- *Neurotransmitter accumulation:* Another pathway to addiction is to inhibit the destruction of the feel-good neurotransmitters. These then accumulate, producing a heightened sense of well-being. This is how cocaine works and, some might say, the SSRIs and SNRIs also.
- *Up-regulation:* Stimulating the body's own production of a particular neurotransmitter can also lead to addiction. Amphetamines are in this category, increasing the output of nor-adrenalin, and its precursor dopamine, a major feel-good neurotransmitter. These neurotransmitters are associated with focus and a heightened sense of purpose. Nicotine acts at one of the receptor sites for acetylcholine. Although acetylcholine can work at several receptor sites, nicotine works at just one of these. What happens after that has yet to be elucidated, but it is generally thought that the release of dopamine is increased, or that there is heightened sensitivity to this chemical.

Whether psychoactive drugs are addictive or not, they interfere with the chemistry of a complicated system and raise the spectre of iatrogenic illness in the immature brain. This is why a sense of outrage at these developments is understandable.

Adult sleep disorders

Sleep disorders are one of the commonest problems seen by general practitioners. Patients typically see themselves as having a medical condition, a fixed-name disease: they say things like 'I've got insomnia', or maybe 'I can't sleep, doc. Could I have depression/sleep apnoea?'

Of course, all possibilities need to be considered. If the doctor replies, 'Yes, I think you are depressed, here's a script for some anti-depressants', the patient might reasonably ask if something else could be tried. But if the doctor were to say, 'I think you have a disruption of your circadian rhythms, and I want you to change your job and get a whole new lifestyle', would the patient opt for the anti-depressants after all?

Circadian rhythms are discussed in Chapter 10, but let us look for the moment at the contrasting lifestyle of a representative of our earliest ancestors. Let us call him Otto. How will he prepare for sleep?

To begin with, he will probably have eaten two meals that day, as dictated by his biological hunger clock (Chapters 8 and 10). The evening meal is prepared around dusk, and is eaten as the light fades. As the meal is digested, there may be storytelling and music around a campfire. The scene is peaceful. And the biochemistry?

Otto is sitting down to eat, a fact which gives his digestive processes a head start on his counterpart in the 21st century. He will not leap up and rush out to a meeting, except in the unlikely event of enemy attack. Thus the opiate-like peptides and neuroactive amines in his food will undergo full digestion to amino acids. These amino acids will help, not hinder, his ability to sleep.

As daylight fades his pineal gland starts to produce melatonin. He has adequate precursors for this in his diet. Vitamins and minerals will be available to catalyse the amino acid tryptophan through serotonin to melatonin (Chart 3.3). By the time the light has gone altogether, he is already becoming sleepy, but not through drugs, alcohol or sugar. These things produce 'dopiness' rather than healthy somnolence. Otto is sleepy because has been physically active during the day, and now has an abundance of circulating melatonin.

As he watches the embers of the fire, the flickering induces alpha wave patterns in his brain. Alpha waves are the slow waves associated with relaxation in the conscious state. (Watching television can also produce alpha waves. Do people become addicted to television because the ancient part of their brain is hungering for the flickering pattern of the fire? This whimsical thought has been the subject of serious consideration.)

Otto's modern counterpart could not conduct his evening more differently if he tried. Let us take the case of John, whom we met in Chapter 6. At dusk he may just be coming home from work. He gives Junior a quick cuddle, eats a rushed meal and heads off to a meeting. On a quiet night he spends a bit more time with Junior, eats with Jean, and goes to his study to do several hours more work. There's an important deadline to meet. His focus on the office problems puts his brain into a state of high alert. He may drink tea, coffee or some other stimulant to keep himself going. He is on a proton pump inhibitor to deal with his irritable bowel and associated digestive disorder. Fatigue is one of the side effects of this drug, but its not the sort of fatigue conducive to sound REM sleep. John sleeps but awakes unrefreshed.

Perhaps the person who comes closest to his caveman ancestor is Fred, slumped in front of the television. At least he has a few alpha waves on his side. On the other hand, if he has a coffee or a beer in his hand, his sleep will not be normal. Fred, like most people, has noticed that his sleep problems are worse if he drinks coffee at night. He prefers a beer. However, while this helps him to nod off, he often finds himself awake several hours later.

Maybe this is due to the two-phase action of alcohol. Sedation is the initial response of the brain but a few hours later, depending on how much alcohol has been consumed, there may be a phase of excitation. Unfortunately, this stage is often reached just when deep REM sleep should be cutting in.

What about melatonin? John has recently read an article in the paper about it. Should you be able to buy it over the counter, as you can in the United States and Britain? Melatonin is a natural, and therefore, presumably, safe product. It may help John sleep, but will it fix his gut problems, his chronic stress? Will it help his relationship with Jean or with Junior? Perhaps his insomnia is a timely warning to look at his lifestyle, his diet, his priorities, before he joins the ranks of those with premature heart disease and his marriage becomes just another statistic.

Sleep disorders in infants and young children

Cot death

Cot death is, of course, a tragedy rather than a disorder, but it is convenient to group it here with other disturbances of sleep. Putting a baby to sleep on its back has reduced the risk enormously. However, babies still die from this condition. What other factors influence risk?

We might expect that cot death would appear in cultural myths and ancient texts, but mentions are so infrequent that we can infer that this is predominantly a disease of civilisation. Cot death seems commoner in the babies of smokers than in babies from non-smoking households. It is commoner in bottle-fed than breast-fed babies. It is also more common in developed and affluent societies than in crowded, poor communities. Over the years, several interesting theories have emerged.

