

**Mark Stevenson** is a writer, entrepreneur, broadcaster, futurologist and founder of The League of Pragmatic Optimists. He has written for Radio 4, *The Times*, *Wall Street Journal*, *Guardian* and *New Statesman*, and is the author of the critically acclaimed *An Optimist's Tour of the Future*. He lives in London and is an adviser to (among others) The Atlas of the Future, The Virgin Earth Challenge and Civilised Bank.

### ***Praise for We Do Things Differently***

‘Stevenson is an excellent storyteller and knows how to make science comprehensible, whether it is drug metabolism or liquid-air engines. The chapters on drug discovery with which the book opens are especially well told. Fascinating.’ *The Times*

‘I have purchased more copies of this darned book than I care to number. I have only to put it down and someone borrows it permanently. This joyous book is a smile between covers, a feast of ingenuity and an incitement to genuinely think. So if you know anyone that either likes thinking or needs to think, give them this book.’ Sir Tim Smit

‘[An] inspirational book. Mark Stevenson has toured the world meeting people who refuse to take “status quo” for an answer. The book works so well because Stevenson gets out there to see things for himself. He’s also good at explaining the technicalities, even to readers (like me) with the engineering nous of a small pebble.’ *Mail on Sunday*

‘A brilliant look at people around the world who are attempting to solve the planet’s most pressing problems by innovative means. It’s a very much needed shot of optimism in these troubling times.’ *Sunday Herald*

‘An inspiring book that makes you feel optimistic about the future; much needed at this moment in time.’ Cornelia Parker, *Observer*

‘A positive set of stories for anyone feeling particularly negative about humanity’s prospects in the coming years. The book is in a way a victim of its own success; the large number of subjects contained within mean it’s necessary to skip from one issue to the next making you wonder how much more to each story we could be missing out on. Nevertheless, Stevenson’s ability to cover such a wide range of challenges should be applauded. Combined with his engaging commentary this certainly has the ability to restore your faith in human ingenuity in the face of adversity.’ *Geographical Magazine*

‘A timely reminder of the power of grassroots innovation to create solutions to some of the world’s big challenges. What makes the book so engaging is not just the incredible ideas and initiatives he discovers, but the way he tells the story of the people themselves – what motivated them; what made them smile; their body language. The pages are alive with the personalities of those engaged with “rebooting” our world.’ *Fifth Estate*



# WE DO THINGS DIFFERENTLY

THE OUTSIDERS REBOOTING  
OUR WORLD

MARK STEVENSON

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# INTRODUCTION

# WINDMILLS

**‘Never interrupt someone doing what you said couldn’t be done.’** – AMELIA EARHART, AVIATOR

There is a man in the sleepy market town of Bishop’s Stortford, Hertfordshire who has found a solution to two of humanity’s biggest challenges – using only his lawnmower and a can of antifreeze. In Boston an engineer with no medical training has given the healthcare profession access to something more powerful than any drug ever created. Just outside the city of Ranchi, north-east India, a young man is growing crops in places that accepted wisdom would suggest that it’s hopeless to farm, while in Brazil an idea first proposed by some neighbourhood activists is achieving something many would consider impossible – it makes politicians popular.

There have always been a subset of people who think differently. A smaller number *do* differently, people who look at the status quo and not only think ‘I could fix that’ but actually roll their sleeves up and start working.

And never have we needed them more.

We live in the eye of a storm, a time in history where human-kind must change the way it organises itself or face disastrous

consequences. Our energy and food systems are increasingly unsustainable, promising an entwined environmental, economic and humanitarian crisis of unprecedented proportions. Democracy, where it exists, is descending into alienating tribalism. Inequality is rife. If you're lucky enough to enjoy a free press, it's likely you don't trust it. The world's healthcare systems are, in reality, astonishingly expensive and labyrinthine *sick-care* systems. And in most parts of the developed world, our education systems still seem trapped in the last century.

It's easy to feel despondent. But for some individuals, the roll call of bad news (not helped by the fact that as far as the media is concerned the bad news is pretty much the *only* news) isn't a cause for despair, but a call to arms. I know because I spend my life hunting them out and trying to learn their lessons. When it comes to the future they are here to remind us that there are many more options available than the leaders of any corporation, political party, pressure group, religion, academic institution or media outlet would have you believe.

