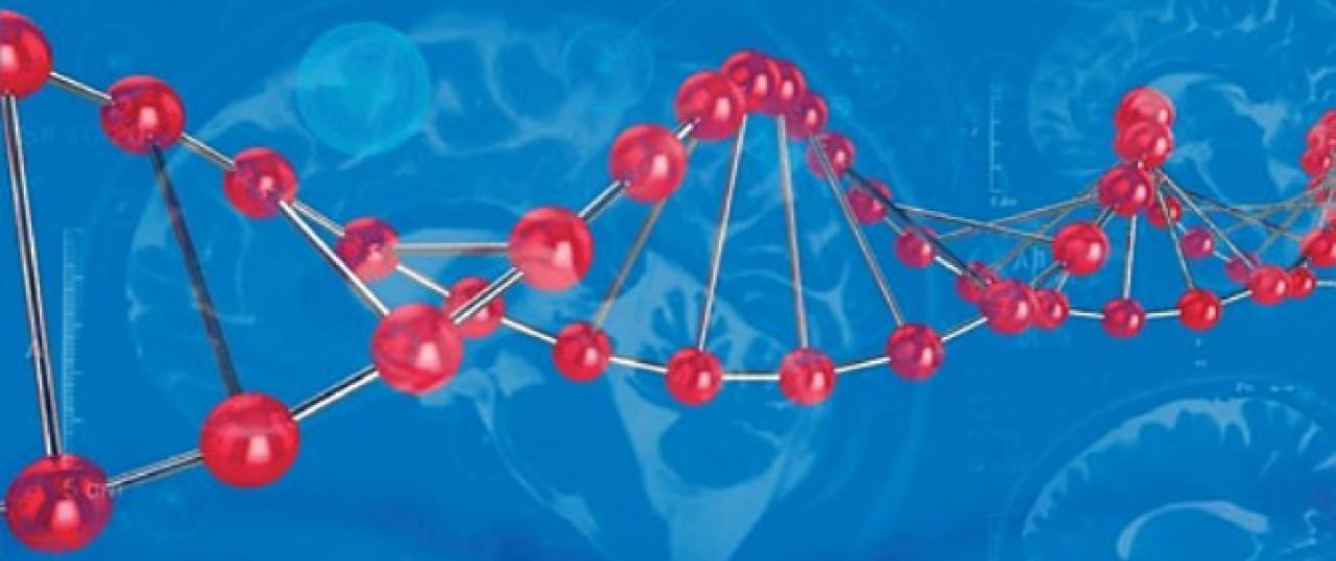
JAMES LE FANU

The Rise & Fall of Modern Medicine

FULLY REVISED AND UPDATED

WINNER OF *THE LOS ANGELES TIMES* BOOK PRIZE



'Excellent' *Financial Times*

'Brilliant' *Daily Mail*

'Fascinating' *Sunday Telegraph*

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Published by Hachette Digital

ISBN: 978-0-748-13143-3

Diagrams by Lynda Payne

Hachette Digital
Little, Brown Book Group
100 Victoria Embankment
London, EC4Y 0DY

www.hachette.co.uk

Contents

ACKNOWLEDGEMENTS

The arduousness of writing has been more than compensated for by the privilege of meeting so many of those who participated in the great events recorded in this book. To them; to the sympathetic souls whose interest has been more important than they realise; to the librarians at the Royal Society of Medicine and the Wellcome Institute for the History of Medicine; to my wife Juliet; to my agent Caroline Dawnay, publishers Philippa Harrison and Richard Beswick and editors Andrew Gordon and Victoria Pepe; and to Vanessa Adams and Caroline Sherbrooke for their prodigious secretarial skills: my thanks.

Dr Digby Anderson, Lord Annan, Bryan Appleyard, Mr John Ballantyne FRCS, Sir Douglas Black, Professor Nicholas Black, Sir Christopher Booth, Dr Thomas Boulton, Professor John Bunker, Dr Bruce Charlton, Mr Bill Cleland FRCS, Sir John Dacie, Dr Ann Dally, Dr Anthony Daniels, Professor Norman Dennis, Professor C. J. Dickinson, Sir Richard Doll, Professor Deborah Doniach, Professor Israel Doniach, Professor R. S. Downie, Sir John Ellis, Professor Peter Ellwood, Professor Renée Fox, Mr Michael Freeman FRCS, Professor David Galton, Dr John Glyn, Mr James Gow FRCS, Dr C. W. Haigh, Professor John Hampton, Dr Myles Harris, Sir Donald Harrison, Dr I. D. Hill, Professor A. V. Hoffbrand, Dr Arthur Holman, Mr John Hopewell FRCS, Dr David Horrobin, Professor Bryan Jennett, Professor Trevor Jones, Dr Michael Joseph, Dr Leo Kinlen, Dr Ghislaine Lawrence, Professor John Marshall, Dr William Marshall, Dr Robert Matthews, Professor James McCormick, Professor Kenneth Minogue, Dr G. Misiewicz, Professor John Moorehead, Mr E. P. O'Donoghue FRCS, Professor Peter Openshaw, Mr Nicholas Parkhouse FRCS, Professor Michael Patton, Sir Stanley Peart, Mr Elliot Philipp FRCS, Mr Michael Powell FRCS, Dr David Pyke, Mr Gordon Rees FRCS, Professor Jonathan Rees, Professor Lesley Rees, Dr Henry Rollin, Dr Jack Scannell, Dr Rupert Sheldrake, Professor Peter Skrabanek, Professor Alexander Spiers, Professor Gordon Stewart, Mr John Studd FRCOG, Professor Raymond Tallis, Dr Tilli Tansey, Dr Wendy Taylor, Professor Tom Treasure FRCS, Mr Patrick Trevor-Roper FRCS, Dr John Wade, Sir David Weatherall, Dr Mark Weatherall, Professor Simon Wesseley, Mr Adrian While FRCS, Dr Elizabeth Whipp, Mr John Wickham FRCS, Sir Michael Woodruff, Dr Nigel Yeatman.

Preface to the Second Edition

Over the past fifty years medicine has metamorphosed from a modest pursuit of limited effectiveness into a massive global phenomenon employing millions and costing (hundreds of) billions. Now, in the vast shiny palace the modern hospital has become, the previously unimaginable goals of transplanting organs and curing childhood cancer have become unexceptional, while every year tens of thousands previously doomed to blindness from cataracts or to immobility from crippling arthritis have their sight and mobility restored. Medicine has become the most visible symbol of the fulfilment of the great Enlightenment Project where scientific progress would vanquish the twin perils of ignorance and disease to the benefit of all.

And yet the more powerful and prestigious medicine has become, the greater the impetus to extend its influence yet further, resulting in the progressive 'medicalisation' of people's lives, to no good purpose and potentially harmful consequences. This takes many forms, from the overinvestigation and over treatment of minor symptoms to the inappropriate use of life-sustaining technologies, anxiety mongering about trivial (or non-existent) threats to health in people's everyday lives, and the propagation of unreasonable expectations about what the current state of medical research can reasonably expect to achieve.

These are no trivial matters. They warrant clear analysis and, if possible, remedial action; yet their significance has for the most part been concealed from view by the common perception, profoundly influenced by medicine's historic achievements, of it being on a continuous and upward curve of knowledge. Here the unknown is merely waiting to be known with, in principle, no limits to its further beneficent advance.

Yet it is not so, for as I proposed a decade ago in the first edition of *The Rise and Fall of Modern Medicine,* the current difficulties and discontents of medicine are ultimately linked to the changing fortune of the three forces that forged the therapeutic revolution of the post-war years – clinical science, pharmaceutical innovation and technical progress. This, in turn, has created an intellectual vacuum within which faulty and unrealistic assumptions of medicine's 'tasks and goals' have flourished. Now, ten years on, the 'massive global enterprise' of medicine remains as powerful as ever – if not more so, and as suggested by the continued exponential increase in National Health Service expenditure and the revenues of the pharmaceutical industry.

But the central thesis of *The Rise and Fall …* still holds, and so for this second edition I have revised but made no substantial changes to the original text. To this I have added an epilogue examining the three most significant factors in the continuing expansion of the medical enterprise over the past decade: the technical innovations that have extended the benefits of medical intervention to an ever ageing population; the ascendancy of The New Genetics in the aftermath of the completion of the Human Genome Project to become the dominant form of medical research; and, most importantly of all, how an ever wealthier pharmaceutical industry has successfully subverted the proper aims of medicine to its own very profitable advantage.