One is that the combination of urine and PVC mattresses produces toxic fumes. Such mattresses did not exist until the last half of the 20th century. Maybe sleeping face up provides air circulation to dissipate the fumes.

Another theory is 'forgetting to breathe'. The idea is that a human baby at birth is an embryonic life form. This is the price of our big brains; a larger head could not navigate the birth canal. Perhaps this 'embryo' has not fully developed its 'automatic breathe' function. In sleep, breathing may slow so much that, unless it is kick-started, it may cease altogether. In a 'natural' environment, it is argued, the sounds or movements of parents in the same bed or siblings in the same room will serve to start it. Some studies have shown that infants who sleep in their parents' bed have an increased risk of cot death. Other studies show that this applies only when the parents are smokers; once smoking was factored out, co-sleeping appeared to be protective.[22]

Bottle feeding is thought to contribute to cot death in one of at least three ways:

- Plastic bottles when heated emit toxic PVC fumes, a risk which is increased when these containers are microwaved.
- Cow's milk lacks some essential nutrients and immune globulins, normally found in breast milk.
- The clinical picture of cot death resembles death by anaphylaxis (allergic shock), raising the possibility that the babies die as a result of anaphylactic shock in response to bovine protein in cow's milk.

Even the hygiene theory (Chapter 6) has been raised. Independent of the role of vaccination, an immune system not matured by the exposure to common germs may be at increased risk from some of these factors.

It is easy to see how one medical problem can have a complexity of possible contributing factors. Unravelling these can be impossible. This is the weakness of single-cause theories for fixed-name disorders. The example also shows the many ways in which deviation from simple lifestyles might contribute to the medical problems most commonly feared in 'civilised' cultures.

Unremitting and relentless infant crying

Family doctors often see babies that cry excessively. This is associated with post-natal depression (cause or effect?), and there is a real risk that a despairing parent may injure the baby.

Locked in her hermetically sealed modern home, alone with her newborn, the mother relates with anguish the stories of a baby who simply won't stop crying.

These mothers often say that the only thing that pacifies the baby is to put it in a pram and wheel it into the street.

What is more natural — the 'white noise' generated by street sounds, the continuous movement of the pram on the pavement, or the deathly stillness of the lonely cot without sound or movement? Babies are primed by nine months of movement and the rhythmic sound of a heartbeat, not to mention thousands of years of human evolution, to sleep through noise, activity and human presence. Perhaps they are screaming in panic at the bizarre situation they find themselves in.

If post-natal depression is linked to the crying, what clue might this give? One possibility is neglect by a depressed mother, and her depression may be the result of deficiencies in zinc, magnesium and essential fatty acids. But if the mother is deficient, there's a good chance that the baby is as well. This will lead to poor sleep, a twitchy nervous system, an irritable infant. Forget the psychology for a moment — this may be a biochemical disorder.

Even in babies whose mothers do not show clinical depression, a marginal deficiency may be enough to trigger a state of chronic irritability. If this seems fanciful to the reader, I offer the personal experience of seeing babies settle miraculously when a breast-feeding mother is supplemented with B-group vitamins, zinc and magnesium.

Summary

Both bedwetting and night terrors show a genetic predisposition, but both are also subject to the considerations just explored. It would be interesting to know whether they are prevalent in tribal settings. Avoiding food allergens and supplementing with essential nutrients has produced promising results in my experience.

Maturation of the central nervous system requires the B-group vitamins, zinc, selenium, essential fatty acids. Magnesium is important in neurotransmission. We know that omega-3 fatty acids concentrate in breast milk, so they must be important. We know the changing status of magnesium, selenium and zinc in the diet. Poor sleep affects not only the child, but the whole family.

Ask whether the department of paediatrics at the university nearest to you is studying these questions. If not, why not?

NEUROLOGICAL DISORDERS

Any disorder which afflicts the brain or the central or peripheral nervous system can be classified as neurological. As with any other organ or organ system, dysfunction can arise in multiple ways. Some conditions are genetic, although these are relatively rare. Some are caused by illnesses such as meningitis and encephalitis. Toxic chemicals and ionising radiation can cause DNA damage, resulting in malignancies. And poor blood supply due to diabetes and vascular disease can cause nerve damage (neuropathies) and brain injury (stroke).

It is hard to do more than generalise. And yet, in terms of prevention and treatment, generalising may be the most valuable thing we can do. I will look briefly at just four neurological disorders: Alzheimer's disease, multiple sclerosis, Parkinson's disease, migraine.

Alzheimer's disease

Dementia refers to loss of brain function, and can be due to many causes. Brains damaged by alcohol, accidents, birth injury or vascular disease can all produce cognitive and emotional responses which could be recognised as 'demented'.

Alzheimer's is in some ways the left-over category. In this condition there is no obvious injury or neglect, just a brain losing its higher functions. Further subdivision recognises that some forms of Alzheimer's can strike at an early age, or they may have a hereditary component, as with the dementia associated with a particular allele of one of the lipid-carrying proteins known as apo E (Chapter 8). This variant can be associated with both sporadic and with late-onset familial cases, but is not considered to be sufficiently predictive to be used as a screening tool.

A link between Alzheimer's, untreated coeliac disease and Down syndrome raises the fascinating question of gluten sensitivity and the brain (compare gluten and autism above). Another aspect of this linkage will be mentioned shortly.

Let's return to our 'typical' family.

Fran's mum, Mary's grandmother, is called Sarah. She is in her early 70s, and since her husband Edward died a few years ago she has been depressed, sleeps badly, and is not eating very well. Her memory recently has been so poor that the family has begun to worry about her. Her skin is dry, and she does not look well. Is she suffering from depression? Or does she have early dementia?