Such pioneers have never had it easy. In 1532 the maestro of change and original political scientist Niccolò Machiavelli's famous political treatise *The Prince* was published. In it he wrote:

*'It ought to be remembered that there is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things. Because the innovator has for enemies all those who have done well under the old conditions, and lukewarm defenders in those who may do well under the new. This coolness arises partly from fear of the opponents, who have the laws on their side, and partly from the incredulity of men, who do not readily believe in new things until they have had a long experience of them.'*



In short, change might sound possible in principle but we'll only believe it if we can see it.

Welcome, then, to *We Do Things Differently* – a follow-up, or more exactly a prequel, to my previous book, *An Optimist's Tour of the Future*. For this is not so much a book about the future as about the here and now. It charts a journey to find the people who, despite the resistance of those who benefit from the status quo, are putting brave and alternative futures on the table – new ways of organising ourselves that address the grand challenges of our age. It features innovators reshaping the education system, exploring new forms of government, reforming the world of healthcare and medicine, re-booting cities and changing the way we think about and produce our food and energy.

These innovators are not tinkering with the existing system, but looking to change the system itself.

Of course the world is replete with armchair sages telling us what they think the future should be like – and how much better it would be if we agreed with them. So, I had one overriding criterion for inclusion in my itinerary. The innovators had to be *succeeding right now in the real world*. Whatever their idea, I wanted to be able to touch it, meet the people making and benefiting from it, see 'the steel in the ground' as the saying goes. It had to be working and I had to be able to see it working.

I travelled from the urban devastation of Detroit to a small town on the Austrian-Hungarian border; from the leading genetics labs in the world to one of the toughest housing estates in Britain. I met brilliant people from all walks of life, from poor farmers to hipster software geeks, from some of the world's highest-ranking scientists to a lone unqualified genius in a shed, from a nightclub owner turned headteacher to an international basketball ace turned engineer. It's a cast of characters who are by

turns inspiring, demanding and driven – the pioneers, architects and builders of a surprising and hopeful future – albeit one that is presently below the radar. People who really do do things differently and invite us to do the same.

There is an old Chinese proverb:

*‘When the winds of change blow some people build walls,  
others build windmills’.*

This is a book about the windmills.

# 1 MY BROTHER'S KEEPER

**'Beware the fury of a patient man.'**

– JOHN DRYDEN, POET

It is with some trepidation that I approach a well-appointed Victorian house in the affluent Boston suburb of Newton. I'm here to meet a man who's been described to me as 'a firebrand' who 'doesn't suffer fools gladly' and 'leaves corpses everywhere'. We meet on the driveway. He's been in the yard preparing to lay some cobblestones. This is the sort of thing he likes to do on holiday (a holiday I'm interrupting, it turns out, adding to my nervousness). 'Sometimes I like problems I can solve completely alone,' he explains. Teamwork, it turns out, hasn't always come easily to him.

He's in obviously rude health – clear skin, piercing eyes, a frame that's clearly no stranger to exercise. At nearly fifty there isn't a hint of middle-aged spread about him and only the merest suggestion of grey in his short, dark brown hair.

'So, what's your deal?' he asks. 'Besides being an important writer that I have to meet?' I can't tell if that's generosity or sarcasm, because his features don't move much when he talks, as if anything overly expressive would amount to a waste of

resources. His whole manner exudes ruthless efficiency. He'd make a great Hollywood villain. But there are flashes of charm too – and despite his reputation as something of a ball-breaker, at his core this is a man guided by a single, benign force. I don't think he could have achieved so much if he wasn't.

Jamie Heywood is a man driven by love.



**In 1998 Jamie's younger brother Stephen, an architect and builder,** found he couldn't turn a key in the door to one of the houses he was renovating. Soon after, the athletic and handsome Bostonian was diagnosed with Amyotrophic Lateral Sclerosis (ALS), more commonly known as Motor Neurone Disease in the UK and 'Lou Gehrig's disease' in the USA – a condition that erodes the nervous system's ability to control our muscles. Sufferers become progressively weaker over time, losing the ability to speak, swallow and, eventually, breathe. 'Luckier' patients (Stephen Hawking being the most famous example) may be spared fatal degeneration in the systems controlling the operation of their diaphragm and swallowing muscles, but they're outliers. For most it's a swiftly arriving death sentence.