INTRODUCTION

The history of medicine in the fifty years since the end of the Second World War ranks as one of the most impressive epochs of human achievement. So dramatically successful has been the assault on disease that it is now almost impossible to imagine what life must have been like back in 1945, when death in childhood from polio, diphtheria and whooping cough were commonplace; when there were no drugs for tuberculosis, or schizophrenia, or rheumatoid arthritis, or indeed for virtually every disease the doctor encountered; a time before open-heart surgery, transplantation and test-tube babies. These, and a multitude of other developments, have been of immeasurable benefit, freeing people from the fear of illness and untimely death, and significantly ameliorating the chronic disabilities of ageing.

This post-war medical achievement is well recognised, but much less appreciated is the means by which it was brought about. For the previous 2,000 years doctors had sought in vain for the 'magic bullets' that would alleviate their patients' suffering and then, quite suddenly and without warning, they came cascading out of the research laboratories just as if medicinal chemists had hit the jackpot (as they had). Or again, in 1945, desirable objectives such as transplanting organs or curing cancer were rightly perceived as being unattainable, as there was simply no way of overcoming the biological problems of the rejection of foreign tissue or the selective destruction of cancer cells. But these and many other obstacles were surmounted. The past fifty years have been a unique period of prodigious intellectual ferment that, quite naturally, invite investigation.

There is a problem, however, in knowing where to start. The scale of the therapeutic revolution has been so vast that any comprehensive history would necessarily run to several volumes. Decisions had to be made about not only what to include and what, regretfully, to leave out, but also how to go beyond a simple chronological account to illuminate themes of more general significance. The compromise I have chosen is illustrated opposite. This list of the major events of this period identifies twelve 'definitive moments' which are considered in depth in a prologue that is necessarily longer than is customary. The rationale of this selection is not of immediate concern but several themes are easy enough to identify, including the decline of infectious disease (sulphonamides, penicillin and childhood immunisation); the widening scope of surgery (the operating microscope, transplantation and hip replacements); major developments in the treatment of cancer, mental illness, heart disease and infertility; and improvements in diagnostic techniques (the endoscope and the CT scanner).

Each of these events is a remarkable story of human endeavour in its own right, but when they are assembled together then, as with the dots of the pointillist, a coherent picture should begin to emerge. The value of such an historical perspective is not necessarily obvious. 'Medicine pays almost exclusive homage to the shock of the new,' writes the editor of *The Lancet,* Richard Horton. 'We place constant emphasis on novelty … this is an era of the instantaneous and the immediate.'[1] This preoccupation with 'the new' leaves little room for history, and indeed medicine has got by well enough with no sense of its immediate past at all. Perhaps the history of twentieth-century medicine is solely of academic interest, an intellectual pastime for retired doctors but of little practical importance?

The Twelve Definitive Moments of Modern Medicine

* A 'definitive' moment	
1935	Sulphonamides
1941	*Penicillin
	'Pap' smear for cervical cancer
1944	Kidney dialysis
1946	General anaesthesia with curare
1947	Radiotherapy (the linear accelerator)
1948	Intraocular lens implant for cataracts

1949	*Cortisone
1950	*Smoking identified as the cause of lung cancer
	Tuberculosis cured with streptomycin and PAS
1952	*The Copenhagen polio epidemic and the birth of intensive care
	*Chlorpromazine in the treatment of schizophrenia
1954	The Zeiss operating microscope
1955	*Open-heart surgery
	Polio vaccination
1956	Cardiopulmonary resuscitation
1957	Factor VIII for haemophilia
1959	The Hopkins endoscope
1960	Oral contraceptive pill
1961	Levodopa for Parkinson's
	*Charnley's hip replacement
1963	*Kidney transplantation
1964	*Prevention of strokes
	Coronary bypass graft
1967	First heart transplant
1969	Prenatal diagnosis of Down's syndrome
1970	Neonatal intensive care
	Cognitive therapy
1971	*Cure of childhood cancer
1973	CAT scanner
1978	*First test-tube baby
1979	Coronary angioplasty
1984	*Helicobacter as the cause of peptic ulcer
1987	Thrombolysis (clot-busting) for heart attacks
1996	Triple therapy for AIDS
1998	Viagra for the treatment of impotence

Needless to say, I do not share this view, but rather, taking my cue from T. S. Eliot – 'the historical sense involves the perception not only of the pastness of the past, but of its presence' – maintain it is not possible to understand the present, and in particular present discontents, outside of the context of this recent past. And what is the nature of these 'present discontents'? Any account of modern medicine has to come to terms with a most perplexing four-layered paradox that at first sight seems quite incompatible with its prodigious and indubitable success.

Paradox 1: *Disillusioned Doctors*

The success of modern medicine should make it a particularly satisfying career, which indeed it is, but recent surveys reveal the proportion of doctors 'with regrets' about their chosen career increased steadily from 14 per cent of the 1966 cohort to 26 per cent of the 1976 cohort to 44 per cent of the 1981 cohort and to 58 per cent of the 1986 cohort.[2] These findings should not be taken at face value, as spasms of self-doubt may become commoner for any number of reasons. Nonetheless, they would seem to be symptomatic of a genuine – and serious – trend. Until very recently – and in marked contrast to the experience of the other liberal professions – virtually all medical graduates went on to practise medicine. But no more. In 1996 one-quarter had no plans to work in the National Health Service, accounting for both the progressive decline in the numbers entering general practice and many hospitals reporting difficulties in recruiting junior doctors. Why should it be that today's young doctors are so much less content than those who qualified thirty or more years ago?

Paradox 2: The Worried Well

The benefits of modern medicine in alleviating the fear of illness and untimely death should have meant that people are now less worried about their health than in the past. But once again, the trend is the reverse of that anticipated. The proportion of the population claiming to be 'concerned about their health' over the last thirty years has also increased in direct parallel to the rise in the number of 'regretful' doctors – from one in ten to one in two.[3] And the most curious thing about this phenomenon of the 'worried well' who are 'well' but 'worried' (that they might not be) is that it is not simply symptomatic of privileged life in the West, where 'people don't know when they are well-off', but that it is medically inspired. The 'well' are 'worried' because they have been led to believe their lives are threatened by hidden hazards. The simple admonition of thirty years ago – 'Don't smoke, and eat sensibly' – has metamorphosed into an all-embracing condemnation of not just tobacco but every sensuous pleasure, including food, alcohol, sunbathing and sex. Further, every year brings a new wave of 'dangers', posed by low-fat milk and margarine, computer screens, head-lice shampoo, mobile phones and much else besides, with Britain's Chief Medical Officer warning that eating three lamb chops a day or its equivalent increased the risk of cancer.[4] This is 'Healthism' – a medically inspired obsession with trivial or non-existent threats to health whose assertions would in the past, quite rightly, have been dismissed as quackery.[5]

Paradox 3: *The Soaring Popularity of Alternative Medicine*

The demonstrable success and effectiveness of modern medicine should have marginalised alternatives such as homeopathy and naturopathy into oblivion. Not so. In the United States there are more visits to providers of 'unconventional therapy' (425 million) than to 'primary care physicians' (388 million annually). As the efficacy of alternative therapies is not routinely tested in clinical trials (which does not mean they do not work), it is only natural to ask why the public should appear to have so much faith in them.[6]

Paradox 4: *The Spiralling Costs of Health Care*

The more that medicine 'can do', the higher will be its cost, which will be further compounded by the continuing rise in the numbers with the greatest need – the elderly. Neither of these two factors, however, can begin to account for the massive escalation in the resources allocated to health care. Thus the budget of Britain's famously 'cheap and cheerful' National Health Service doubled from £23.5 billion in 1988 to £45 billion in 1998. This financial largesse suggests that the almost universal belief that the problems of the Health Service would simply be solved by more generous funding, must be incorrect.[7]

In summary, then, the four-layered paradox of modern medicine is why its spectacular success over the past fifty years has had such apparently perverse consequences, leaving doctors less professionally fulfilled, the public more neurotic about its health, alternative medicine in the ascendancy and an unaccounted-for explosion in Health Service costs.

It is important to keep a sense of proportion about all this. In general, doctors do find fulfilment in their work, and in general people appreciate the benefits of modern medicine, as anyone whose mobility has been restored by a hip replacement or whose spirits have been lifted by an antidepressant will testify. But the same point could be put the other way. It is precisely because medicine *does* work so well that the discontents reflected by these paradoxes are worthy of explanation.

These are complex matters and there are many reasons for each of these paradoxes. But 'History is a high point of advantage from which alone men can see the age in which they are living' (G. K. Chesterton), and from the high point of advantage of a historical perspective on medicine's last fifty years it is possible to perceive there might also be a unifying explanation that can be inferred from the chronology of Definitive Moments – with the massive concentration of important innovations from the 1940s through to the 1970s followed by a marked decline. There has been, as suggested in the title of this book, a 'Rise and Fall', which provides the key to understanding the paradoxical discontents of modern times.