When she begins to have 'accidents' on her way to the toilet, a geriatrics team decides she needs residential care. This is difficult for her and the family, but is felt to be for the best. Sarah's signs of dementia were at first thought to be due to depression. There is, indeed, much overlap between the two conditions—sleep disturbance, lack of interest in food and, of course, short-term memory problems.

But the either-or nature of this question, depression or Alzheimer's, shows how easy it is to fall into the traps of diagnostic categories. Sarah may well have suffered from depression after Edward's death, considering that she and Edward had almost never spent a day apart in the past 50 years.

Sarah found that, once she was cooking only for herself, she now lacked the motivation to make the meat and three vegetables which had been the mainstay of their meals; soon, an egg on toast was enough. Gradually, except for the once or twice a week that she ate at Fran's, the egg was left out, and it became just tea and toast. Fish on Friday had been a ritual, but now it was too much trouble. Fran tried to keep an eye on things, but she didn't see what got thrown out. Sarah had always been rather independent. Fran felt she was intruding.

After the 'accidents' become obvious, Fran accompanied Sarah to a routine doctor's visit. The question of bowel problems was broached with a very defensive Sarah. Was there a bowel infection or, worse still, a bowel cancer? Thyrotoxicosis (an over-active thyroid gland) can cause diarrhoea, but the tests were negative. Pellagra was not on the list of possibilities.

Pellagra, or classical Vitamin B3 deficiency, was discussed in Chapter 5 as part of the three Ds: dementia, diarrhoea and dermatitis. Does this sound like Sarah? Could a Third World disease really exist in the midst of plenty? Sarah has been well looked after, taking diuretics for hypertension, anti-depressants since Edward died, and a mild sedative for sleep. She has had something to lower her cholesterol (a disorder that responds to Vitamin B3), something to 'firm up' her bowel, and a variety of skin lotions. Now the geriatricians are talking about a (very expensive) drug called Aricept.

Aricept is described as a 'gift' by its promoters, although it is one of the most expensive drugs on the market. Along with cholesterol-lowering drugs and a few other medications, Aricept helps blow out health budgets throughout the Western world. And yet the summary by clinicians of the efficacy of this drug, subsidised by the government, is 'disappointing'. At best, it delays the progression of dementia by about six months.

If the doctor prescribes selenium, Vitamin B3 or B12, who will pay? The pensioner medical benefits do not as a rule cover vitamins and minerals.

If we take the view that fixed-name disease treats symptoms not causes, Sarah demonstrates many missed opportunities here. First there was her depression. Loss of appetite is common in depression and also during mourning. Perhaps a vicious cycle set in. Zinc deficiency is a recognised problem in the elderly.[23] Low zinc levels in turn produce anorexia. As tea and toast becomes the mainstay, a cycle of vitamin and mineral deficiencies is set in train. This in turn leads to sleep disturbance and deepening depression. After all, the production of serotonin, melatonin and dopamine all depend on a range of enzymes, which require Vitamin B6, B12 and folic acid (Chart 3.3).

Then there were Sarah's other medical problems. After Edward had his first heart attack, Sarah had testing that showed mild hypertension, raised cholesterol, and raised homocysteine. The diuretic for her hypertension removes not only sodium from the body, but other valuable trace elements. The cholesterol-lowering drug produces gastro-intestinal disturbance as well as many other side effects. Did this affect her appetite or contribute to her 'accidents'? And would it be churlish to mention that cholesterol has both structural and biochemical roles within the brain?

The fact of raised homocysteine was noted at the time, but no specific treatment was thought necessary. Now we know that raised homocysteine is associated with an increased risk of Alzheimer's, heart disease and cancer, and that folic acid and the B-group vitamins are the best way of bringing it down. Would a multi-B vitamin have slowed the onset of Sarah's dementia? Current evidence suggests that it would.

Here are the nutrients that are thought to benefit dementia and Alzheimer's: Vitamin C, Vitamin E, B-group vitamins, folic acid, zinc, magnesium, selenium, copper and omega-3 fatty acids.[24]

Here is a list of nutrients which are connected to the treatment of Sarah's other problems (again, not comprehensive). What does the overlap tell us?

- *hypertension:* omega-3 fatty acids, magnesium, Vitamin C, Vitamin E, zinc, selenium
- *raised cholesterol:* omega-3 fatty acids, Vitamin C, B-group vitamins, especially B3 and B5

- *depression:* B-group vitamins, zinc, selenium, omega-3 fatty acids, magnesium.[25]

So we can begin to make a case that, even before Edward died, Sarah's diet was subject to all the problems discussed throughout this book. After his death the limitations increased, and the brain began to pay the cost. Do we have any clinical evidence for this? There is one interesting bit of corroborative evidence.

The risk of dementia is known to be high in people with coeliac disease and in those with Down syndrome. Down syndrome, in turn, is strongly associated with coeliac. In coeliac disease, one of the earliest abnormalities is the malabsorption of vitamins, minerals, and fats. There is the tantalising thought that the link between coeliac and Alzheimer's, possibly even between Down syndrome and Alzheimer's, is not genetics but a nutrient deficiency (see also Chapter 10).

Multiple sclerosis (MS)

MS seems to correlate with the adoption of the Western diet, among other factors. It afflicts the young, and thus hurts people at the most productive time of their lives. (It usually makes its first appearance between the ages of 20 and 40, and rarely after the age of 50.) And finally, it appears to be on the increase throughout the world, even in cultures where it was relatively rare before.

