CHAPTER 1

Atom

I Am Tired

I am tired, cutting down the bracken . . .
Gaelic folk song

ALISON

All things are full of weariness. A man cannot utter it.
Ecclesiastes 1:8

My patient, Alison, was tired, and so was I. She was the seventh of my ten new cases that morning. I was standing in for a senior colleague and had assured him, with the excessive generosity of youth, that I would have no problem dealing with his work. I had meant what I said at the time but, as I read this seventh letter of referral, my already flagging spirits flagged a little further: 'Thank you for seeing this pleasant woman of 38 . . . tired for some time, especially in the mornings . . . trouble coping with the housework . . . seen by yourself a few years ago . . . Diagnosis almost certainly "chronic fatigue"' – this problem looked to have a snowball's chance in hell of a solution in the fifteen minutes left at our disposal.

What the mind does not know the eye will not see. I did my best with Alison, or so I thought, as I listened to her story and examined her weary limbs. She was indeed a 'pleasant woman' – dark-haired, dark-eyed, undemanding but in need of help. She was tired, no doubt, more so in the mornings than later in the day. She woke with a headache, which improved as the hours wore on. Slowly but surely, her symptoms were worsening. She could cope, but her fatigue had taken the joy out of her life. A look through her notes confirmed that she had seen my colleague a few years before. He had detected an abnormal blood result, further tests had not revealed a cause and matters had been left there by mutual agreement. Had I been sharper, or less stretched, I might, perhaps, have seen the light during our brief encounter. But I was young and busy: too busy to pause and think afresh about Alison's predicament, and too inexperienced for my thinking to get me anywhere much. What was certain was that I had nothing useful to say when we parted: my initial pessimism had been entirely justified. As I handed Alison a card for some blood tests and prepared to see my next patient I expected nothing more to come of our meeting, a humdrum, unedifying, 'clinical episode'. Two days later I was on holiday, purging my own fatigue, renewing my enthusiasm for life.

THE WELL OF WEARINESS

> Lying down was not for Oblomov a necessity, as it is for a sick man or for a man who is sleepy; or a matter of chance as it is for a man who is tired; or a pleasure, as it is for a lazy man: it was his normal condition.
>
> Ivan Goncharov, *Oblomov*

Oblomov, the amiable but indolent hero of Goncharov's nineteenth-century novel, is generally to be found in a dressing gown at midday.

Goncharov's introduction nicely summarises the principal causes of such a state of affairs. Until recently I lived in Presbyterian Edinburgh where working too hard and sleeping too little was the commonest cause of fatigue. Sometimes the habit of overwork develops so gradually that it goes unnoticed, as it had done for a particularly conscientious employee who consulted me on account of his tiredness. His working day ordinarily extended from 8 a.m. to 6 p.m., but over the years he had developed the habit of returning home to work a little, taking an early supper, retiring to bed at 9 p.m., and rising again at two to sneak three or four hours of paperwork during the early hours before lying in luxuriously from 5 till 7 a.m. Overwork was his normal condition, and he took much persuading that it might, conceivably, be the explanation for his growing world-weariness.

Then, as Goncharov implies, serious illness of almost any kind can be fatiguing. The cause can remain mysterious for a while, but usually a careful assessment by an experienced hand, and sometimes a few tests, reveals the underlying problem – a slowly failing organ, a deep-seated infection or, worse, an inapparent, metastasising cancer. But what of a drenching fatigue that permeates every tissue of the body, soaks the whole being in torpor, slows the system to standstill, all in the absence of any ascertainable physical disorder: is this an illness – or is it a sin?

When I fall ill, I find it hard to believe that I will ever be restored to the blessed, contented normality of health. Once I am well again, I find it just as hard to believe in the possibility of illness, that I might be stricken by one of those improbable afflictions our nature has in store. The same may possibly be true for you, and it seems to be especially hard for energetic folk to acknowledge the reality of fatigue. Industrious, striving, busy people – including of course most doctors – are simply baffled by the contradiction of chronic, disabling exhaustion in what appears otherwise to be a perfectly healthy body. It is enormously tempting to regard the problem as a moral one, a failure of will, a species of laziness, a sin – the sin of sloth.