But when this historical account opens, such matters are still a long way off. Imagine, rather, that Europe is in the throes of war, children are still dying from whooping cough and polio, the inmates of mental asylums are lucky to see a doctor from one year's end to the next, and curing cancer or transplanting organs seem like unattainable fantasies. And yet there is a terrific sense of optimism in the air. Medicine's greatest epoch has already begun, and the possibilities of science seem limitless.

The Lord hath created medicines out of the earth; and he that is wise will not abhor them.

ECCLESIASTICUS 38:4

A LENGTHY PROLOGUE

Twelve Definitive Moments

The history of modern medicine starts sometime in the 1830s, when a few courageous physicians acknowledged that virtually everything they did – bleeding, purging, prescribing complicated diets – was useless. The distinguished medical commentator Lewis Thomas elaborates:

> Gradually over the succeeding decades the traditional therapeutic ritual of medicine was given up [to be replaced by] meticulous, objective, even cool observations of sick people. Accurate diagnosis became the central purpose and justification for medicine and as the methods improved, accurate prognosis also became possible, so that patients and their families could be told not only the name of the illness but also, with some reliability, how it was most likely to turn out. By the time this century had begun, it was becoming generally accepted as the principal responsibility of the physician.[1]

By the time this history begins, doctors had become very skilled at diagnosing what was wrong – deploying the simple skills of taking a history, conducting an examination and doing a few simple tests on blood and urine – but, the 'therapeutic ritual' having been jettisoned, the cupboard of specific remedies was virtually bare. The efficacy of some of the traditional remedies derived from plants – such as the heart drug digoxin from the foxglove and aspirin from the bark of the willow tree – had been vindicated. Several forms of immunisation of varying effectiveness had been developed for the treatment of the infectious diseases, and the chemical salvarsan had been found to be specifically successful against syphilis. The only other two significant therapeutic developments had been the discovery of vitamins (though vitamin-deficiency diseases were rare enough) and the isolation of hormones such as thyroxine and insulin for the treatment of diseases caused by their deficiency, hypothyroidism and diabetes respectively.[2]

But that was about it. The pattern of human disease had changed little over the previous 2,000 years. The problems of infectious disease – both acute and chronic – dominated medical practice, culling the young either early in infancy or later from the lethal childhood illnesses such as whooping cough and measles. The causes of the diseases that emerged from adolescence onwards – schizophrenia, rheumatoid arthritis, multiple sclerosis – were unknown and had no specific remedies. Those who survived into old age were vulnerable to the chronic degenerative diseases of ageing – cataracts clouded their sight, arthritic hips limited their mobility – and succumbed to the age-determined illnesses of the circulatory disorders and cancer.

In general the nation's health had been gradually improving over the previous 100 years, infant mortality rates were in decline and the average lifespan was, albeit modestly, slowly increasing, trends that could plausibly be attributed to social improvements in housing and diet. There were, however, three 'new' diseases that had recently emerged to become major causes of untimely death in middle age: peptic ulcers, heart attacks and cancer of the lung. Their cause was not known and, as ever, there were no effective treatments. The purpose of this book is to describe what happened next, starting with an account of the 'twelve definitive moments' – the 'canon' – of modern medicine.

1

1941: Penicillin

The discovery of penicillin is, predictably, both the first of the twelve definitive moments of the modern therapeutic revolution and the most important. Penicillin and the other antibiotics that followed rapidly in its wake cured not only the acute lethal infections such as septicaemia, meningitis and pneumonia, but also the chronic and disabling ones such as chronic infections of the sinuses, joints and bones. This in turn liberated medicine to shift its attention in the coming decades to a completely different and up till then neglected source of human misfortune: the chronic diseases associated with ageing, such as arthritic hips and furred-up arteries.

Antibiotics transformed doctors', and indeed the public's, perceptions of medicine's possibilities. If a naturally occurring non-toxic chemical compound produced by a species of fungus such as penicillin could make the difference between whether a child with meningitis should live or die, it was only natural to wonder whether other ghastly and baffling illnesses might not yield to similar simple solutions. Perhaps cancer might be curable, or schizophrenia might be treatable?

In the public imagination antibiotics came to symbolise the almostlimitless beneficent possibilities of science. Yet this is not entirely merited, for, as will be seen, the discovery of penicillin was not the product of scientific reasoning but rather an accident – much more improbable than is commonly appreciated. Further, at the core of antibiotics lies an unresolved mystery: why should just a few species of micro-organisms produce these complex chemical compounds with the capacity to destroy the full range of bacteria that cause infectious disease in humans?

On 12 February 1941, a 43-year-old policeman, Albert Alexander, became the first person to be treated with penicillin. Two months earlier Mr Alexander had scratched his face on a rose bush, a trivial enough injury perhaps, but the scratches had turned septic. Soon his face was studded with abscesses draining pus, his left eye had had to be surgically removed because of the infection and now his right eye was endangered in a similar way. His right arm drained pus from an infection deep in the bone and he was coughing up copious amounts of phlegm from cavities in his lungs. He was, as Charles Fletcher, the doctor who was to administer the penicillin, recalls, 'in great pain, desperately and pathetically ill'. Dr Fletcher subsequently described what happened:

> Penicillin therapy was started every three hours. All Mr Alexander's urine was collected and each morning I took it over to the pathology laboratory on my bicycle so the excreted penicillin could be extracted to be used again. There I was always eagerly met by the members of the penicillin team. On the first day I was able to report that for the first time throughout his illness Mr Alexander was beginning to feel a little better. Four days later there was a striking improvement … he was vastly better, with a normal temperature and eating well and there was obvious resolution of the abscesses on his face and scalp and right orbit [eye].[1]

But on the fifth day, 17 February, the supply of penicillin was exhausted. Inevitably, his condition deteriorated and he died a month later. It would, of course, have been much better for Mr Alexander had more penicillin been available, but in a way his death has a metaphorical significance – a reminder to future generations of the crucial transitional moment between human susceptibility to the purposeless malevolence of bacteria (and there can be nothing more purposeless than dying from a scratch from a rose bush) and the ability, thanks to science, to defeat it. 'It is difficult to convey the excitement of witnessing the amazing power of penicillin,' comments Professor Fletcher. Over the next few years he observed 'the disappearance of the "chambers of horrors"' – which seemed the best way to describe the old 'septic wards' in which Albert Alexander and thousands like him had spent their last days. When more supplies of penicillin became available four more patients were

treated, including a 48-year-old labourer with a vast carbuncle on his back 4 inches in diameter that vanished, 'leaving no scar', and a fourteen-year-old boy 'extremely ill' with a bone infection – osteomyelitis – of the left hip complicated by septicaemia.[2]

More than fifty years later this first description of the use of penicillin has lost none of its power to amaze. Reading it one has the impression of witnessing a miracle, whose origins, as is well known, lay in the chance observation made by Alexander Fleming in his laboratory at London's St Mary's Hospital over ten years earlier. As a microbiologist Fleming's research work involved growing colonies of bacteria on special plates called petri dishes and observing their behaviour in different circumstances. He had, for example, recently shown that the chemical lysozyme, present in tears, could inhibit the growth of several types of harmless bacteria. But then in 1928, returning from his summer holidays, Fleming, picking up a petri dish standing in a pile waiting to be washed, noticed how a contaminating mould (later identified as *Penicillium notatum)* had inhibited the growth of a colony of staphylococcal bacteria that can cause many different types of infectious illness. He then extracted the juice from the mould (which he called penicillin) and showed it was capable of inhibiting the growth of a whole range of bacteria. Curiously, however, when other scientists tried to replicate the accidental method by which he had made his discovery, they were quite unable to do so.

It was not until 1964, almost forty years later, when Fleming's former assistant Ronald Hare investigated the matter in detail, that the reason emerged. Hare found that this failure to replicate Fleming's original observation was because the growth of the penicillium mould occurred at a different temperature (20 degrees Celsius) from that of the staphylococcus, which grows best at a temperature of around 35 degrees Celsius. So what had happened?

