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Philip Ball, author of *Critical Mass*

TRANSFORMER

The deep chemistry of life and death

NICK LANE

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In memory of
Ian Ackland-Snow

Contents

to this mortal process of continuing,
it is the movement that creates the form.

Richard Howard

Introduction

LIFE ITSELF

From space it looks grey and crystalline, obliterating the blue-green colours of the living Earth. It is criss-crossed by irregular patterns and convergent striations. There's a central amorphous density, where these scratches seem lighter. This 'growth' does not look alive, although it has extended out along some lines, and there is something grasping and parasitic about it. Across the globe there are thousands of them, varying in shape and detail, but all of them grey, angular, inorganic … spreading. Yet at night they light up, glowing in the dark sky, suddenly beautiful. Perhaps these cankers on the landscape are in some sense living – there is a controlled flow of energy, there must be information and some form of metabolism; some turnover of materials. Are they alive?

No, of course not; they are cities. We know them intimately from the inside, even if most of us know little about the flow of energy and materials through our own cities. We know them mainly by their visible structures, buildings on a map. But an empty city with no power, no energy flow, no traffic, no jostling crowds, is an eerie place, chilling and post-apocalyptic. Dead. What brings a city to life is the people, their movement from place to place, along with the flow of materials that sustains our daily existence – electricity, heat, water, gas, sewage.

It would not be misleading to say that a city is brought to life by the controlled flow of energy and material in this way. Set up a time-lapse camera on a busy street downtown and we get a sense of this flow, obeying laws of flux that we can barely guess at. In my mind's eye, we could rise above the conurbation and picture this combined flux, map out the jumbled flow of people, lights and power, pulsating down some streets, just a residual overflow in others, some districts a hive of bustling activity, others nearly dormant until the evening when the commuters return home and the lights flick on. We could map out the flux that animates a city. Certainly, we can imagine a city this way, but mostly all we notice are the buildings. The structure.

A cell is a city of a sort. It too has buildings, or at least physical structures. Unlike our own constructions a cell is not dominated by gravity, and is truly built in three dimensions. If you shrink yourself down to the size of a molecule, the 'cityscape' is dizzying. Membranes sweep past your view: curving, fluid walls, swooping overhead or plunging down below. Traffic streams past on colossal cables, extending out in all directions. Traffic as you've never seen before: great mechanical contraptions, machines the size of buildings, pistons whirring faster than the eye can see. The great citadel of the nucleus, heart of the metropolis, looms in the distance, miles away from you, but dominating your field of view. All is hustle and bustle. Unlike any human city, the vast sweeping walls themselves move and conjoin and dissociate again. Zoom out, and the whole city of the cell can change shape and move around, reassembling its internal structures as it does so. From out here, through the lens of a microscope, we can watch the trafficking of goods through the cell, lit up by fluorescent dyes like a town at night, all electric reds and blues and greens. Yet everything I have described is buildings, the structures of the cell. We can picture this marvellous city on a scale less than thousandths of a millimetre; we can visualise the movement of its parts like never before. But the cell is animated on a smaller scale still. Even the most powerful microscopes can't discriminate the moment-by-moment flow of energy and materials that animates all life, the unceasing changes that transform small molecules over millionths of seconds, and distances of less than a millionth of a millimetre. Deep within these marvellous moving structures, the flow of energy and matter is still invisible, as hard to imagine as the restless electrons that power our conurbations and the people within. Perhaps for that reason, we have a tendency to discount its importance to life.