Victims of chronic fatigue are keenly sensitive to this reaction to their plight. As a result, chronic fatigue has become one of the most politicised of ailments. Its very existence – as a medical disorder – has been debated in Parliament, and our Chief Medical Officer of Health recently found it necessary to reassert that it is a 'real and serious illness'. The heated argument often seems to turn as much on faith as on science, but science can in fact shed light on the puzzling problem of chronic fatigue.

The problem turns out to be an old one: 'neurasthenia', nervous exhaustion, a diagnosis made among women of good family in Victorian England, and the 'effort syndrome' of the trenches of the First World War are the direct ancestors of the myalgic encephalomyelitis – 'ME' – of the 1950s, yuppie flu of the 1980s and today's chronic fatigue. Are these conditions 'real'? Of course they are – common and important causes of distress and disability. Are they disorders of body or of mind? I hope to convince you, little by little, as this book unfolds, that this distinction is far more tenuous than we usually believe. But, just for the present, it is probably best to answer 'both': how could chronic fatigue and inactivity possibly fail to impinge on both fitness and feelings?

It is always dangerous to argue back from treatment to cause, but the treatments which have been shown to work for chronic fatigue are revealing: gradually increasing amounts of exercise – a 'physical' approach; and cognitive behaviour therapy – a 'talking treatment' – that aims to identify and modify the mistaken beliefs which sometimes drive our behaviour. What do these treatments aim to achieve? They aim to heal the mind via the body – and body via mind.

I assumed, on that busy morning, that Alison and I were travelling through some part of this difficult territory. I knew well enough that there are some traps for the unwary in the diagnosis of fatigue, unusual disorders which develop so inconspicuously that their signs can long be missed. I had encountered a few of these previously: Addison's disease, a lack of the adrenal hormones that we need to survive under stress, can give rise to a background of malaise and fatigue for months or years before the problem comes to light; narcolepsy, with its overwhelming need for sleep, can be mistaken for chronic fatigue, or for straightforward laziness; sarcoidosis, a mysterious tuberculosis-like inflammation can, like tuberculosis itself, cause a state of chronic exhaustion. I had such thoughts at the back of my mind. But none of them quite fitted the bill.

ATOMS AND THE VOID

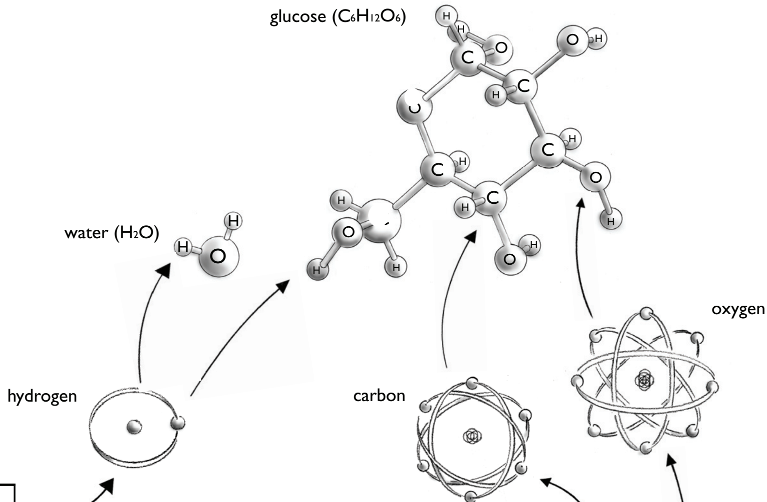
In truth, there are atoms and a void.
Democritus

I returned, refreshed, from my holidays a couple of weeks later. I can't clearly recall the moment when I found out what had happened to Alison. I am surprised by this. It must reflect the protective amnesia which shrouds one's most abject moments. I think our ward round simply tailed off in Intensive Care, and as my colleagues began to recount the tale of our patient there, I realised that I knew her – that two weeks before we had been sitting face to face elsewhere in the hospital, as she told me about her fatigue. What on earth had happened?