Firstly, the penicillium mould that had 'floated through the window' was not a commonly occurring strain but rather a rare one that had wafted up from the laboratory below, where a fellow scientist and fungus expert, C. J. LaTouche, was working. Fortuitously this rare strain just happened to produce large amounts of penicillin. Some spores, it must be presumed, contaminated a petri dish on which Fleming had been growing some colonies of staphylococci. Inexplicably, but essential for his subsequent discovery, Fleming did not, prior to going on holiday, place the dish in the incubator but left it out on the laboratory bench. Consulting the meteorological records for London at the end of July 1928, Ronald Hare discovered that while Fleming was away there had been an exceptionally cool nine-day period – which would have favoured the growth of the penicillium mould – after which the temperature rose, which would have stimulated the growth of the staphylococcus. The penicillium mould was by now producing sufficient quantities of penicillin, and on his return Fleming noted that the pinhead-sized yellow spots on the plate, each of which represented a colony of the staphylococcus, had an unusual appearance. 'For some considerable distance around the mould growth the colonies were obviously undergoing lysis [dissolution].' Thus, without the 'nine cool days' in London in the summer of 1928, Fleming would never have discovered penicillin.[3]

Fleming was much luckier than he realised, but he was then remarkably indolent in exploring the therapeutic potential of his findings. He used juice extracted from the penicillium mould to cure a colleague suffering from the mild bacterial infection conjunctivitis, but by the following year he had abandoned any formal research into its further clinical use, because of the prevailing view that naturally occuring chemicals such as penicillin were likely to be too toxic to be used to treat infectious diseases.[4] Fleming did not take the matter further because he did not think it worth pursuing, 'a good example of how preconceived ideas in medicine can stifle the imagination and impede progress'.[5]

So the near miraculous properties of penicillin had to be rediscovered all over again ten years later by Howard Florey and Ernst Chain in Oxford, which was preceded, interestingly enough, by recapitulation of Fleming's work on the antibacterial properties of lysozymes in tears. Howard Florey had arrived in Britain from his home country of Australia in 1922, and after graduating from Oxford rapidly ascended the academic ladder. He was prodigiously industrious, very good with his hands and had the knack of attracting others as, or more, talented than himself to work as his collaborators. In 1935 when still only thirty-seven he was appointed Professor of Pathology at Oxford and promptly recruited Ernst Chain, a young German Jewish chemist refugee from Nazi Germany. Florey's scientific interests included the study of the chemistry of the body's natural secretions, so he initially hoped that Chain's talents would be able to elucidate their biochemical structure. 'When Florey and I in our first meeting discussed the future research programme in the department, Florey drew my attention to a very startling phenomenon,' Chain recalled. This was Fleming's observation, made back in 1921, that lysozymes in tears and nasal secretions were capable of dissolving thick suspensions of bacteria, though how they attacked the cell walls of bacteria was unknown. It took only a year for Chain to show that lysozyme was a complex enzyme. While writing up this work for publication, he looked around for other instances of compounds that might destroy bacteria and inevitably came across Fleming's original paper describing the effects of penicillin.

By now it should be clear why Chain and Florey were to succeed where Fleming had failed. The skills of a microbiologist like Fleming lay in the observation and interpretation of experiments with bacteria; the skills of a biochemist like Chain lie at a deeper level, in identifying the biochemical mechanisms that underpin the microbiologist's observations. And so just as Chain had so rapidly solved the question of the biochemistry of lysozyme, it was only a matter of time before he would unravel the mechanisms of the action of penicillin and appreciate its real significance.

Nonetheless, at the outset neither Chain nor Florey believed penicillin would have any 'clinical applications' in the treatment of infectious diseases, so the precise sequence of events that persuaded them to change their minds is of some interest. Firstly it seems that Chain was intrigued to find that penicillin was 'a very unusual substance'. It was not, as he had imagined it would be, an enzyme like lysozyme, but rather it turned out to be 'a low molecular substance with great chemical instability'. In brief, he had no idea what it was, so 'it was of obvious interest to continue the work'. Secondly, he had the biochemical skills to extract and purify (though not to a very great extent) penicillin, which when tested against bacteria grown in culture proved to be twenty times more potent than any other substance. Thirdly, when penicillin was injected into mice it was apparently 'non-toxic'. This last point was vital, for, as already pointed out, probably the most important reason why Fleming had failed to pursue the possibilities of penicillin was the common belief that any compound capable of destroying bacteria would necessarily harm the person to whom it was given. Finally, in a classic experiment Chain and Florey demonstrated that penicillin could cure infections in mice: ten mice infected with the bacterium streptococcus were divided into two groups, with five to be given penicillin and five to receive a placebo. The 'placebo' mice died, the 'penicillin' mice survived.[6]

Florey naturally hoped the publication of the compelling results of the mice experiment in *The Lancet* would prompt interest from major pharmaceutical companies for, a man being 3,000 times larger than a mouse, it would require prodigious quantities of penicillin to assess its effects in humans. But these were difficult times. The previous year Britain had declared war on Germany and the British Expeditionary Force of 350,000 men had just been driven on to the beaches of Dunkirk to be evacuated by an improvised armada of ships that somehow survived the repeated attacks of the German dive-bombers. This shattering defeat, in which Britain lost the equivalent of an entire army, made the prospect of a German invasion almost inevitable and heralded the Luftwaffe's daily assaults on London in the Battle of Britain.

At this desperate moment, when the future of Britain lay in the balance, Florey decided, astonishingly in retrospect, to commit the puny resources of his laboratory in Oxford to making enough penicillin to test in humans. 'The decision to turn an academic university department into a factory was a courageous one for which Florey took full responsibility … if his venture had failed it would have been seen as an outrageous misuse of property, staff, equipment and time, and Florey would have been severely censured.'[7]

The hallmark of Florey's university-laboratory-turned-penicillin factory was improvisation, the penicillium moulds being grown on hospital bedpans and the precious fluid extracted and stored in milk jugs:

> [In] the 'practical' classroom, the washed and sterilised bedpans were charged with medium and then inoculated with penicillin spores by spray guns. They were then wheeled on trolleys to what had been the students' 'preparation' room, now converted into a huge incubator kept at 24° Centigrade. After several days of growth, the penicillin-containing fluid was drawn off from beneath its mould by suction … The air was full of a mixture of fumes: amyl acetate, chloroform, ether. These dangerous liquids were pumped through temporary piping along corridors and up and down stairwells. There was a real danger to the health of everyone involved and a risk of fire or explosion that no one cared to contemplate.[8]

By the beginning of 1941 there was just enough penicillin for the first trial in humans. On 12 February Charles Fletcher administered the first injection directly into the policeman Albert Alexander's vein, with the results just described. Seven university graduates, including two professors and ten technical assistants, had worked every day of the week and most nights for several months to achieve these results. In June Florey travelled to America, where eventually four major drug companies took up the challenge of the mass production of penicillin.

Come the end of the war, in 1945, Florey and Chain shared, along with Fleming, the Nobel Prize. Their achievement was not just the development of penicillin but rather the clarification of the principles by which *all* antibiotics were subsequently to be discovered. Florey, in his acceptance speech, spelled them out: first, the screening of microbes to identify those that produced an antibacterial substance; then, the determination of how

to extract the substance; then testing it for toxicity and investigating its effect in animal experiments. And finally, tests in humans.[9]

We now know, though Florey did not when he gave his speech, that penicillin was not just 'a lucky break'. Rather the screening of tens of thousands of species of micro-organisms over the next few years revealed a handful that produced a whole further range of antibiotics (see page 23) whose profound impact on medicine has already been mentioned; but four further points are worth noting. It can be difficult to appreciate the comprehensiveness of the antibiotic revolution. There are many different types of infectious illness, from the trivial such as a sore throat to life-threatening meningitis. The bacteria involved behave in different ways, both in how they spread themselves around and how they damage the body's tissues. So, an attack of meningitis can kill within twelve hours while tuberculosis may take ten years or more. And yet there is not one of the hundreds of different species of bacteria that cause disease in humans that is not treatable with one or other antibiotic.

Then, while the mechanism of action of antibiotic-producing bacteria might seem simple, their effects are both very diverse and highly complex. They can interfere with the enzymes that make the cell wall, blow holes in the lining of the cell, disturb the transport of chemicals across the lining, or inhibit the manufacture of proteins in the cell.[10]

Next, the chemistry of antibiotic molecules is very unusual. It was hoped in the early days following the discovery of penicillin that the drug could be synthesised, thus avoiding the necessity of growing the penicillium mould in vast fermentation plants. But that was not to be, as one of those involved, John C. Sheehan, subsequently commented:

> Behind the feat of elucidating the structure of penicillin lay the deceptively simple problem of understanding how one carbon atom is bound to one nitrogen atom. When these two atoms are properly connected this gives penicillin its antibiotic properties. When the carbon and nitrogen atoms do not connect, the penicillin compound is not penicillin. Thousands of chemists, biochemists, organic chemists, physical chemists, microbiologists, technicians and government bureaucrats struggled for years to make those atoms hook up with each other. Millions of dollars were spent from public and private treasuries. But despite the money and labour lavished on the problem, the enchanted ring of penicillin could not be mastered.[11]

Finally, despite the complexity and diverse mechanisms by which antibiotics work, the process of their discovery turned out to be astonishingly simple. All that was required, as Florey pointed out in his Nobel Prize speech, was the screening of micro-organisms to identify the handful that could destroy other bacteria, and then identification of the active antibiotic ingredient. Thus, though antibiotics are commonly perceived as a triumph of modern science, scientists alone could never have invented or created them from first principles. They are, rather, 'a gift from nature', which raises the question of what their role in nature might be.