Few things are as inscrutable as a cell. In the seventeenth century, when the Dutch microscopist Antonie van Leeuwenhoek unveiled the cosmos hidden in a drop of water, he marvelled at the little 'animalcules' that lived out their lives there, all whirring parts and purpose. For all our deep explorations of the cityscape of the cell, the behaviour of these protozoa is as beguiling and nearly as mysterious to us today. Do these microscopic blobs of animated protoplasm know what they are doing as they chase and consume each other? Surely not! But to our naive eye, it almost looks as if they do – as if these tiny beings have hopes and fears and pains of their own. As if they feel some joy or relief when they tear themselves free from the mechanical rotating jaws of some minuscule gyrating predator. Some 350 years after van Leeuwenhoek, we now know what most of these whirring parts do, what they're made of, how they function. We have taken them apart, in centrifuges or with optical tweezers, read out the code that specifies their structures, deciphered the regulatory loops that lend an illusion of purpose, listed all their parts. And yet underneath it all, we are barely any closer to understanding what breathes life into these flicks of matter. How did they first emerge from the sterile inorganic Earth? What forces coordinate their exquisite behaviour? Do they experience any sort of feelings?

For decades, biology has been dominated by information – the power of genes. The importance of genes is unquestionable, yet there is no difference in the information content of a living protozoon and one that died a moment ago. The difference between being alive or dead lies in energy flow, in the ability of cells to continually regenerate themselves from simpler building blocks.[1]

If there is a view from modern biology, it is that genetic information structures the flow of energy and materials. To a first approximation, biology is understood in terms of information networks and control systems. Even the laws of thermodynamics, which govern the behaviour of molecules and their interactions and reactions, can be recast in terms of information – Shannon entropy, the laws of bits of information. But this view generates its own paradox at the origin of life – where does all this information come from? Within the realm of biology, we already have a simple explanation: natural selection sifts through random differences, favouring what works, eliminating what doesn't, generation after generation. Information accumulates with function over time. We can quibble over details, but there is no conceptual difficulty here. At the origin of life, though, this view will not do. Place information at the heart of life, and there is a problem with the emergence

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1 When I talk about energy flow, I'm really referring to what physicists call 'free energy', which is to say the energy available to power work (rather than being dissipated as heat). That goes for the whole book. And when I talk about building blocks, I'm referring to small molecules such as amino acids or nucleotides, which can be joined together to form giant macromolecules such as proteins or DNA, respectively. Again, that goes for the whole book.

of function, which is to say, the origin of biological information. Not only that, but there's a problem in understanding the troubling trajectory of evolution, not least the long delays between abrupt changes, such as the emergence of animals in the Cambrian explosion, despite the continuous exploration of genetic sequence space – information – across life. There are problems, too, in understanding why we age and die, why we are still suffering from diseases such as cancer, despite decades of research, and most fundamentally, how subjective experiences can give rise to the conscious mind.

Thinking about life only in terms of information is distorting. Seeking new laws of physics to explain the origin of information is to ask the wrong question, which can't be answered precisely because it is not meaningful. A far better question goes back to the formative years of biology: what processes animate cells and set them apart from inanimate matter? The idea that there is a vital force, that life is fundamentally different from inanimate matter, was disproved long ago and is now only wheeled out as a straw man to burn – even though it's an understandable illusion for anyone who has shared van Leeuwenhoek's captivation with busy animalcules. Yet biochemistry – my own discipline, which deals with the flow of energy and materials through cells – has, with a few notable exceptions, been blithely indifferent to how this unceasing flux might have arisen, or how its elemental imprint could still dictate the lives and deaths of cells today, along with the organisms they compose. You and me.

This book will explore how the flow of energy and matter structures the evolution of life and even genetic information, leaving an indelible stamp on our own lives. I want to turn the standard view upside down. Genes and information do not determine the innermost details of our lives. Rather, the unceasing flow of energy and matter through a world in perpetual disequilibrium conjures the genes themselves into existence and still determines their activity, even in our information-soaked lives. It is the movement that creates the form. I want to capture an extraordinary renaissance that is currently hiding in plain sight: how textbook biochemistry is simultaneously galvanising new paradigms on the origin of life and cancer, to name but two fields. How could such disparate questions, separated by billions of years and gulfs in planetary environment be linked? At the core of this emerging view is an amazing, conflicted cycle of reactions that uses energy to transform inorganic molecules – gases – into the building blocks of life, and the reverse. To understand this cycle of energy and matter is to resolve the deep chemical coherence of the living world, connecting the origin of life with the devastation of cancer, the first photosynthetic bacteria with our own mitochondria, the abrupt evolutionary leap to animals with sulfurous sludges, the big history of our planet with the trivial differences between ourselves, perhaps even the stream of consciousness. In this book, we will see that understanding the deep chemistry that animates life, and fades as we die, illuminates some of the enduring mysteries of biology and our own existence.