What had happened was this. As luck would have it, Alison's visit to the hospital to see me had marked a turning point in her condition. Over the next few days, fatigue had turned into exhaustion. Her morning headaches worsened until she could hardly bear the throbbing when she woke. It was all she could do to drag herself out of bed and start the day. And then, one morning, just as my holiday ended, it was more than she could do. Her husband tried to wake her before he left for work. He stroked her face, then rocked her shoulder, then shook her bodily. Try as he might he could not wake her, for the good reason that she was no longer asleep, but in coma. The cause of her coma was elementary, or, even, elemental – betrayed, on arrival in hospital, by the blueness of her lips. When my thoughts in clinic were turning to ME and yuppie flu, they should have been directed to the absolute basics of life, the atoms and the elements that lie at the foundation of our lives – for here lay the explanation of Alison's exhaustion and her coma.

The idea that matter is composed of invisible particles, or atoms, is as ancient as the notion that a limited number of primary substances, or elements, underlies the diversity of things. The Greek philosopher Leucippus arrived at the idea of the 'atomos' in the fifth century BC by asking himself whether matter could be indefinitely divided or whether it becomes, at some point, indivisible. He decided that it must be indivisible: atoms were its smallest microscopic units. His pupil Democritus developed the theory, proposing that all atoms, 'strong in solid singleness', were identical in substance but differed in size, shape, position and speed: their combinations and recombinations gave rise to the multitudinous properties of things. These thoughts contain the seeds of modern chemistry, not to mention the germ of evolutionary theory, as these early atomists realised that those combinations of atoms best fitted to their environment would survive and prosper. The richest source of knowledge of these ancient ideas is not a textbook but a poem, the wonderful *De rerum natura*, 'On the Nature of Things', written four hundred years later, in the lucid intervals of his recurrent madness, by the Roman poet Lucretius.

These insights were prescient. They lived on, disguised and distorted, in the classical theory of the four elements – earth, air, fire and water. They encouraged the alchemists in their pursuit of the philosopher's stone – which 'will convert to perfection all imperfect bodies that it touches' – during the Middle Ages. But it was not until the seventeenth century that these ideas began to take their modern form. The troubled, deeply religious Oxford scientist Robert Boyle recognised that there were not four but numerous primary substances, all composed of particles. He realised that these substances, the elements, could exist in solid, liquid and gaseous forms. In *The Sceptical Chymist*, published in 1661, he defined the elements as 'certain primitive and simple, or perfectly unmingled bodies; which not being made of any other bodies, or of one another, are the ingredients of which . . . perfectly mixed bodies are immediately compounded, and into which they are ultimately resolved'. One hundred years later the Parisian scientist and administrator Antoine Lavoisier made it his overarching aim to identify these 'undecomposable, elementary substances' which, through myriad combinations and transformations, underlie the shifting appearances of the chemical world. In 1789, the year of the French Revolution, Lavoisier proposed 33 candidates for this role, of which 25 have stood the test of time.



1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	57 *La	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra	89 +Ac	104 Rf	105 Ha	106 Sg	107 Ns	108 Hs	109 Mt	110 110	111 111	112 112	113 113					

1. The Periodic Table

The periodic table shows the elements, organised according to their chemical properties. Some heavier elements are omitted: 117 elements have been observed. All the elements that abound in living things lie in the first four rows: these include hydrogen (H), carbon (C), nitrogen (N), oxygen (O), sodium (Na), phosphorus (P), chlorine (Cl), potassium (K), calcium (Ca), iron (Fe). The atoms of elements combine to form molecules of compounds: the figure shows the very simple molecule of water (two atoms of hydrogen and one of oxygen) and the more complex molecule of glucose (six atoms of carbon, six of oxygen, 12 of hydrogen).

At the start of the nineteenth century, the son of a Westmorland handloom weaver, a devout, reclusive Quaker, John Dalton, reintroduced the term 'atom' for the smallest ingredients of the elements. Just as Democritus had proposed, he recognised that the atoms of different elements were identical in substance but differed in size. By the time the Russian chemist Dmitri Mendeleyev published his Periodic Table in 1869, clarifying the identities, properties and relationships of the eighty or so elements then recognised, the atomic theory of the elements was established. It is absolutely fundamental to understanding the world we live in: the American physicist Richard Feynman said that if we were able to pass on just one sentence of scientific knowledge to another civilisation it should begin: 'All things are made of atoms . . .' . It is also fundamental to understanding much human disease.