Pathology

When one part of the body wants to 'talk' to another part of the body, it can do so in many ways, but most of them fall into one of two categories:

- chemical messengers, such as hormones and neurotransmitters, in the bloodstream
- electrical messages sent via nerves.

For rapid transmission, the nervous system is the most effective. We withdraw our hand from a hot stove before our brain has consciously registered that it is hot. We respond to pain even when we are asleep or in a coma. (The speed of response to pain is one way, in fact, of measuring the depth of coma.)

Nerves can transmit messages with such impressive speed because of the myelin sheath which is wrapped around nerve cells within the brain, the spinal cord, and the peripheral nervous system. The myelin sheath is like the insulation around electrical wiring. Electrical insulation is vital for protecting us from electrocution, but its primary purpose is to prevent leakage of electrical energy. Without insulation the signal would be delayed, severely weakened, or lost altogether.

MS results in patchy removal of the myelin sheaths of various nerve cells. Sometimes certain sheaths recover, only to have others succumb. Once the demyelination becomes permanent, the function of that nerve cell is effectively lost.

Theories about causes

MS has long been regarded as an autoimmune disease. As with most autoimmune diseases, there appears to be a genetic predisposition. Recently, there has been a challenge to the autoimmune theory,[26] and it will be interesting to see this line of inquiry unfold. But it is the identification of common factors in MS patients which has made it a fascinating subject for neurologists and epidemiologists alike.

From the earliest recognition of MS as an entity, it became apparent that there was a clear global variation according to latitude. In the northern and southern hemispheres there were typically 50–100 cases per 100,000 population, compared with 5–10 cases in the tropics. With this kind of distribution, and in the absence of an obvious causative agent, theories abounded. Suggestions included viruses, ethnic variance, geography, diet, and a lack of minerals and vitamins. Let us look at each of these.

The regional predictability typical of MS is commonly associated with a virus or a parasite such as malaria. Certain viruses have been shown to cause other demyelinating diseases, but with MS no such culprit was found. Many viruses have been suggested, most prominently measles and herpes, but these infections are not confined by latitude. Still, many feel that a virus may play at least some role in the illness.

With regard to ethnic variance, as so often happens, it was the exceptions which proved to be most interesting. Scots are by far the most vulnerable group, with an incidence of 153 per 100,000 in the Orkney and Shetland Islands. In Japan, where the latitude leads one to expect an intermediate incidence, the figure was just 2 per 100,000.

Racial and sex variations were also noted, in that Caucasians were more at risk than Asians, and Black races least of all. Caucasian women were found to be twice to three times as susceptible as Caucasian men. The disease is almost unknown in Australian Aboriginals, particularly those living most nearly the traditional lifestyle. But these racial variations still did not explain the latitude effects, or the exceptions.

Was it the Celtic gene? Many Scots and other Celts migrated to similarly cold climates. Did they simply take the gene with them? Were the victims of MS in *warmer* climates typically of Celtic origin? Some epidemiologists traced the movements of thousands of Scots who had migrated around the world, including Scots living in warm climates such as Australia. It seemed that moving from a low-risk area to a high-risk area made a difference *only* if the move was made before the age of 15. Whatever the detrimental effects of living in a risk zone, it appeared that they exerted their influence early in life.

So if we are looking for a single agent, we still do not have the answer. These are some of the other correlates:

- European diets may be classified as either 'beer and butter' or 'wine and oil', typical of Germany and Scandinavia and of Greece, Italy, Portugal respectively. The wine and oil food cultures confer a significantly lower risk of developing MS.
- Cultures which consume a diet based on dairy and gluten are associated with greater risk than those with a high rice and vegetable intake. In keeping with the autoimmune theory, these foods may be acting as antigens. However, it is also true that the dairy-gluten diet has more saturated fats. The role of dietary fats in MS will be discussed shortly.
- Minerals and vitamins, as we would expect, have a role to play. Another correlate which emerged was an association between thyroid problems and MS, and Parkinson's disease and MS. In this case, the link seemed to be iodine deficiency. Other studies showed that living in low-selenium areas increased the risk. Compared with a typical Western selenium intake of 30–50 mcg per day, the protection provided by a traditional Japanese diet (over 200 mcg) is not hard to grasp.
- Levels of Vitamin B12 have been implicated. Certain dietary, metabolic and digestive factors can lower B12 levels. Occasionally these can be

genetically determined, in which case cause and effect may be difficult to separate. Whatever the genetic picture, intramuscular injection of B12 in the form of methyl cobalamin can have dramatic benefit in acute flares.[27] My own experience of this has been very positive.

- Attention has recently focused on Vitamin D. Sun exposure may explain the latitude correlations, and this effect may also operate at high altitudes. In Switzerland it has been shown that the risk of MS decreases with increase of altitude, where ultraviolet radiation, necessary for the conversion of Vitamin D, increases.[28]
- The protective role of fish, in terms of its EFA content, is discussed shortly. Cold-water fish, such as sardines and herrings, are rich in Vitamin D.
- MS appears to be associated with heavy metal poisoning. Heavy metals such as lead and mercury have direct neurotoxic effects, and they also compete with desirable minerals like selenium by occupying the same receptor sites (Chapter 3: Chemistry).
- Chemical poisoning has also been implicated. Formaldehyde exposure has been linked to various neurological conditions, including MS. And studies comparing the blood of MS patients with that of controls have shown significant differences in the levels of toxic chlorinated pesticides, volatile aromatic hydrocarbons, volatile chlorinated hydrocarbons, and volatile aliphatic hydrocarbons. In one such study the MS patients had no less than 14 different intracellular minerals, including potassium, chromium, calcium and magnesium, which were abnormal, along with an overall deficiency of B-group vitamins. The epidemiologist concluded: 'All of these abnormalities suggest membrane damage, which is usually triggered by pollutants.'[29]

Membranes and essential fatty acids

How do these various findings fit in with the geographical distribution of MS? If membrane damage is a common factor, then the ability to *repair* damaged membranes becomes relevant. (Membrane physiology was discussed in Chapter 5: EFAs.) What dietary influences are peculiar to high-risk and low-risk areas?