The dynamic side

To understand this flow of energy and matter and all it portends, we must first look to where biology has turned a blind eye since the ascent of information. The golden age of biochemistry began with a realisation that cells are not made of an amorphous protoplasm composed of inscrutably complex 'living' molecules. One of the founding fathers of biochemistry, Sir Frederick Gowland Hopkins, dedicated much of his long career through the first four decades of the twentieth century to promoting what he called the 'dynamic side' of biochemistry: the idea that the basic molecules of life are quite simple and can be analysed by conventional chemical methods – but that they are funnelled down specific pathways, in which one molecule is converted through some small chemical change into another form, again and again, each time fashioned by a catalyst with specific properties. Life, for Hopkins, was the combination of information, which specifies the protein catalysts (enzymes) that channel these pathways, and flux – the flow of molecules down particular pathways to form new materials for building or rebuilding the city of the cell.

I've used the word flux a few times already, and I'll use it again throughout the book. Before getting any further, let's pause for a moment to clarify exactly what I mean by it. Flux is a form of flow, but with one crucial difference. Water can flow in a river, or traffic down a street. What goes in at one end and what comes out at the other is the same thing – water, or cars. In biochemistry, flux is the flow of things that are transformed along the way. Imagine a car entering a street; let's say it's a VW Beetle. No sooner has it gone ten yards down than there's a blinding flash and it abruptly turns into a Porsche. Then another flash and it's become a Volvo. Bang! It's a white van. Zap! Now it's a minibus. Flash! It's a tractor, which leaves the street. But the strangest thing about this street is that the same thing keeps on happening: only VW Beetles ever enter the street; only tractors ever leave. The same succession of transformations takes place each time. Let's imagine that sixty VW Beetles enter the street every minute, one per second. Each of them is transformed in a series of blinding flashes into sixty tractors. That's flux: the total number of vehicles that passes down the street, each one transformed into the same type of tractor. Of course, that's just this street. Take a look at the street around the corner. There you'll see only Vespa scooters entering, transforming into Harley motorbikes. And just across town there's a canal where canoes change into speed boats.

This is the strange world of metabolic flux. Even a simple bacterial cell can undergo as many as a billion transformations per second, an incomprehensible number. You might say that there's a lot of repeat streets in a cell (with the same thing happening in each of them) but there may be several hundred vehicles entering a street *every second*, each one reliably going through exactly the same succession. This is the flux that makes up the metabolism of the cell, which we will grapple with in this book. Metabolism is what keeps us alive – it is what being alive *is* – the sum of the continuous transformations of small molecules on a timescale of nanoseconds, nanosecond after nanosecond. If we live to the age of eighty, we will have lived through nearly three billion billion (3×10^{18}) nanoseconds-worth of metabolism. No wonder we run down. We can't actually see any of this happening before our eyes, even now, but we can infer what is going on from some of the ingenious methods I'll tell you about, methods that go back to those intrepid explorers of the nanocosm, like Hopkins a century ago, who first understood that the secret of life lies in the entrained flow and rapid transformations of many plain, simple molecules.

That was before the double helix of DNA, before the information revolution in biology, before we knew much at all about how cells work. It was in fact a glorious hypothesis, based on a handful of findings in the nineteenth century – notably that some molecules of life, such as urea, could be synthesised from scratch by chemists and were in no way magic, rebutting vitalism; this was 'merely' biological chemistry, with normal chemicals that behaved according to normal rules of chemistry.