CONSUMED BY FIRE

We only live, only suspire,
Consumed by either fire or fire
T.S. Eliot, 'Little Gidding', *Four Quartets*

Alison's predicament was a case in point, as it turned out. What had happened, as I discovered during that dismal ward round, was simple enough. Her breathing had gradually failed overnight. Her blood had been starved of oxygen and had become overladen with the main waste product of our body's chemical processes, carbon dioxide. The brain has an unquenchable thirst for oxygen: in its absence consciousness rapidly fails in less than a minute. But matters, mercifully, had not progressed too far. Once diagnosed, the disturbance of the blood gases could be reversed by a short spell of artificial ventilation, which rapidly restored both chemistry and consciousness. It cured her headaches, which had signalled the accumulation of carbon dioxide in her blood as she slept, and it began to renew her *joie de vivre*. The cause of this near-catastrophe soon came to light: a profound, selective, weakness of the muscles which open the lungs to life-giving air, a nearly fatal faltering of the bellows which fan the fires of our existence.

The notion that the air contains an active principle that is consumed both by flames and by living creatures, both by inanimate combustion and by animate metabolism, dates back to the seventeenth century at least. It was well known by then that an animal enclosed in a glass vessel would die after some minutes, and that it would do so more quickly if a lighted candle were placed in the vessel too: 'it clearly appears that animals exhaust the air of certain vital particles . . . that some constituent of the air absolutely necessary to life enters the blood in the act of breathing'. Richard Lower, who published his *Tractatus de corde* in 1669, had discovered that this 'spiritus nitro-aereus' changed the colour of the blood as it passed through the lungs, from the dark purple which runs in our veins to the bright red of our arteries. His colleague Robert Hooke, Boyle's assistant in Oxford, showed that the act of breathing itself was not essential for this transformation, provided a current of air was continuously blown over the lungs.

The precise nature of the active principle eluded discovery for a hundred years. Heating mercuric oxide in 1772, the Swedish pharmacist-chemist, Karl Scheele, isolated 'fire air', the fraction of the atmosphere which, he found, supported fire. Scheele was a modest but intrepid man, given to sampling the properties of novel chemicals at first hand: he died in his forties, probably from poisoning by mercury. His *Experiments on Air and Fire* had not yet been published when, in 1774, using the same method, the English chemist Joseph Priestley also obtained a novel 'air' in which 'a candle burned with an amazing strength of flame'. On a trip to France, Priestley shared his discovery with Antoine Lavoisier. Within a few years Lavoisier had named the substance 'oxygen' and clarified its role in fire and life. The bright flame of the candle and the warm glow of the body are indeed alike in their chemical nature. Each depends on 'oxidation', a chemical bonding with oxygen, drawing a measurable weight of the gas from the surrounding air. We are all exquisitely regulated, very slow burning, chemical stoves, 'one of those fires without light'.

Lavoisier went to the guillotine in 1789, condemned because the 'Republic has no need of savants'. By the time of his death, it was clear that four of the elements he had identified – hydrogen and oxygen, both of which Lavoisier named, together with carbon and nitrogen – were the prime ingredients of living things. We depend absolutely on the oxygen of the atmosphere to keep the flame of our metabolism alight: it is the gas in which we burn the fuels that sustain us – and our brains. But our bodies also abound with 'fixed' oxygen, which constitutes 65 per cent of our body weight: combined with hydrogen in water, and with hydrogen, carbon, nitrogen and phosphorus in the larger molecules from which our bodies are constructed – like DNA, carbohydrates, fats and proteins. We accommodate a few other elements, to be sure: a watery solution of sodium, chlorine, potassium, magnesium and calcium, the elements dissolved in the seas in which all life was born, still bathes our tissues, and our evolution has put traces of heavier elements, like copper, cobalt, zinc and iron, to ingenious uses in the nooks and crannies of our cells. But nonetheless the elements that compose us can just about be numbered on our fingers and toes.