Dates of the discovery and sources of the more important antibiotics[12]

Name	Date of discovery	Microbe	Source
Penicillin	1929–40	*Penicillium notatum*	Air, London
Streptomycin	1944	*Streptomyces griseus*	A chicken's throat
Chloramphenicol	1947	*Streptomyces venezuelae*	Mulched field, Venezuela
Chlortetracycline	1948	*Streptomyces aureofaciens*	Soil
Cephalosporin C, N & P	1948	*Cephalosporium sp.*	Sewage outfall, Sardinia
Neomycin	1949	*Streptomyces fradiae*	Soil, New Jersey
Oxytetracycline	1950	*Streptomyces rimosus*	Soil
Nystatin	1950	*Streptomyces noursei*	Farm soil, Virginia
Erythromycin	1952	*Streptomyces erythreus*	Soil, Philippines
Novobiocin	1955	*Streptomyces spheroides*	Pastureland, Vermont
Vancomycin	1956	*Streptomyces orientalis*	Soil, Borneo and Indiana
Kanamycin	1957	*Streptomyces kanamyceticus*	Soil, Japan
Fusidic acid	1960	*Fusidium coccineum*	Monkey dung, Japan
Lincomycin	1962	*Streptomyces lincolnensis*	Soil, Lincoln, Nebraska
Gentamicin	1963	*Micromonospora purpurea*	Soil, Syracuse, New York

The most obvious and commonly accepted explanation is that antibiotics are 'chemical weapons' produced by bacteria to maximise their own chances of survival against other organisms in the atmosphere and the soil. This was certainly the view of Selman Waksman, the discoverer of streptomycin for the treatment of tuberculosis. Waksman was, by training, a soil microbiologist and knew more about the ways in which bacteria in the soil interacted with each other than anyone else in the world. His reason for studying bacteria in the soil as a potentially potent source of antibiotics was as follows:

> Bacteria pathogenic for man and animals find their way to the soil, either in the excreta of their hosts or in their remains. If one considers the great numbers of disease-producing microbes that must have gained entrance into the soil, one can only wonder that the soil harbours so few capable of causing infectious diseases in man and in animals. One hardly thinks of the soil as a source of epidemic. It has been suggested the cause of the disappearance of these disease-producing organisms is to be looked for among the soil-inhabiting microbes [which are] antagonistic to them and bring about their rapid destruction in the soil.[13]

Waksman received the Nobel Prize in 1952 for his discovery of streptomycin, and yet in the following years he came to realise that his original perception of antibiotics as 'chemical-warfare' weapons deployed by bacteria in the soil must be mistaken. He noted the ability to make antibiotics was limited to a very few species and so could not play an important role in the ecology of microbial life. Further, the ability of microorganisms to produce antibiotics turned out to be highly dependent on the quality of the soil, and indeed they were only reliably produced in the artificial environment of the laboratory. And so, if antibiotics did not act as bacterial 'chemical weapons' in the struggle for survival in the soil, what did Selman Waksman believe their role to be? They are, he observed, a 'purely fortuitous phenomenon … there is no purposeness behind them … the only conclusion that can be drawn from these facts is that these microbiological products are accidental.'[14]

This is a very difficult concept to accept. It seems inconceivable that bacteria, the simplest of organisms, should have the ability to produce such complex molecules which then serve no purpose in their survival, but as Leo Vining, a biologist from Dalhousie in Canada, observed at a conference in London in 1992, 'Even accepting these products [antibiotics] have a role, does not mean that we can readily agree upon or perceive what that role might be'.[15]

The story of penicillin and the other antibiotics that followed is thus very different from that so often presented – and usually perceived – as the triumph of science and rationalism in the conquest of illness. The unusual climatic circumstances that led to Fleming's discovery of the antibacterial properties of the penicillium mould were quite staggeringly fortuitous. The crucial decision that led to its mass production – Florey's resolve to turn his university laboratory into a penicillin factory when a German invasion was imminent – was a triumph of will over reason. Lastly the question of how, and more particularly why, a handful of the simplest of micro-organisms should have the ability to create these complex chemicals, or why they should exist at all, is simply not known. This, 'the mystery of mysteries' of modern medicine, will be revisited.


image
not
available

2

1949: Cortisone

Cortisone – commonly known as 'steroids' – is the second of the two drug discoveries that created the modern therapeutic revolution. Whereas the first, antibiotics, defeated an external enemy – the bacteria that caused infectious disease – cortisone mobilised the body's capacity to heal itself. This concept requires some elaboration. The human body as a robust and self-sufficient organism must be able to heal itself. This is seen most obviously in the recovery after a wound to the skin or a fracture to the bone but it is, of course, a generalised phenomenon much exploited by doctors over the centuries. Given time, rest, warmth and adequate nutrition, many illnesses will simply get better. These self-healing properties of the body are so pervasive that it was natural to infer there must be some physical or spiritual force to guide them. For the anatomist John Hunter it was a 'vital spirit', for the French physiologist Claude Bernard 'homeostasis' and for the physician William Osler the 'vis medicatrix naturae'.

Cortisone is not by itself the 'vis medicatrix naturae'; yet, through its influence on the body's response to stress and inflammation, this naturally occurring hormone cures or ameliorates upwards of 200 differentillnesses and so can probably be described as its main component. As with antibiotics, cortisone's discovery was entirely unanticipated, based on a series of fortuitous and coincidental events that stretched back nearly two decades.

The story of cortisone is synonymous with Dr Philip Showalter Hench, head of the Division of Medicine at the Mayo Clinic in Rochester, Minnesota, a large, powerful man of relentless determination. His speech was very loud, and, because of a severe cleft palate, difficult to understand, but nonetheless he spoke incessantly and in time became a magnificent lecturer.

On 26 July 1948 a young woman of twenty-nine, Mrs Gardner, was admitted under Dr Hench's care. Her rheumatoid arthritis – from which she had suffered for more than five years – had proved to be relentlessly progressive despite every form of available treatment. 'Many joints were stiff, swollen, tender and painful on motion,' Dr Hench observed. 'Her right hip joint had been eroded away so she could only walk with the utmost difficulty and was essentially confined to a wheelchair.' Two months later she was no better and Dr Hench turned to a biochemist colleague, Edward Kendall, who informed him that the pharmaceutical company Merck had just synthesised a quantity of Compound E – now known as cortisone – which is secreted by the adrenal gland. The following morning a small amount of Compound E arrived by airmail in a special-delivery package. 'We began with daily injections of 100mg,' Dr Hench recalls. 'During that day no change was apparent, the patient ventured only once out of her room as walking was so painful.' But two days later, on 23 September, 'when she awoke, she rolled over in her bed with ease and noticed much less muscular soreness'. The following day 'her painful muscular stiffness was entirely gone'. Scarcely able to walk three days previously, she now walked with only a slight limp. Four days later 'she shopped down town for three hours, feeling tired thereafter – but not sore or stiff'.[1]

Over the following three months Philip Hench treated a further thirteen patients, each as severely afflicted as Mrs Gardner, and presented the results to his fellow physicians at a meeting in April 1949.

> The lights were turned down and a colour film began flickering on the screen. First came the 'before treatment' pictures in which patients with characteristically deformed joints struggled to take a few steps. Suddenly an electrifying gasp swept through the audience as the 'after treatment' scenes appeared and the doctors saw the very same patients jauntily climbing steps, swinging their arms and legs and even doing little jigs as if they had never been crippled at all. Even before the film ended, the watching physicians

Firstly, as Hench had originally predicted, steroids are effective in a wide variety of different pathological processes, including allergy (anaphylactic shock, asthma, rhinitis, conjunctivitis and eczema); autoimmune disorders (the connective tissue disorders, haemolytic anaemia, chronic active hepatitis and myasthenia gravis); life-threatening infectious disease (septic shock, tuberculosis and meningitis); acute inflammatory disorders (polymyalgia, optic neuritis, psoriasis); and potentially lethal swelling of the brain and spinal cord following injury.