Overall, dietary fat seems to emerge as one of the most important factors in the vulnerability to MS. This is not surprising, as between 70 and 80 per cent of the myelin sheath is composed of fat. Dietary lipids are directly incorporated into lipid membranes. In Norway, Scotland and other high-risk countries, the level of risk in genetically-close groups is closely linked to the amount of fish consumed.

EFAs help to keep the structure of the membrane healthy, but they also have functions which go beyond scaffolding. The omega-3s are necessary to the biochemical elongation of other fats integral to the structure of normal myelin. Deficiency of omega-3 interferes with that, independent of the structural role of the omega-3 itself.

Omega-3s also control the production of inflammatory prostaglandins. Saturated fats and those EFAs which end up as arachidonic acid, all promote inflammatory pathways (Chart 5.3). MS is certainly an inflammatory disease. Hence the benefits of steroids in acute flares.

The functions of omega-3s have been discussed in Chapter 5 and do not need repetition, but two important points are:

- EFAs are significant in modifying any potential for autoimmune disease.
- EFAs help to determine how the genetic code is read.

These points may have a bearing on the age of migration and its effect on susceptibility to MS.

So what implications are there in EFA consumption and the prevalence of MS at extreme latitudes? Many of these nations eat a lot of cold-water fish. Certain racial groups are more vulnerable, and the fairer the skin, the weaker the resistance. Perhaps the groups whose diets naturally contain cold-water fish, those in the higher latitudes whose skin is naturally fair, somehow genetically have less tolerance of omega-3 deprivation?

Many of the plants which are naturally rich in omega-3s come from cold climates. This makes sense. Omega-3s, with their anti-freeze function, are protective against cold. With fish, flaxseeds, walnuts, algae and leafy greens, those who evolved with this kind of diet would rarely have lacked these EFAs. Of course, people from warm climates also need omega-3 fatty acids in their diet. But as with many things, there may be variable degrees of tolerance to deficiency states.

Genetically, we know that some people have sluggish delta-6 enzymes (Chart 5.3).Which enzyme system you have inherited will determine the facility with which you convert EFAs into protective PG-1 and PG-3. Unless you eat appropriate foods in sufficient amounts, there is an increased risk of inflammatory disorders. We might conclude that MS is one of those.

Digestion has a role in most illnesses, and MS is no exception. If membrane damage is a factor, then the membranes lining the gut are as likely to be affected as any other membranes in the body. Damaged gut membranes make for a leaky gut, impairing the absorption of protective vitamins, minerals, and EFAs. And if MS is an autoimmune disease, absorption through a leaky membrane of large protein particles will favour the development of an autoimmune process. All of which highlights yet again how inappropriate it is to look for single agents in fixed-name conditions.

Parkinson's disease

Parkinson's disease is a relatively common condition afflicting more than 1 per cent of people older than 55. After the age of 85, this figure rises to more than 5 per cent, indicating the degenerative nature of the problem.

Parkinsonism is a collection of problems rather than one entity. There are certain characteristic symptoms, and post-mortem shows characteristic damage to certain nerve cells in the brain. The classic symptoms include:

- *Gait:* Loss or reduction of arm swing when walking, shortened but often accelerated stride, and impaired balance.
- *Tremor at rest:* This is often an early diagnostic sign, most noticeable in the hands, and usually asymmetric at first. Conscious movement of the affected limb will often stop the tremor for the duration of the action.
- *Rigidity:* When a limb is passively moved by another person, there is a 'cog-wheel' resistance as the rigid limb gives way in short bursts.
- *Akinesia:* This refers to the difficulty such patients have in initiating a movement. It is like watching a person who is anxious about escalators trying to judge when to put their foot forward onto the moving steps.

The underlying damage to brain cells varies according to the different types of Parkinsonism, but it is often divided into two groups, idiopathic and atypical.

Idiopathic Parkinson's

This form is characterised by the features listed above, and symptomatically at least, responds well to treatment with the drug levodopa, which is converted to dopamine in the brain. Post-mortem examination shows the normally dark *substantia nigra* in the mid-brain is pale, signifying loss of dopamine-producing neurones. The remaining damaged neurones contain abnormal structures known as Lewy bodies and neurofibrillary tangles.

Strictly speaking, diagnosis can only occur after death, because this degree of accuracy is not possible on a living brain. Up to 10 per cent of people with this form of Parkinson's are thought to develop symptoms before the age of 40, but this is only recognised retrospectively. Studies of twins indicate that there is a strong genetic component to early-onset Parkinson's.

Besides levodopa, a wide range of other medications is employed in the treatment of Parkinson's. None are able to halt or even slow the disease, but all give symptomatic relief. Many have side effects which are prohibitive in individual patients.

This illness has been labelled idiopathic, the term used to represent a fixed-name disease which has no known cause. Yet for many years now, researchers have shown connections between the risk of Parkinson's and environmental factors.