The atoms of each element are its smallest distinctive units. They are very tiny indeed: the size of a hydrogen atom is around a ten-millionth of a millimetre. Atoms combine with one another to form molecules, gangs of mutually attracted atoms. In this way, elements team up to form compounds, like the carbon dioxide we exhale, with one atom of carbon and two of oxygen in each of its molecules, CO_2, and the water we drink, H_2O. Are atoms really the smallest divisible units of matter? Well, alas for simplicity, of course they are not: much of the twentieth century's physics was devoted to exploring the world within the atom, its central nucleus and orbiting electrons, and to discovering the vast quantities of energy that can be derived from splitting or fusing these nuclei. The quest for the ultimate constituents of matter continues today, along the path Leucippus and Democritus first opened up, invoking ever more abstruse entities, such as leptons, quarks and strings. But at the level at which we mostly lead our lives, using naked eye and bare hand, the inventory of the elements, chemically pure, atomically uniform, like gold and silver, lead and iron, carbon and oxygen, is fundamental. Though oxygen is the particular hero of this chapter, carbon deserves a special mention. Its atoms have a unique propensity to enter into stable combinations with one another, and with the atoms of other elements. Carbon contributes to nearly ten million known compounds: the chemistry of carbon, 'organic chemistry', is therefore the chemistry of life.

We have borrowed these elements, the stuff of our lives, from the stars. The atoms from which we are built were formed there, by nuclear fusion, at temperatures so astounding that the simplest nuclei, of hydrogen and helium, fused together to generate their heavier companions, later to be flung around the universe as dying stars erupt. We really should be more startled by the exotic nature of our basic components. We think of physics as the science of matter, biology as the science of life, and tend to look to biology for an explanation of our human selves. But whatever the ultimate constituents of matter turn out to be, you and I are as intimate with them as it is possible to be: we are built from them – we are they, no more, no less.

ELEMENTAL AFFLICTIONS

We live at the bottom of an ocean of the element air
Evangelista Torricelli

You may have sampled symptoms like Alison's if you have climbed to altitudes at which the falling oxygen pressure in the thinning atmosphere begins to take its toll – typically over 10,000 feet. A sense of mounting effort and worsening breathlessness may be followed by full-blown altitude sickness, ushered in by nausea, dizziness, insomnia and a pounding headache. The sudden decompression of an aircraft at 30,000 feet results in more dramatic oxygen deficiency: unless the supply is swiftly restored, the 'time of useful consciousness' before the brain fails is a mere minute.

It is unusual for neurological diagnoses to focus on a single element, but there are some important exceptions. Sodium, the metallic element contained in sodium chloride, our table salt, and calcium, familiar from calcium carbonate, chalk, are both abundant in our body fluids, and essential for electrical signalling in nerves. If calcium levels fall in the blood – as they will do if the hormone which maintains them, parathyroid hormone, is underproduced – nerves become hyper-excitable, entering a state of 'tetany': tingling, muscular spasms, often affecting the hands and feet, and even convulsions ensue. Hyperventilation in the course of panic attacks, a much more common occurrence than deficiency of parathyroid hormone, has a similar effect: the resulting reduction in the level of carbon dioxide in the bloodstream makes it more alkaline than usual, which in turn reduces the amount of electrically active calcium. By contrast, if parathyroid hormone is overproduced and levels of calcium rise, our muscles become leaden, action effortful and the mind befuddled. Abnormal levels of sodium in the blood, whether low or high, also disturb the workings of the brain, to cause confusion, seizures and finally coma. These are generally reversible once the cause is spotted, but over-rapid correction of depressed sodium levels can cause irreparable brain damage.

Heavier elements sometimes give rise to atomic disease, most commonly when we are poisoned by them. Hippocrates, in 370 BC, suspected that a patient's abdominal pain was due to his work as an extractor of metallic lead from ore, the first recorded case of 'Saturnism', named after the alchemical term for lead. Daniel Defoe, in the eighteenth century, described an encounter with a miner of Derbyshire lead who seemed to have risen from 'the dark regions' themselves, 'pale as a dead corpse, his hair and beard a deep black, his flesh lank, and, as we thought, something of the colour of lead itself'. The metal finds its way into the nervous system, damaging our nerves and the blood vessels of the brain, but lead poisoning, common in the days of lead piping and lead-based paints, is nowadays a rarity.