Biochemistry became the study of how these simple molecules were interconverted one into another. Did you just trip over the word 'simple'? None of this is simple, but there are levels of complexity. The molecules that I'm talking about are small, containing between one or two and up to about twenty carbon atoms, but most of them have fewer than ten carbons. Think of these as carbon 'skeletons', in which the carbon is bound to itself plus hydrogen and oxygen atoms – with, less commonly, nitrogen, sulfur or phosphorus – giving each of them their distinct properties and tendencies to react. These are the building blocks that make up cells, little more than a few hundred types of molecule in total. The giant 'macromolecules' that form the fabric of the cell, notably DNA and proteins, are actually long chains, strings of these building blocks linked together following genetic instructions that (then) remained utterly mysterious.

The glorious hypothesis that cells are animated by the continuous directed flow of simple materials and energy turned out to be true for all life. Painstaking experiments showed that the way bacteria respire with oxygen or grow in its absence is remarkably similar to how our own heart cells behave in similar circumstances. In the 1920s, another great Dutch pioneer of microbiology, Albert Kluyver, marshalled new evidence for the unity of biochemistry. His slightly maniacal phrase 'From the elephant to butyric acid bacterium – it is all the same!' (I hear it accompanied by a burst of hysterical laughter) was later famously paraphrased as 'Anything found to be true of *E. coli* must also be true of elephants.' While deliberately mischievous, there is more than a little truth in this outrageous assertion – the biochemical pathways that produce the basic building blocks of life are indeed conserved across practically all cells. Several decades later, at the dawn of molecular biology, the idea that the genetic code is universal, encoding the same twenty amino acids (the building blocks of proteins) across all life, owed much to this beguiling conception of the unity of biochemistry. The 'universal genetic code' is now a well-worn phrase, but the idea was not established rigorously at the time. It just felt right, precisely because it resonated with the unity of biochemistry.

The digital jungle

The dawn of molecular biology! It must have been intoxicating. Darwin had given order to biology a century earlier. The discovery of genes and the laws of heredity made intellectual sense of evolution. But the molecular mechanisms of inheritance remained a black box until Crick and Watson made an inspired leap to grasp the full meaning of Rosalind Franklin's beautiful, cryptic X-ray photographs of DNA (which in turn rested on Maurice Wilkins's revealing early work; it's giant's shoulders all the way down). The story that Crick burst into the Eagle pub in Cambridge and announced that he knew the secret of life is sadly apocryphal, but it has the ring of deeper truth.

The double helix of DNA is perhaps the most meaningful icon in all science. DNA is composed of two long chains of 'letters' that snake around each other into the farthest distance, each strand providing an exact template for the other. As soon as you see it, you can grasp in principle how heredity works: when the two strands are prised apart, each serves as the template to build a fresh complementary strand, giving two copies, a new double helix for each daughter. And you can grasp in principle how the genetic code works: each strand of DNA contains just four types of letter, with millions, nay billions, of these arranged in sequence down the length of the chain. Four letters might seem limited compared with, say, the twenty-six letters of the English alphabet, but the Morse code only has two letters and can convey the same meaning. We might not enjoy listening to the works of Shakespeare in blips and bleeps but technically there is no loss of meaning, and the canon can be reconstituted in full. The same goes for DNA; indeed, Shakespeare's sonnets have been encoded in synthetic DNA. Likewise, the 3,000 million letters that make up the entire human genome are enough to code for you – your limbs, your heart, your eyes, your predispositions, albeit with a Shakespearean scope for interpreting meaning. Just as an actor might confer sympathy or antipathy to a character while declaiming the same lines, so too the same gene – the same lines of code – can have very different effects depending on the context. Genetic determinism has little meaning.

Principle is one thing; working out the details took half a century and counting. The first attempts to decipher the code of life were made by physicists, including Crick himself, who sought (and found) a mathematical beauty; but all of them turned out to be utterly wrong. The reality is far messier. The genetic code is riddled with redundancy. An amino acid is encoded by a triplet of letters, known as a codon. There can be anywhere between one and six different codons encoding the same amino acid. All this redundancy seems to limit the consequences of mutations, and so has some biological value. But there was no hiding the bewilderment of the protagonists: the beautiful pared-down symbolism of the double helix vanished without trace in the endless stretches of code that seemed to be bereft of any meaning at all, what became known as 'junk DNA'. Barely 2 per cent of the human genome codes for proteins. Arguments persist over what proportion serves a regulatory purpose; up to 20 per cent might be a generous estimate.[2] The rest seems to have little information content. But whatever the answer, for all its sprawling incoherence, the code is a source of endless fascination. Genomes are a fantastical jungle of digital patterns, mingling sense and nonsense in a similar way to computer code or the internet – meaning riddled with viruses and gobbledegook. Biology has become the study of information with all its quirky content.