When Stephen was diagnosed, Jamie immediately set about trying to save him, no small ambition given a) a cure for the condition had completely evaded the medical profession since it was first identified in 1824, b) Jamie, a graduate in mechanical engineering, had absolutely no medical training, and c) if Stephen's disease progressed at the rate of most sufferers he had less than four years. Within three days of Stephen's diagnosis Jamie had quit his engineering job in San Diego, relocated to the basement of the family home in Boston and incorporated the

world's first not-for-profit biotech company with the sole aim of finding a cure. The first \$10,000 to fund what became the ALS Therapy Development Institute (ALS TDI) came from Stephen. Jamie raised another \$400,000 in the first year alone, and ten times that the following one – enough to rent premises (and refit them into what is now the largest ALS lab in the world) and attract leading researchers to his fledgling enterprise. Like I said; ruthless efficiency. And love. It's a hell of a combination.

Time was of the essence, which meant creating a new drug from scratch wasn't an option. Even if ALS TDI discovered a new wonder drug *on day one*, it would probably be too late for Stephen; he'd die before the six years required to get it approved, a period dominated by ever more involved and expensive clinical trials required by the Federal Drug Administration.\* (These trials rightly seek to validate any drug's effectiveness, determine ideal dosages and explore side effects.) Instead the strategy was to screen drugs already approved for the treatment of other conditions and see if they might *also* be effective against ALS. Doctors are allowed to prescribe drugs 'off label' (to treat a condition they weren't originally developed for) if there's good research to suggest this might help. In fact, drugs finding alternative uses to those they were originally developed for is common. For example, Raloxifene, now a breast cancer drug, was originally developed to treat osteoporosis. Sildenafil, initially proposed as a medicine for angina and hypertension, became one of the most lucrative drugs of all time thanks to its effect on an entirely different condition. It is now best known by its brand name: Viagra. If ALS TDI could find something that was already out there, the chances of saving Stephen were much higher.

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\* ... and that was being optimistic – an industry rule of thumb is that the average 'time-to-market' (from discovering a drug to general availability) is twelve years.

Stephen's disease progressed slower than average. Four years after diagnosis he was still alive, though chair-bound. Jamie describes his brother as 'invincible'. From his wheelchair (customised by Jamie) he continued to oversee house refurbishment projects, including the 'carriage house' next to Jamie's home (where he and I are now talking). Stephen got married to Wendy and had a son, Alexander ('equipped with his first, full-sized power drill at the age of two'). His sense of humour was legendary, emerging even in the prospect of death, insisting he wanted his end to be heroic – saving someone from a fire. But, he joked, it would have to be a fire that spread slowly, and there would need to be ramps because he'd be in a wheelchair.

In 2002 there was a hint that ALS TDI's strategy might pay off. A study from Johns Hopkins University School of Medicine showed that mice with a particular version of ALS lived longer if they were given the anti-inflammatory drug Celebrex. Here was a hot lead. 'Immediately Stephen's doctor and I collaborated and he started on the drug at a higher than normal dose,' says Jamie. At the same time he started trying to replicate the Johns Hopkins research because 'I'm an engineer by training, which means I like to validate things.'

The problem was they couldn't get the same result. In fact, in ALS TDI's rerun of the study there was no difference between unmedicated mice (the 'control group' in the parlance of scientists) and those that had been given Celebrex. Both groups died at the same rate. To be sure, they ran the study three more times with the same unhelpful result on each occasion: the mice dosed with Celebrex showed no advantage over the unmedicated 'control' group. How could this be? The conclusion Jamie reluctantly drew was that the original study was flawed. 'We realised there must have been something wrong with the control group in the Johns Hopkins study. Celebrex wasn't extending the lives of the

mice that took it. Instead the mice in their control group had died *earlier* than average for some reason.'

But if that research was flawed, could other studies that ALS TDI had been basing some of its own efforts on be trusted? Luckily, from the outset Jamie had been intent on running his operation in a manner more akin to an engineering company than a traditional research lab: because they're often involved in building things that (if they go wrong) can instantly and spectacularly kill people (bridges, aircraft, roller-coasters, etc.), engineers place a strong emphasis on repeated and robust testing.

Accordingly, Jamie had created a lab whose mice numbers dwarfed previous experimenters in the field. By the time of the Celebrex study ALS TDI had already run trials involving over 10,000 mice with the disease, four times more animals than all other ALS studies in history combined – data it now subjected to a mathematical reality check called a Monte Carlo simulation. The results were horrifying.