Lead was never intended to cohabit in our cells, but some heavy elements are used by the body in trace amounts for specific, highly regulated, purposes. Iron is one such, helping to transport oxygen in our blood cells and to bind it elsewhere; copper another. These guests need careful handling by their hosts: the consequences can be dire if these elements are allowed to accumulate in the wrong places or fail to get where they are needed. The body's failure to handle copper normally underlies two grave inherited diseases. Both are thought to result from inherited abnormalities in proteins that 'transport' copper to the sites where it is needed. In Wilson's disease, copper accumulates in eye and brain (as well as liver), causing disorders of movement, mood and mind which are sometimes mistaken for signs of a primarily mental disease before the condition reveals itself fully. It usually comes to light in teenagers or in early adulthood. It can be effectively treated with chemical remedies that leach the excess copper from the body. The related, but more severe, condition of Menke's disease causes poor growth, lax skin, kinky hair and neurological decline in infants. In this condition the body fails to incorporate copper in the small group of enzymes – proteins that facilitate chemical reactions in our cells – in which it plays a vital part. These include the enzyme cytochrome oxidase, which returns us to the atomic hero of the chapter, as cytochrome oxidase completes the process by which our cells generate energy in the presence of oxygen. If copper is important in normal functioning, one would predict a syndrome of copper deficiency. New disorders are constantly being recognised, like new species: in 2001 copper deficiency was recognised for the first time as a cause of neurological illness. It causes difficulty in walking and disturbed sensation in the legs as a result of dysfunction of the spinal cord, usually in people who have been absorbing copper poorly following stomach surgery, often performed many years before.

Conditions like Wilson's disease, and the heavy elements which cause them, are biological rarities. The principal elements of life, hydrogen, carbon, nitrogen and oxygen, are lightweights in the periodic table, with atomic numbers, reflecting their atomic weights, of

1, 6, 7 and 8. The key to their role in our lives is their fertile capacity to combine with each other, forming the molecules of life, our genes, proteins, sugars and fats. These are the constituents of all our organs, including the brain. It is easy to forget that the myriad possibilities of human life flow ultimately from the humble but mysterious atoms that compose us.

LIFE-FORGIVEN

Life-forgiven and more humble,
able to approach the Future as a friend . . .
W.H. Auden, 'In Memory of Sigmund Freud'

Alison's story ends more happily than I feared it might. Life forgave us both. Her underlying condition proved to be rare indeed, so rare that we reported it in a scientific paper as a hitherto unreported consequence of an uncommon muscle disorder, 'multicore myopathy' – named after the cylindrical cores that are visible under the microscope within the muscle fibres. Alison's myopathy especially affected her diaphragm, the two-humped muscle which lies beneath the lungs, and flattens, pushing out the abdomen, when we inhale. This was the reason it had escaped our notice – routine neurological examination fails to assess the diaphragm.

This muscle is particularly important to us in sleep, as gravity no longer keeps our abdominal organs in their place when we lie down. If the diaphragm fails, breathing in sleep can fail too, as Alison's did. But over the past half-century respiratory physicians have refined simple techniques for assisting breathing overnight, maintaining the pressure of oxygen in the lungs. One of these suited Alison well, restoring her oxygen levels to normal, extinguishing her headaches and greatly relieving her fatigue. Her muscles have gradually weakened elsewhere, and this we could not cure, but her life was no longer at risk.

As for me, I felt foolish, though no one rubbed salt in the wound. I wanted to hide. But on second thoughts, instead of nervously concealing them, we should examine, even celebrate, our failures and mistakes. Rather than being negligent or shameful, as a rule, they are a fact of life, a plain reflection of human imperfection. They have so much to tell us about ourselves that they deserve our scrutiny, offering our best chance to learn and grow. With their help we can avoid repeating history. Such pious thoughts, needless to say, were far from my mind that day in Intensive Care. In fact, despite my holiday, I suddenly felt very tired.