- One study demonstrated that people who used pesticides in the home had a 70 per cent higher risk of getting the disease.[30]
- In another study on rats, the common pesticide Rotenone gradually destroyed the dopamine-producing neurones, resulting in a clinical picture of Parkinsonism. This natural plant product acted by inhibiting one of the mitochondrial enzymes. The enzyme is also inhibited by a chemical called MPTP, a known contaminant of heroin. Some heroin addicts developed Parkinson's after exposure to this chemical.[31]
- A study published in *The Lancet* threw light on the role of poisons and the genetic aspect as well.[32] Of the many genes involved in the production of enzymes to detoxify poisons, one important enzyme called GSTP is known to be polymorphic. The allele (gene variant) known as GSTP1 seemed to be protective against developing Parkinson's. A person who had only one, or no, copies of the GSTP1 allele had an increased the risk of Parkinson's, but only if they had handled pesticides.

- Other research has shown that the combinations of lead and copper, lead and iron, and iron and copper, increased the risk of developing Parkinson's disease up to fivefold.[33]
- In a 1996 study in Germany of 380 patients, there was a significant over-representation of people who had had occupational exposure to organochlorines and alkylated phosphates. Wood preservatives and general anaesthesia also appeared to be risk factors.[34]

In his book on chemical sensitivity, William J. Rea lists the following chemicals as being associated with the development of Parkinson's:

- 1-methyl-4-phenyl-1,2,3,6,tetrahydro-pridine (MPTP)
- organophosphate pesticides
- petroleum derivatives plus pesticides
- carbon tetrachloride and carbon disulfide (CS_2)
- *Cycas circinalis*, a neurotoxic plant from Guam
- hexachlorobenzene (a fungicide).[35]

Many of these studies go back to the 1970s and 1980s, yet 30 years later we are still describing Parkinson's disease as idiopathic. Neurotoxins may not be the only things to trigger Parkinson's and they may not even be the cause, but as many of them are ubiquitous in the environment it is hard to understand the lack of interest in them in the assessment of this disease.

Research has long indicated that oxidative damage to the cells of the substantia nigra is one of the most significant initiators of Parkinson's disease. In the early 1970s, Gerald Cohen and Richard E. Heikkila from the Mount Sinai School of Medicine in the United States found that a synthetic toxin could produce Parkinsonism in animals by the formation of at least two different kinds of free radical. One of the 'fingerprints' of free radical damage is the formation of lipid peroxides (Chapter 5: Vitamin E), which they were able to demonstrate.[36] The high fat content of the brain makes it particularly vulnerable to lipid peroxidation.

Oxidative damage can occur in various ways. An overload of metals such as iron and copper can act as a source of free radicals. Chemicals can do this, too. Alternatively, these substances may damage the redox enzymes. Even a simple deficiency of the anti-oxidants required to support those enzymes could result in lipid peroxidation. These are not either-or options. Probably a complex of insults triggers the events which lead to the diagnosis of Parkinson's disease.

Although Parkinson's is a fixed-name disease, or even a fixed-name syndrome, perhaps it is actually another free radical disorder. It is different in presentation, but not in kind, to other free radical diseases such as arthritis, heart disease and cancer.

Atypical Parkinson's

Atypical Parkinson's refers to a collection of other syndromes which have clinical and pathological similarities to each other, but vary to a greater or lesser extent. Notably, Lewy bodies are not usually a feature of these other forms.

It has been estimated that up to 25 per cent of Parkinson's disease is misdiagnosed because many other conditions can mimic it. These include Wilson's disease (an inherited tendency to copper overload) and cerebrovascular disease. There is also a form of dementia which can be accompanied by Lewy bodies and can mimic Parkinson's.

Perhaps best-known in the category of the atypical forms is drug-induced Parkinsonism. Many prescription medications actually work against the effects of dopamine (usually unintentionally), and in certain people Parkinson-like effects can be seen early in treatment. The vulnerability to this side effect is unpredictable, and it may have a genetic basis. Early withdrawal of the medication is mandatory in order to avoid long-term damage.

Some recreational drugs have been associated with the development of Parkinson's disease. In recent times a scandal erupted when there was evidence of tampered results in studies purporting to show that the drug Ecstasy could induce the illness.

Treatment

Three senior neurologists have said 'no treatment has been shown to arrest or slow the neurodegenerative process' of Parkinson's.[37] But a wide range of nutritional treatments for Parkinson's have shown varying degrees of benefit. On theoretical grounds alone, this should not be surprising. Oxidative damage can be halted, and sometimes reversed, by appropriate anti-oxidants.

Vitamin C is a chameleon, as we have seen (Chapter 4). It can act as an antioxidant, and by donating electrons it can act as a catalyst to enzyme reactions. Interestingly, it is also a competitive antagonist at dopamine receptor sites. This means it can mimic or block the action of dopamine, in a manner analogous to the phyto-oestrogens when they occupy oestrogen receptor sites. Vitamin C has been shown to antagonise the effects of amphetamines, and to enhance the effect of the anti-psychotic drug haloperidol. (Psychotic illness such as schizophrenia is associated with excess dopamine production.) There is a role for Vitamin C in schizophrenia, autism and Parkinson's. Used early in Parkinson's, it is claimed that it can delay the need for levodopa.

There are positive reports on the use of other nutrients as well. However, the trials are marred by following the methodology of the standard drug trial. Trials on single nutrients, such as folic acid and Vitamin E, have unsurprisingly been disappointing. When they are used in consort, we could reasonably expect a favourable outcome.

Various nutrients, such as the omega-6 fatty acids, Vitamins C, E, B3, B6 and beta carotene, and minerals such as magnesium and iodine, have had apparently beneficial results. A recent trial of co-enzyme Q10 has confirmed a role for this nutrient in Parkinson's.[38]

Migraine

It is Friday morning, and there are two migraine patients in the waiting room. One is Louise, aged 17, and the other is Astrid, who turned 50 on her last birthday.