Secondly, the precise causes of many of these diseases remain unknown and herein lies the truly revolutionary significance of steroids, in that they subverted the common understanding of how medicine should progress. It would seem obvious that a proper understanding of disease would be indispensable to developing an effective treatment, but the discovery of steroids permitted doctors to pole-vault the hurdles of their own ignorance, or, mixing metaphors, the inscrutable complexity of disease was dissolved away in the acid bath of steroid therapy where, in practical terms (at least for the patient), the only really important question – 'What will make this better?' – was resolved by the simple expedient of writing a prescription for cortisone. And yet this 'panacea' – which, despite their limitations, steroids certainly are – is a naturally occurring hormone, which brings us back to a necessary reconsideration of the functions of cortisone in the body and why it proved to be therapeutically so beneficial in so many different illnesses.

Cortisone plays a crucial role in the body's ability to heal itself – the *vis medicatrix naturae* – through its effects on the process of inflammation. Consider an infected joint, which is painful and swollen because of the damage caused by invading bacteria. The white blood cells secrete powerful enzymes to destroy the bacteria and remove the damaged tissue – this is the 'inflammatory' phase of healing, which is followed by 'resolution', when the debris is removed and new tissue laid down. Thus, during the 'inflammatory' phase, the symptoms of pain and swelling in an infected joint are as much the result of the powerful enzymes secreted by the white blood cells as part of the process of healing as of the infecting bacteria themselves. When, as happens with rheumatoid arthritis, the healing process cannot eliminate the 'cause' (which is not known), the inflammation persists along with its symptoms of pain, redness and swelling, which further damages the tissues of the joint.

Diseases responsive to steroid therapy

Diseases responsive to steroid therapy

- Addison's disease
- Anaphylactic shock
- Aspiration syndromes
- Behçet's syndrome
- Bites and stings
- Blood disorders
  - Cold haemagglutinin disease
  - Haemangioma
  - Haemolytic anaemia
  - Hypereosinophilia
  - Hypoplastic anaemia
  - Macroglobulinaemia
  - Thrombocytopenic purpura
- Cancer
  - Leukaemia
  - Hodgkin's disease
- Cerebral oedema
- Cogan's syndrome
- Congenital adrenal hyperplasia
- Connective tissue disorders
  - Systemic lupus erythematosus
  - Polymyalgia rheumatica
  - Polymyositis
  - Dermatomyositis
- Epilepsy
- Eye disorders
  - Allergic conjunctivitis
  - Iritis
  - Uveitis
  - Keratitis
  - Sympathetic ophthalmia
  - Post-cataract surgery
  - Corneal graft rejection
  - Optic neuritis
  - Retinal vasculitis
  - Scleritis
- Gastrointestinal disorders
  - Ulcerative colitis
  - Crohn's disease
  - Haemorrhoids
  - Hypercalcaemia
- Infections
  - Glandular fever
  - Leishmaniasis
  - Leprosy
  - Meningitis
  - Pneumocystis carinii pneumonia
  - Septic shock
  - Tuberculosis
- Kidney disorders
  - Lupus nephritis
  - 'Minimal change' nephritis
  - Membranous nephropathy
  - Renal transplant
- Liver disorders
  - Chronic active hepatitis
  - Alcoholic liver disease
  - Biliary cirrhosis
  - Sclerosing cholangitis
  - Liver transplants
- Male infertility
- Neurological disorders
  - Bell's palsy
  - Coma
  - Multiple sclerosis
  - Myasthenia gravis
  - Polyneuropathies
- Organ and tissue transplantation
- Respiratory disorders
  - Asthma
  - Sarcoidosis
  - Chronic obstructive pulmonary disease
  - Fat embolism syndrome
  - Croup
  - Acute eosinophilic pneumonia
  - Pulmonary eosinophilia
  - Fibrosing alveolitis
  - Rheumatoid disease and osteoarthritis
- Rhinitis
- Skin disorders
  - Alopecia
  - Eczema
  - Contact dermatitis
  - Infantile eczema
  - Atopic dermatitis
  - Dermatitis herpetiformis
  - Seborrhoeic dermatitis
  - Neurodermatitis
  - Psoriasis
  - Lichen sclerosis
  - Pemphigus
  - Pemphigoid
  - Pyoderma gangrenosum
  - Urticaria
- Spinal cord injury
- Thyroid disorders
- Vascular disorders

(From Martindale, *The Extra Pharmacopoeia,* 31st edition, Royal Pharmaceutical Society, 1996. Readers are referred to this source relevant references.)

Cortisone in several different ways orchestrates and controls this inflammatory response and, as the fundamental pathological feature of rheumatoid arthritis is the persistence of inflammation, so cortisone will, by suppressing it, result in an improvement in symptoms. Thus Hench's real achievement was much greater than demonstrating cortisone's effectiveness in improving the symptoms of rheumatoid arthritis. He opened the way to the understanding that many illnesses share the unifying feature of being caused by uncontrolled or excessive

inflammation. Put another way, prior to Hench there was no sense that this vast range of diseases were connected at all and it was certainly inconceivable they might all be ameliorated by a naturally occurring hormone.

This therapeutic potency of cortisone could never have been anticipated, and so it could never have been created from first principles. It is thus, just like antibiotics, best conceived of as 'a gift from nature' whose discovery was quite fortuitous. Retracing Hench's odyssey one is struck by the extraordinary improbability that the therapeutic use of steroids was ever discovered at all. It all started with a chance conversation with a patient whose symptoms had improved during an attack of jaundice, a striking phenomenon perhaps, but, as at the time rheumatoid arthritis was thought to be an infectious illness, there were no theoretical grounds for Hench to follow through the implications that some substance produced by the body would have therapeutic properties – but he did.

Hench would never have been able to fruitfully pursue his hunch that there must be a 'Substance X' had it not been for the coincidence that Edward Kendall, whose brilliant skills as a biochemist were at the time centred on an apparently unrelated area of research – the nature of the hormones secreted by the adrenal cortex – was working in the same hospital.

The quantities of hormones produced by the adrenal glands were far too small to allow their therapeutic potential to be investigated, so there the matter would have rested had it not been for the rumour about Luftwaffe 'super-pilots' that stimulated the research programme that would eventually lead to the discovery that Substance X was, in fact, Compound E. When it came to treating his first patients with rheumatoid arthritis it was fortuitous that Hench chose a dose large enough and prepared in such a way as to give the dramatic results that generated the interest of fellow physicians to investigate the functions of the drug further. Finally, as has been noted, Hench got it right for the wrong reasons, since steroids, as it turned out, are not a particularly good treatment for rheumatoid arthritis but are very effective for many other illnesses.*

It is only necessary to add that, fifty years later, the means by which cortisone controls the inflammatory response are still not clear. It influences the changes in the local blood supply, the attraction of cells to clear the injured tissue and the proliferation of healing tissue, but there is as yet no unifying hypothesis of how these powerful effects work together.

3

1950: Streptomycin, Smoking and Sir Austin Bradford Hill

The advent of antibiotics and cortisone created a mood of such excitement and eager anticipation of further medical advance that some form of celebration was called for. Hugh Clegg, editor of the *British Medical Journal,* saw the year 1950, the mid-point of the century, as the perfect opportunity to invite the Great and the Good to look back over recent achievements and anticipate those to come. They duly obliged, and the *BMJ* of 7 January 1950 opened with a wide-ranging review by Sir Henry Dale FRS. 'We who have been able to watch the beginnings of this great movement,' he concluded inspiringly, 'may be glad and proud to have lived through such a time, and confident that an even wider and more majestic advance will be seen by those who live on through the fifty years now opening.'[1]

Similar sentiments were expressed by other distinguished knights of the profession, including Sir Henry Cohen, Professor of Medicine at Liverpool, and Sir Lionel Whitby, Regius Professor of Physic at Cambridge. But, as it turned out, the mid-point of the century proved to be more than a convenient opportunity to reflect on the past and crystal-ball-gaze into the future. Two apparently unrelated events, each of great significance in itself, occurred later in the year, ensuring that 1950 was literally a watershed separating medicine's past from its future. The first was the demonstration that two drugs, streptomycin and PAS (para-amino salicylic acid), given together over a period of several months, resulted in a 'marked improvement' in 80 per cent of patients with tuberculosis. The second was the convincing proof that smoking caused lung cancer.

These two events represent what historians of science call 'a paradigm shift', where the scientific preoccupations particular to one epoch give way to or are displaced by those of another. Thus, for the 100 years prior to 1950 the dominant paradigm had been 'the germ theory', in which medicine's main preoccupation had been to find some effective treatment for infectious diseases. Tuberculosis remained the last great challenge. Without doubt the most notorious of all human infections, the tubercle bacillus alone had proved resistant to treatment because its apparently impermeable waxy coat protected it against antibiotics like penicillin. But now, thanks to streptomycin and PAS, it seemed that even this, 'the captain of the armies of death', could be defeated. And just as the threat of infectious diseases started to recede, so it was to be replaced by a different paradigm or preoccupation – the non-infectious diseases such as cancer, strokes and heart attacks. The incrimination of smoking in lung cancer showed that the cause of these diseases might be just as specific as that for infectious illnesses, but rather than a bacterium being responsible, the culprit was people's social habits. If smoking – which was almost universal following the Second World War – caused lung cancer, then perhaps other aspects of people's lives, such as the food they consumed, might cause other diseases.