Perhaps the simplest way to understand a Monte Carlo simulation is to consider the chances of getting a particular score when rolling a pair of dice. Listing all the possible combinations will soon reveal that you're more likely to roll a seven than any other number. Out of the 36 possible combinations, you'd quickly ascertain that six of them (or just under 17%) will yield you a '7', while the chances of getting a twelve (one combination) are just under 3%. A Monte Carlo simulation is a more complicated way to arrive at the same percentages, by rolling the dice many, many times (say 10,000) and noting down how often each number occurs. Over time you'd find that sevens occur roughly 17% of the time and twelves far less – and the more often you roll the dice, the more accurate the results become. While this technique is massive overkill for working out the chances of rolling a particular combination of dice, it is

useful if you have a more complicated question to answer like, ‘what’s the likelihood of an unmedicated mouse with ALS living for 150 days as opposed to 170 days?’ – and you have enough data to crunch.

ALS TDI’s Monte Carlo simulation revealed a terrible truth: that at least half, and probably most, of the medicated mice in all previous ALS trials had lived longer as a result of random chance. To be sure they reran the actual experiments from a fifth of the previous studies (the most promising ones) in their own lab, but with much larger numbers of animals. Sean Scott, who led the research, told *Nature* ‘we were heartbroken, because even using dramatically more animals than any of those other labs ... we just could not get any of those drugs to work’. In other words, all of the previous studies into ALS were unwittingly bogus. Worse, clinical trials that had been set up based on those studies had been money and time down the drain. Unsurprisingly, in the light of ALS TDI’s analysis, they all failed to replicate the false promise of the early studies.

The emotional impact on Jamie was enormous. He’d set out to save his brother, had found funding for, and built, the biggest ALS lab in the world – a lab he hoped would accelerate the pace of research. Instead he’d discovered that the field was, in reality, a long way behind where everyone thought it was. With time running out, Jamie was further away from his goal than ever.



**How could the majority of medical research into ALS therapies be spurious and nobody realise?** The answer is more disheartening than you might think, because it’s not just ALS research that turns out to be suspect. Nearly the entire medical research profession suffers from bias and bogus results.



Much of the credit for this revelation goes to Dr John Ioannidis, who's built a formidable career in 'meta-research' (essentially research about research). His seminal 2005 paper 'Why Most Published Research Findings Are False' proved, scientifically, that many medical findings are based on shoddy research. His team at Stanford's Meta-Research Innovation Center continue to demonstrate over and over again that the conclusions of published studies in medicine (conclusions doctors collectively refer to when prescribing drugs) are often misleading, overstated, non-replicable or 'accurate measures of the prevailing bias'.

How can this be? The answer is that medical researchers, like the rest of us, hope. They hope their studies will yield results that answer the questions that bother them. Day to day, in order to keep that dream alive, they need to secure grant funding – which is much easier if their research is considered promising and published in the prestigious journals that the funders pay attention to. All of this can unconsciously guide their actions, says Ioannidis. 'At every step in the process, there is room to distort results, a way to make a stronger claim or to select what is going to be concluded. There is an intellectual conflict of interest that pressures researchers to find whatever it is that is most likely to get them funded.'

Ioannidis is clear that, while scientists may be knowledgeable about their specialisms, many are less able to design and operate a study that will put checks and balances on any unconscious bias. The potential potholes for an unskilled study designer are numerous. They pose the wrong questions, design studies without reference to existing evidence, recruit the wrong participants (or too few), take the wrong measurements or analyse data erroneously all within a system that encourages scientists to publish in well-regarded journals, who (to maintain their reputation) reject most of the papers submitted to them, and

*especially* those that report negative results rather than positive ones. ‘Currently we reward the wrong things,’ says Ioannidis, ‘people who submit grant proposals and publish papers that make extravagant claims’, which means ‘the hotter a scientific field ... the less likely the research findings are to be true’.

For drugs companies, the hope takes a different form – the desire for greater profits. Take the case of Reboxetine, a drug for depression made by Pfizer. *The Economist* reported how the firm published trial data for the antidepressant showing a beneficial effect on over 65% of patients but neglected to publish the results of six further trials that, if taken into account, gave an average figure of just 11%. (Two of the unpublished trials actually showed patients fared *worse* on the drug.) As a doctor would you be more inclined to prescribe a drug reported effective 65% of the time, or 11%?

Harvard Medical School’s Dr Marcia Angell, for two decades an editor of the prestigious *New England Journal of Medicine*, summed up the situation with extraordinary candour:

*‘It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines.’*

Since Ioannidis’ initial research there has been a growing acceptance within medicine that there is a genuine problem to be addressed. An oft-quoted statistic is that dodgy research wastes over \$100 billion a year. Depressing, isn’t it?



**I first heard Angell’s quote as part of a speech given by Jamie Heywood at the Drug Information Association’s (DIA) 50th Anniversary conference – a talk he gave after being awarded**