Louise is in her last year of school, and is a good student. She works hard, and if her grades are good enough, she hopes to study medicine. Louise has been suffering from what is known as *classic migraine* since puberty. Classic migraine is characterised by aura, visual disturbance, severe pain, photophobia and vomiting, although not all attacks show all of these features. Louise's headaches are often associated with her periods and always seem to come at the worst times. Today she has a major assignment due and has been working hard on it because the marks will go towards her final assessments. She is in the throes of an attack and looks wretched. She is holding a plastic bucket because she feels she might vomit. Her mother is outside parking the car, having taken the morning off work to bring her to the surgery.

Astrid, by contrast, is flipping idly through a woman's magazine. Today is a routine appointment not specifically related to her migraines. She heard Louise checking in and offered her place in the queue. Astrid doesn't usually get as sick as Louise does with her headaches, but it has happened a couple of times. She knows why people say that if it were a dog, you would shoot it. Astrid can have a headache twice within a week. They are more frequent during times of stress and before her period. With simple painkillers she can get through the day. At night she will take an anti-histamine and go to bed early. She fits the typical profile of someone suffering from *common migraine*, where the symptoms are similar to classic migraine, but much milder. She is pleased to note that as she approaches menopause, the headaches seem to be lessening.

Who gets migraine?

The medical literature is full of stories of people like Astrid and Louise. As women outnumber men three to one in this condition, the typical patient is likely to be female. The headache was first described in ancient Egypt, and there have been many well-known victims, including Charlotte Bronte, van Gogh, and possibly Charles Darwin.

Because it is common, migraine receives a lot of press. Louise feels that if she ever studies medicine, she may specialise in migraines! She has read how, once a migraine is triggered, a whole set of biochemical and neurological events known as the 'migraine cascade' are set in train. This may then lead to the full catastrophe of pain, vomiting and visual disturbance. With all that knowledge about the trigeminal nerve, neuropeptides, serotonin, and so on, surely there's an answer?

The treatment

Louise will be treated for her acute attack with injections for pain and nausea. She has already had several consultations and tried a range of preventive medicines. These have made her sleepy or forgetful, and in most cases have been ineffective. The newer triptans are not recommended for people under 18. Her doctor, like many of his colleagues, finds that his patients complain that triptans only delay the headaches, and many say they cannot afford the medication. Yet they were introduced with such a fanfare: 'The end of the headache that has lasted thousands of years!' After a few deaths, cautions were issued against their use in patients with cardiovascular disease. They were found to be risky when used in conjunction with one of the commonest migraine treatments, ergotamine. All in all, Louise and her doctor would prefer another option.

So why do I and my colleagues feel a sense of despair when we see Louise and others sitting there with their plastic buckets? Menopause may bring relief, but that is a long way off for Louise.

Research into migraine has brought forth many drug therapies, but no cure. What's more, migraine seems to be on the rise. The former estimate of 1 in 10 has been revised to 1 in 6.[39] And more children and teenagers are developing migraine in its various manifestations.

The research

Is migraine another fixed-name disease? Perhaps we have failed to make a difference because we have focused on the symptoms rather than the cause.

Researchers have been looking at neurotransmitters for decades now. Everything from the trigeminal nerve to the brainstem has been studied. PET scans have made all sorts of observation possible. Migraine has been painstakingly classified into a catalogue of variants; impressive as an exercise in taxonomy. Yet in 2002, Ninan Mathew of the Houston Headache Clinic told *Time* magazine what any migraineur knows: 'At one time people thought that migraine was a disorder all its own and that tension-type headache was totally separate. Now we know that headaches are not all that clear cut.'[40]

More than 50 per cent of migraine sufferers have a family history of the condition. Could there be a 'migraine gene'? Common migraine has a complex inheritance pattern which suggests the involvement of several genes. There is a nasty form of migraine known as familial hemiplegic migraine (FHM), in which there is an increased risk of strokes during an attack. The first FHM gene was located on chromosome 19 and seemed to implicate calcium channels.[41] But some people with FHM did not have this particular gene. And then, in February 2003, a mutation in the gene for sodium and potassium channels was found.[42] A second gene had been implicated.

Nutritional deficiency

Magnesium has been shown to be reduced in blood, saliva and cerebrospinal fluid of migraineurs. This may be a cause, rather than an effect, of the migraines.

Magnesium is a smooth muscle relaxant, and part of the migraine cascade involves spasm of the cerebral vasculature. Migraineurs are acutely aware of the throbbing of scalp arteries, and vascular spasm is a significant aspect of the strokes which occur during migraine. Arteries are contracted into a spasm by the smooth muscles which control their diameter.

Magnesium also modifies the functions of hormones and neurotransmitters. Demands on magnesium supply reach a peak in the premenstrual phase of the female cycle. Women with symptoms of premenstrual tension, including headache, have been shown to have lower than expected blood levels of magnesium. And low levels of magnesium increase the sensitivity of blood vessels to the neurotransmitter serotonin.

As we have seen, one of the 'migraine genes' had to do with calcium channel dysfunction. Magnesium is the other half of the story. Magnesium and calcium are like twins, always requiring an equilibrium throughout the body.

