determined.

In the final analysis, readers will have to make up their own minds whether the overall story is convincing.

A final issue to consider and clarify is whether opioids such as those from beta-casein and gluten are causing the *syndromes* of autism and schizophrenia or whether they are causing or exacerbating the *symptoms* of these syndromes. The syndrome, or underlying condition, may well be genetic in origin, with only some human genotypes being susceptible. However, the symptoms either only appear, or else are greatly exacerbated, when BCM7 is absorbed into the bloodstream through the intestines and then manages to get across into the brain. So although the opioids may not be the fundamental problem, they do irreversible damage in susceptible people. That is why people like Jorgen Klaveness talk of the importance of an early start with dietary intervention.

NOTES

1 *New Scientist* v158.n2139(June 20, 1998); pp42–45.

2 See Knivsberg *et al* (2002) in Autism and Schizophrenia section of Bibliography.

3 A detailed review of existing scientific studies of the GFCF diet is provided in Christison and Ivany (2006). See Autism and Schizophrenia section of Bibliography.

4 See Elder *et al* (2006) in Autism and Schizophrenia section of Bibliography.

5 See U.S. National Institutes of Health clinical trials database, www.clinical trials.gov/ct/show/NCT100090428?order=1. Accessed 25 April 2007.

6 Accessed from the UCLID Centre of the University of Pittsburgh website. www.uclid.org:8080/uclid/re_autism.html. Accessed 25 April 2007.

7 See Christison and Ivany (2006) in Autism and Schizophrenia section of Bibliography.

8 See Dettmer *et al* (2007) in Autism and Schizophrenia section of bibliography. This paper reports an inability to find these urinary peptides using an online HPLC method. However, other scientists are questioning this methodology.

9 The patent application number under the International Patent Application Treaty is WO 02/19831 A1 and is dated 14 March 2002. The application also carries the earlier NZ identifier of PCT/NZ01/00186.

10 See Reichelt and Skjeidal (2006) in Austism and Schizophrenia section of Bibliography.

11 See Sponheim *et al* (2006) in Autism and Schizophrenia section of Bibliography.

12 See A2 Corporation website, www.a2corporation.com