That's not intended to be critical. The information revolution has transformed everything in biology, from the study of individual cancer cell lines to the development of embryos, to the deepest reaches of evolutionary time, right back to the first stirrings of life on this planet. Sequencing even overturns cherished ideas of behaviour – sparrows for example, turn out to be far less faithful to their partners than their bearing suggests; nearly a third of offspring are fathered by philandering cheats. Nothing in biology has escaped digital scrutiny. But while our exhaustive exploration of the digital jungle has changed the way we think about everything, it has also helped us forget some lessons from the past. The 'dynamic side' of biochemistry now rarely escapes the pages of dusty textbook histories. It does not seem to add much to the power of information. That's a fallacy. This book aims to show that the flow of energy and matter through cells structures biological information rather

2 There are all kinds of interactions between 'regulatory RNAs' that do not involve any proteins at all. RNA is a working copy of a short section of DNA, where the exact sequence of letters in the DNA is transcribed into the same sequence of letters in the RNA copy. This copy can be read off into a protein, or alternatively can bind to other RNA molecules directly. In this case the RNA sequence does not really 'code' for anything; the letters in one string of RNA simply interact with those in another. I'm using the term 'code' very loosely here, to mean the DNA sequence that somehow gives rise to an organism. In any case, in stricter usage, the genetic code should be termed the genetic cipher. Cryptographers can get very cross about this.

than the other way around. Information is obviously important, but it's only part of what makes us alive.

Molecular machines

Biochemistry followed a rather different path, although until recently it too turned its back on the dynamic side. Genes code for the sequence of amino acids in proteins, typically several hundred of them joined together in a string. Yet genes only code for the sequence itself, not the way that this string coils into knots and helices and sheets to give a protein its three-dimensional shape. We have still not unravelled all the rules that govern how a protein folds reproducibly into a particular shape, specified only indirectly by its DNA sequence. Ironically, artificial intelligence algorithms have recently made some progress on this question, but we're not quite sure how they did it. Biochemists, though, have become very good at resolving the architecture of giant protein molecules.

The greatest advances have drawn on the same recondite technique that Rosalind Franklin brought to bear on DNA in the early 1950s, X-ray crystallography, albeit with an enormous increase in power and resolution since then. Perhaps the consummating achievement of crystallography was Venki Ramakrishnan's structure of the ribosome – the astonishing molecular machines, virtually whole factories, that process the genetic code to build new proteins. This is no repetitive structure like DNA, but an enormous assemblage of a quarter of a million atoms, each with its own precisely defined positions. I use the plural here, because proteins are genuinely machines, with moving parts that carry out specific functions. A single protein typically has several conformational states and will switch from one to another at extraordinary speeds – hundreds or thousands of times per second. Understanding precisely how these molecular machines work has preoccupied some of the best minds in biochemistry for decades. Those of us who don't solve the structure of proteins for a living look at the pages of journals such as *Nature* with a mixture of jealousy and admiration, for every issue seems to contain at least two papers detailing the atomic structure of the latest machines. In comparison, even the whole genome sequence of another domesticated species, once all the rage, has begun to pale.

These two themes, information and structure, have combined as the dominant paradigm of medical research in recent decades. We can sequence genomes and search for small differences in sequence between people prone to some condition and those who are resistant. There might be thousands, if not millions, of variations in single DNA letters that predispose to particular diseases, but only a few of these are incriminated so regularly that they stand out as medical targets. If these genes code for a protein, then its structure can be solved in both the normal and defective forms, and it becomes a rational drug target, or may be fixed by gene editing. The idea sounds perfectly reasonable, equivalent to fixing a broken part in a car. But as we've seen, cells are more like cities than cars, and the reality of targeting specific genes is often diabolically complex.