A study observed the effects of supplementing migraine patients with high doses of oral magnesium.[43] Before the end of the second month of supplementation, therapeutic benefit was statistically significant; it included a reduction in both the frequency and the severity of attacks. A separate group of women with 'menstrual migraine' were also shown to respond. Yet to my knowledge, no migraine clinic in Australia has trialled magnesium, or routinely incorporates it into its treatment regimes. Some hospital departments claim to use intravenous magnesium in the Emergency Room for acute migraine. The pain and risk of stroke are both derived from arterial spasm, so the benefit of releasing spasm does not need to be spelled out.

One of my patients went to the Emergency Department of a large teaching hospital suffering severe migraine. She was injected with pethidine and sent home. When the effects of the pethidine had worn off, the migraine returned. She was frightened because there was a family history of migraine and of stroke at a young age, and she was feeling numbness and weakness on one side. I phoned the hospital and spoke to a neurological registrar. Yes, he thought intravenous magnesium would be a good idea. I sent her in. When I phoned him back, he said that he had not given her the magnesium because she was 'too sick for that'. He'd given her pethidine again.

As well as magnesium, B-group vitamins have a role to play. More than one study has shown that supplementation with Vitamin B2 has reduced the frequency of migraine by up to 50 per cent.[44] The list of foods rich in B2 is extensive. Notably absent however, are milk, white flour, sugar, refined carbohydrates, saturated fats — the backbone of the Western diet. Vitamin B6 is another key nutrient. Many of the drugs used to treat migraine actually perpetuate the problem by depleting central nervous system endorphins (nature's own pain relievers), and by suppressing the receptor sites for them.[45] B6 is probably the single most important tool for reversing this situation.

Part of the migraine cascade involves the swelling and inflammation of blood vessels when inflammatory mediators are released into the circulation. As our bodies experience a fall in the ratio of omega-3s to omega-6s, another defence against migraine is lost. The efficacy of fish oil as a treatment for migraine has been shown in several small studies.[46]

Migraine clinics could conduct large studies of combinations of these nutrients, but they resist treatments not involving the pharmaceutical industry.

Diet

That the modern diet seeks out and reveals our genetic weaknesses is, of course, a central theme of this book. The 'genes for migraine' provide examples. Magnesium deficiency can result not only from an absolute deficiency, but also from imbalance relative to calcium. High dairy consumption, calcium supplements taken without equal amounts of magnesium, and other aspects of the Western diet, certainly promote this disequilibrium.

We have also seen that sodium and potassium pumps are implicated in the cast of migraine genes. The ratio of sodium to potassium in the Western diet was discussed in Chapters 3 and 8. If the migraine cascade results in part from genetic vulnerability in the ion channels, such alteration in the ratios of calcium to magnesium and sodium to potassium may affect people with genes that cannot meet the challenge.

Genetic sensitivity might be unmasked in other ways also. Some people are especially sensitive to the 'warning' chemicals embedded in our food. Foods high in natural chemicals which affect blood vessels and act like neurotransmitters are often associated with migraine. These chemicals include tyramine, histamine, salicylate and amines. Is increased sensitivity to such chemicals an asset or a liability? Are genes for this sensitivity a 'disease' or an adaptive advantage?

- *Tyramine* is found in chocolate, Vegemite (and all its relatives), pickled herrings, red wine (especially Chianti) and cheese. One patient of mine, a refugee from an illustrious migraine clinic, lost all her headaches and was able to cease taking the powerful drug methysergide when persuaded to give up her Vegemite habit. The eminent professor had told her that migraine had nothing to do with food.
- *Salicylates* are found in fruits and vegetables. They are at their maximum in fruit and vegetables which have been picked before they are ripe.
- *Histamine* is found in cheese, salami, sausage, and wine. Histamine headaches are well established in the medical literature.

People who have a genetically determined deficiency of the enzyme *phenolsulphotransferase* cannot metabolise dietary amines as well as others. Some food additives and some dietary phenols (such as in red wine), are known to actually inhibit this enzyme. It's too bad if you weren't born with a lot of it to start with.

Monosodium glutamate (E621–623) and the E numbers 102, 110, 210–219 (benzoic acid derivatives) and 220–227 (sulphite and metabisulphite derivatives) have been shown to precipitate migraine. Proteins in milk, wheat and other grains are strongly associated with migraine headache. But is that because we eat too much of them, or do not digest them properly? Suggest removing them from diet and many people are convinced that there is nothing left to eat.

Environmental factors

Besides stress, most migraine patients report a range of environmental triggers for their headaches. Predominant among these are pollution, petrochemicals, perfumes (a spin-off of the petrochemical industry), glare, flicker, strobe lighting, and even stripes. The last three of these may be compared to the way in which epilepsy and its auras can be triggered by strobe lighting, and motion sickness is related to visual perception. It seems reasonable that similar cues might trigger the migraine cascade. Flickering on the periphery of the visual field can provoke unease, which in evolution may have been protective against being stalked by predators.

Pollution and petrochemicals are poisons and their role in migraine is simple. Volatile agents go straight up the nostrils, through the cribriform plate, and into the brain. It is an instant warning system for toxic gases. The air is not good, move on, the volcano might erupt. At the same time, these poisons can saturate or even inhibit many of our detox enzymes. These enzymes then are left with no capacity to detox the natural food chemicals involved in migraine.

In summary, the fixed-name disease of migraine is probably nothing more than the cumulative effects of a stressful life lived in a polluted environment. The word pollution encompasses food, air and water. The immune system, to deal with these multiple stressors, struggles on a diet deplete in magnesium, B-group vitamins, essential fatty acids, and all the rest.

Migraine is a common, but eminently treatable, condition. The diagnosis, however, should be made by a trained medical practitioner, because migraine can mask brain tumours, epilepsy, strokes and several other neurological disorders.