The ramifications of this paradigm shift were to be of great importance, but surprisingly that is not the main reason for its inclusion in the pantheon of 'definitive moments'. Rather it is the manner in which it was brought about. Prior to 1950, the cornerstone of reliable knowledge in medicine was the cumulative wisdom acquired through everyday practice. The notion that the validity, or otherwise, of specific treatments might be objectively tested was hardly ever raised. But the demonstration of the curability of tuberculosis and the role of smoking in lung cancer changed all this, for both relied on statistical methods of proof that soon permeated every aspect of medicine to become the main – indeed the sole – arbiter of 'scientific truth'. This was almost entirely due to the influence of one man, Austin Bradford Hill, Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine. Bradford Hill was not medically qualified and had no formal training in statistical methods, at which, on his own admission, he was 'not very proficient', viewing them rather as being 'common sense applied to figures'. Nonetheless he was to guide statistics to a dominant position within medicine whose subsequent indiscriminate application would eventually exert a most baleful influence.

This intellectual ascendancy of statistics is essentially the story of Bradford Hill's life. He was born in 1897 into a distinguished Victorian family, at least one of whose members in each of the preceding four generations had featured in the *Dictionary of National Biography,* including his father, Sir Leonard Hill, Professor of Physiology at the London Hospital, who, *inter alia,* developed a machine to measure the blood pressure and in a series of self-experiments conducted by himself and his junior lecturer, Dr Major Greenwood, showed that 'the bends' in divers, caused by the formation of bubbles of nitrogen in the blood, could be prevented by slow uniform decompression.[2] Powerfully influenced by the stimulating atmosphere of his home life, Bradford Hill decided to follow his father into medicine but, when the time came to enter medical school, Britain was at war with Germany so instead he joined the Royal Naval Air Service as a pilot. In January 1917 he was posted to the Aegean and joined a party of a dozen officers at Charing Cross Station to travel by train to the toe of Italy. 'It was on this exhausting, overcrowded and unhygienic journey, I would guess, I picked up the tubercle bacillus,' he subsequently recalled. Based on the tiny island of Tenedos just off the Turkish coast, he had a quiet time, other than the occasional flying accident, in the last of which his engine failed at 11,000 feet, leaving him no alternative other than to glide down to the narrow airstrip. 'I misjudged by about 10 yards and landed on the edge of a muddy lake. The plane stood on its nose and broke its propeller.' Within five months he had become seriously ill with a cough and a fever, the tubercle bacilli that had been multiplying in his lungs were identified in his sputum and he was 'invalided home to die'. To his own astonishment, and that of his doctors, he responded to the only two treatments for tuberculosis available at that time – bed-rest and an artificial pneumothorax (the introduction of air into the pleural cavity to collapse down the lung and thus slow the spread of the infection). In 1919 he was discharged from hospital with a 100 per cent disability pension (only given to those whose disability is deemed so severe as to preclude them from any further gainful employment), which he continued to draw for the next seventy-four years till his death at the age of ninety-three.[3]

Though Bradford Hill had survived tuberculosis, a medical career was now out of the question. At the suggestion of his father's erstwhile physiology lecturer, Dr Major Greenwood, he opted for a correspondence course in economics at London University, which he passed with second-class honours. In 1928 Major Greenwood was appointed the first Professor of Vital Statistics at the recently opened London School of Hygiene and Tropical Medicine, and in 1931 he appointed Bradford Hill as Reader in Epidemiology. Thus began their long collaboration. These details of Bradford Hill's early life illuminate what was to follow. His frustration at being unable to fulfil his childhood ambition of following his father into medicine only heightened his fascination with every aspect of the medical sciences. It may have been the fascination of an outsider, but this was only to his advantage. From this Olympian vantage point he was able to take a detached and critical view of medical developments. He was particularly lucky that his mentor, Greenwood, was that rarity in medical circles, a full-blooded intellectual, whose perception of the contribution statistics could make to medicine was driven by his strong historical sense of past achievements, particularly in the field of public health, reinforced by his contact with the mathematical polymath Karl Pearson (of whom more later), who in his turn had been a protégé of one of the greatest of all Victorian intellectuals, Francis Galton. It is to these roots of medical statistics that we now turn before taking up again the thread of Bradford Hill's career.

For many, statistics are numbers to which complex mathematical formulae can be applied to produce conclusions of dubious veracity and from which all wit and human life is rigorously excluded. Certainly, any single statistic by itself is a dreary thing, but when they are linked together over months and years then patterns begin to emerge and it is possible to see things that previously were hidden. An unarguable event such as death lends itself particularly well to the statistical method, and when the numbers in any town or region are recorded over a brief period it is possible to appreciate that in the aggregate they represent the distinct biological phenomenon of an epidemic. This is the simplest form of epidemiology – literally the study of epidemics – which, nonetheless, has the power to change the world for the better.

This beneficent capacity of statistics was seen most strikingly in the great movement for sanitary reform in the mid-nineteenth century, when William Farr – 'a very great Englishman' in Greenwood's words – was compiler of abstracts in the General Register Office. In his thirty-fifth annual report Farr drew attention to the yawning differential in childhood mortality rates between the rich and poor and asked: 'What are the causes? Do they admit of removal? If they do admit of removal, is the destruction of life to be allowed to go on indefinitely?'[4]

The crucial point to inspire twentieth-century epidemiologists was that statistical enquiry, by determining the underlying causes of ill health such as poor sanitation, provided the means for the prevention of disease on a massive scale, so 'statisticians' potentially had an infinitely greater effect in improving the health of the nation than white-coated doctors with their airs and graces.

There was, as already mentioned, a second and very different use of statistics. The mathematical techniques invented by Karl Pearson of University College to interpret biological variations in height, blood pressure or any other physiological characteristic made it possible to infer general rules about groups of people rather than individuals, and were relevant to experiments to test the efficacy of treatments from which it was possible to deduce whether the results were 'significant'. In an illustrative example famous for its inconsequentiality, Ronald Fisher – a pupil of Pearson's – poured a cup of tea

> and offered it to the woman standing beside him. She refused, remarking that she preferred milk to be in the cup before the tea was added. Fisher could not believe that there would be any difference in the taste and when the woman suggested an experiment be performed, he was enthusiastic. An immediate trial was organised, the woman confidently identified more than enough of the cups of tea into which the tea had been poured first to prove her case.

In his classic book *The Design of Experiments,* published in 1935, Fisher used this example 'to state the terms of the experiment minutely and distinctly; predicted all possible results, ascertaining by sensible reasoning, what probability should be assigned to each possible result under the assumption that the woman was guessing'.[5]

Thus Greenwood's main intellectual legacy, which he was to pass on to Bradford Hill, was essentially two-fold: the historical contribution of statistical methods to elucidating the cause of substantial public health problems; and the importance of conducting properly designed experiments to test whether a new treatment was effective.

In 1945 Greenwood retired and Bradford Hill was duly appointed as his successor. The paradigm shift in which he was to play so important a role was just five years away. Its two components – the trial of streptomycin and PAS in the treatment of tuberculosis and the elucidation of the causative role of smoking in lung cancer – are here described separately, though they were occurring at the same time. Accordingly the rise of the power and influence of statistics in medicine began to appear inevitable.