Remember that many proteins are catalysts – enzymes – which convert one molecule into another slightly different form. Vivid as it may be, our earlier metaphor of metabolic flux as traffic transforming in size and shape as it passes down a street fails to emphasise that this doesn't happen spontaneously, at least not in biochemistry as we know it today. Each transformation is catalysed by an enzyme. To force the metaphor a bit too far, we have to imagine the street lined with giant machines (we'd better say they're invisible) that convert one car into another. This succession of giant machines each acts in turn down the street (a metabolic pathway) to change one vehicle into the next. In cells, the output is a product that is useful to the cell in some way – perhaps an amino acid that is used to build a new protein. The problem is that there is often more than one way to do the same thing. Just as there are multiple routes from A to B across the city – different streets we could take to the same destination – so too in the cell there are other ways to get to the same place. In effect, there's more than one street that turns out tractors; around the corner, there's a street that converts jeeps into tractors. If one street gets blocked, then the traffic flow shifts and compensates. But a cell is more sophisticated than a city. If a road becomes blocked, the traffic signals its impotent frustration with blaring horns. Something similar happens in the cell but here the signal of frustration travels straight to the genes, where contingency plans are immediately implemented. Alternative route too narrow to accommodate extra traffic flow? No problem: widen the road. Unlike a city, where harassed local authorities may procrastinate for months, the genes encoding alternative pathways are upregulated in hours, in effect widening the bypasses to accommodate extra traffic.

So the flux of energy and materials through the cell shifts. It might not be quite as good as the main highway, but you could hardly tell the difference. Now think about alternative routes in terms of how a drug acts. Target a particular gene or protein, and the cell redirects metabolic flux to minimise obstructions to function. Just how well it can do this depends on scores of other normally trivial genetic differences, or diet, or other forms of stress such as smoking, weight or age, and these differences account for many of the unpredictable responses to drug treatments. Cancer is a prime example. Drugs typically work for some people but not everyone, or work for a while and then start to falter. The problem is not so much the target itself but the context. Cancer cells grow and evolve. To do that they need to make all the building blocks for growth, which requires constant metabolic flux. Blocking flux at one particular place is like closing a road – it's only a matter of time before the traffic finds another way through, perhaps facilitated by a new genetic mutation, and the cell reverts to uncontrolled growth. Whereas normal cells face constraints in their flux – they have certain tasks in a tissue, such as making hormones or neurotransmitters, or detoxifying poisons – that's not true of cancer, as we'll see. Cancer cells simply switch to another flux pattern and keep on growing. The problem is not information alone; the deeper, underlying problem is flux. It's the dynamic side of biochemistry again.

Satnav metabolism

There's a new name for this that reflects the modern 'omic' age: metabolomics. We have known all the steps in the major metabolic pathways for decades – they were laboriously worked out, step by step, from the 1930s onwards, with a leap forward in the post-war years, when radioactive tracers enabled the fate of specific carbon atoms to be tracked (as we'll see in Chapter 2). Metabolomics is much the same thing, but now with the aid of powerful techniques such as mass spectrometry. Instead of seeking the commonalities – the same metabolic pathways in different cells – metabolomics looks for the differences: how does the flux of materials and energy through one of my heart cells differ from that in one of yours? It is closer to a satnav-enabled road map, showing live congestion, but it's still a snapshot in time. We can take a sample of cells and look at the distribution of flux at one moment, or over a short period of minutes or hours.[3] Will it be the same next week, next month, next year? Start over. We are a long way from rising above the cell and picturing the combined flux of energy and materials in real time over a lifetime. Metabolism remains invisible and elusive, even if we know it keeps the cell alive.

But these subtle differences in flux also emphasise one dramatic way in which cells differ from cities. Different cities are similar in that they all have roads, but the actual road map obviously differs from town to town. That's partly true of cells too, but perhaps the most extraordinary fact is that all cells share the same basic road plan, at least for the city centre itself. What differs is the congestion or the size of the roads, not the layout. The unity of biochemistry means we all share the same city-centre map. What defines this map? You might say 'genes', but that is far from true. We'll see that genes did not 'invent' metabolism, but the reverse. In any case, genes change and evolve, but the pathways they are supposed to code for remain essentially unchanged. As the poet Edna St Vincent Millay wrote, 'life isn't one damn thing after another, it's the same damn thing again and again'. A bacterial cell living deep down in the crust of the earth makes its letters for DNA through the same succession of steps that you do, even if many of its genes have diverged almost beyond recognition. Genes are far more malleable than metabolism. Likewise, if a gene in a cancer cell

3 Even this can be hard to interpret. A high concentration of some intermediate in the cell does not necessarily imply high flux – it might reflect a high rate of flux, with the intermediate being constantly replenished at high levels, or it could reflect the opposite – almost no downstream flux, so the intermediate gradually builds up; in effect, a car park. To understand which one requires a lot of context and subtle interpretation. There are times when it feels as if metabolomics should just be called gnomics.

mutates, and now promotes uncontrolled cell growth, this does not open up some new metabolic pathway, but rather diverts flux down existing pathways, even if it dramatically reverses the flow down a one-way street. Traffic flow might change but the map itself rarely does.

The reason that city street-plans differ but the central metabolic maps of cells do not is quite simple: cells descend from a common ancestor, but cities do not. Cities are similar by analogy, not homology. When we think about inheritance we tend to think about genes, but to leave any descendants a cell must be capable of growing, repairing and ultimately replicating itself, and to do that it needs a fully functional metabolic network. To be alive means to have a continuous flow of energy and materials through this whole network, nanosecond by nanosecond, minute by minute, generation after generation. We do not merely inherit inert information in the form of genes – our inheritance includes this living metabolic network in the egg cell, a flame passed from generation to generation, without pause, right back to the emergence of life. Core metabolism has changed little in part because it was never powered down in its four-billion-year history. The genes are custodians of this flame, but without the flame life is – dead.

Yet despite its unceasing flow, metabolism has been turned on its head. There is no better example of the crazy contingency of evolution, or the ability of life to cobble together a workable solution to the utter transformation of conditions on Earth, from the suffocating anoxia of the first two billion years to the energised atmosphere of the age of animals, without which we could not exist. At the heart of the cell is a merry-go-round of energy and matter known as the Krebs cycle, after the venerated biochemist Sir Hans Krebs, who first conceived this iconic cycle of reactions in the 1930s. It's also sometimes called the 'citric acid cycle' or the 'tricarboxylic acid cycle', but let's stick with the more personable name in this book. Unlike most metabolic pathways, which run in straight lines, the Krebs cycle leaps out from our metabolic maps with a Platonic sense of perfection, the perfect circle at the centre of everything, yet elusive still in meaning more than eighty years after its discovery. Elusive, in part, because biochemistry moved on long ago, enchanted by the marvellous mechanics of molecular machines. But elusive most of all because this apparently perfect cycle of energy and matter in fact conceals a strained balance of opposites, a yin and yang, which touches on all aspects of life.

The Krebs cycle

Generations of biochemistry and medical students have been obliged to learn the steps of the Krebs cycle by rote. Despite its iconic status it has earned little love or real understanding. That's partly the problem with visualising biochemistry: this is an invisible and abstruse set of reactions, each step an ostensibly trivial rearranging of carbon, hydrogen and oxygen atoms (see pages 286–7). But beyond that, even its true function is obscure. The textbooks tell us that the Krebs cycle generates energy by stripping out hydrogen atoms from the carbon skeletons of food and feeding them to the ravenous beast that is oxygen (well, they might not put it in exactly those terms). This is the process of cellular respiration. The energy released at each step is ingeniously captured and put to use in the cell, while the inert carcasses of water and carbon dioxide are discharged into the outside world. But why is it a cycle at all? Why not just a few simple steps? Krebs himself suggested one plausible answer: burning very small carbon skeletons is not an efficient process, he argued, so a cycle was necessary. The later