The Clinical Trial: Streptomycin, PAS and the Cure of Tuberculosis

Bradford Hill had personal reasons for being interested in the treatment of tuberculosis, having himself only just escaped from being yet another mortality statistic for the disease at the cost of two years' convalescence and an artificial pneumothorax. In 1946 he joined the Tuberculosis Trials Committee, which had been set up to evaluate a new drug, streptomycin, that two years earlier in the United States had been shown to be capable of killing the tubercle bacillus. It had been unnecessary to formally test whether or not penicillin worked in humans because the results were immediate and dramatic. But the efficacy of streptomycin in tuberculosis was not quite so straightforward because the tubercle bacillus, in its waxy shell, is very resilient and the damage it causes the lungs and other organs is more chronic. Accordingly, streptomycin had to be given for several months before there was any obvious improvement. Nonetheless there was no obvious reason at the time why doctors should not, as they had done in the United States, give streptomycin to patients and see what happened. If it worked, that was fine; if not, then nothing was lost. Bradford Hill was, however, determined that streptomycin should first be put to the test in a properly conducted trial, comparing the outcome with those not given the drug. His view prevailed, but only because of the fortuitous circumstances that streptomycin was extremely difficult to acquire in Britain at that time and so for the foreseeable future many would be unable to benefit from it. Bradford Hill resolved to make a virtue out of this necessity, as he subsequently recalled:

> We had exhausted our supply of dollars in the war and the Treasury was adamant we could only have a very small amount of streptomycin. This turned the scales. I could argue in this situation it would not be immoral to do a trial – it would be immoral not to, since the opportunity would never come again as there would soon be plenty of streptomycin. We could have enough of the new drug to use in about fifty patients and I thought this was probably enough to get a reliable answer.[6]

Bradford Hill's position was to be more than vindicated, though not by showing whether streptomycin worked (which was in a sense predictable), but for showing that after a while, and for important reasons, it stopped working. Further, the fact that the treatment of tuberculosis was (almost) the first treatment to be formally tested in this way is highly significant. Tuberculosis was after all much the commonest lethal infectious disease in the West. The fact that this new drug was being tested in the context of a formal experiment designed by Bradford

He then goes on to emphasise

> the advantages of this random allocation of patients ensures three things: it ensures that neither our personal idiosyncrasies nor our lack of balanced judgement has entered into the construction of the different treatment groups; it removes the danger that believing we may be biased in our judgement we endeavour to allow for that bias and by thus 'leaning over backwards' introduce a lack of balance from the other direction; and, having used a random allocation, the sternest critic is unable to say that quite probably the groups were differentially biased through our predilections or our stupidity.

This would all seem entirely reasonable and the lucidity of Bradford Hill's prose only makes it seem even more so. From the beginning of 1947 three London hospitals started admitting patients into the first streptomycin trial, in which fifty-five patients were to be given streptomycin for four months, the results being compared with fifty-two 'controls' who were to be 'treated' with bed-rest and, if necessary, the collapse treatment of the lung that Bradford Hill himself had undergone almost thirty years earlier. The allocation to 'treatment' or 'control' was determined by a series of random numbers devised by Bradford Hill and placed in a set of sealed envelopes.

By the end of six months, twenty-eight of those given the streptomycin were markedly improved and only four had died, compared to fourteen deaths among those unfortunate enough to have been randomly allocated to the 'control' group. This finding, that those given streptomycin 'did better' than those who were not, scarcely justifies the considerable time and energy devoted to the organisation of a randomised trial but, in a way that Bradford Hill could scarcely have anticipated, his insistence that streptomycin be objectively evaluated was to be completely (if tragically) vindicated. There was a fundamental limitation in the use of streptomycin to treat tuberculosis. Patients certainly improved but the requirement that treatment should last several months guaranteed that some of the tubercle bacilli would become resistant to the streptomycin and, when this happened, their condition subsequently deteriorated again.[20] The streptomycin trial had been so intelligently organised that it was a straightforward matter to assess the potential seriousness of this problem of resistance, and the clear statistical presentation of the results brought home the full gravity of the problem – as revealed by an 'update' published three years later, by when thirty-two of the fifty-five patients treated with streptomycin had died.[21]

The authoritative verdict of Bradford Hill's first trial was thus much more compelling than the resolution of the issue of whether or not streptomycin worked. Rather, it made it absolutely clear that streptomycin represented 'a false dawn' where an initial impressive improvement in a patient's condition was followed by a subsequent relapse that was closely related to the development of resistance. From this perspective there could be no greater vindication of Bradford Hill's espousal of the objective evaluation of new treatments over the subjective impression of doctors.

His methodical approach immediately pointed to the next step, which was to repeat exactly the same trial but this time, in the hope of combating the problem of resistance, combining streptomycin with Lehmann's PAS. This second trial started in December 1948 and exactly one year later, long before the study was complete, the organisers took the unprecedented step of issuing an interim communication that they had 'demonstrated unequivocally that the combination of PAS with streptomycin considerably reduces the risk of the development of streptomycin-resistant strains of tubercle bacilli'.[22] With the publication of the full results in November 1950 the benefits of the combination of the two drugs was glaringly obvious: thirty-three of the participants in the first trial had become resistant to streptomycin, compared to only five in the second trial. No longer, as happened at the first trial, did patients respond initially to treatment only to die several years later from a recrudescence caused by resistance to streptomycin. With streptomycin and PAS the survival rate soared to 80 per cent.[23]

This was not the end of the story. Over the next ten years tuberculosis treatment became ever more refined and successful, with the introduction of other drugs, notably isoniazid in 1952 and rifampicin in 1970.[24,25] It soon became clear that the combination of three drugs was even better than two, and that if given continuously for a period of up to two years then virtually every patient could be cured of the disease. This happy situation persisted until the late 1980s when the difficulties of treating AIDS patients with tuberculosis led to the emergence of tubercle bacilli that were 'multiply resistant' to all antituberculous drugs, raising the spectre that once again tuberculosis would become, as it had been prior to 1950, essentially an 'incurable' disease.

As a final reminder of that time, it is appropriate to recall the fate of George Orwell, who died in 1950 aged forty-seven, just a few months before the results of the combination of PAS and streptomycin were published. Orwell had first been diagnosed as having tuberculosis back in 1938. His condition improved with bed-rest and lengthy convalescence in Morocco, but he suffered a relapse in 1946, soon after moving to a remote farmhouse on the island of Jura in the Hebrides, where he had gone to complete the last and greatest of his books, *Nineteen*

Eighty-Four. He managed, through the influence of David Astor, the proprietor of the *Observer,* to obtain a small quantity of streptomycin. Initially all went well and a month after starting treatment he wrote to his friend Julian Symons: 'I have been having the streptomycin and it is evidently doing its stuff. I haven't gained much weight but I am better in every way.' He was, however, one of the unlucky ones who developed a strong allergic reaction to the drug, in the form of a terrible rash and blisters such that he was no longer able to continue with treatment. His tuberculosis returned and he died in University College Hospital on 21 January 1950 from a massive haemorrhage into both his lungs. The famous literary critic Cyril Connolly wrote subsequently:

> The tragedy of Orwell's life is that when at last he achieved fame and success he was a dying man and knew it. He had fame and was too ill to leave his room, money and nothing to spend it on, love in which he could not participate; he tasted the bitterness of dying. But in his years of hardship he was sustained by a genial stoicism, by his excitement about what was going to happen next and by his affection for other people.[26]

Orwell's fate has profound symbolic significance. Like the experience of the Oxford policeman Albert Alexander, who was the first person to receive penicillin, Orwell's brush with streptomycin is a reminder to future generations of the difference that anti-tuberculosis drugs would make to so many people's lives. Orwell died on the cusp of the paradigm shift. Another couple of years and he would have been spared the bitterness of a premature death to live on for several more decades. Who knows what else he might have achieved?

In the aftermath of the brilliant and lucid manner in which tuberculosis had been shown to be a treatable disease, the Randomised Controlled Trial (shortened to RCT) blossomed, just as Bradford Hill had hoped, to become the standard way of evaluating new drugs. As his protégé Richard Doll observed in 1982: 'Few innovations have made such an impact on medicine as the controlled clinical trial designed by Sir Austin Bradford Hill … thirty-five years later the structure, conditions of conduct and analysis of the currently standard trials are, for the most part, the same. Its durability is a monument to Sir Austin's scientific perception, common sense and concern for the welfare of the individual.'[27] A minority were unconvinced. In a letter to the *British Medical Journal* in 1951, 'a blast of the trumpet against the monstrous regiment of mathematics', a physician from Sunderland, Dr Grant Waugh, comments on

> the outbreak in epidemic form of a disease of pseudoscientific meticulosis. The symptoms of the condition are characterised by: a) evidence of a certain degree of cerebral exaltation; b) an inherent contempt for those who cannot understand logarithms; and c) the replacement of humanistic and clinical values by mathematical formulae. The systemic effects of this disease are apparent; patients are degraded from human beings to pricks in a column, dots in a field, or tadpoles in a pool; with the eventual elimination of the responsibility of the doctor to get the individual back to health.[28]

Behind the bombast Dr Waugh was making a serious point, for, as will be seen, clinical trials were not infallible and when improperly conducted could give rise to false conclusions that could not be rectified by any amount of objectivity conferred by 'randomisation'. The RCT, however, was to prove utterly indispensable in the evaluation of the explosion of new drugs that occurred in the 1950s and 1960s. The thalidomide tragedy in 1960 forced governments around the world to insist that all new drugs be formally tested for their effectiveness and safety in randomised controlled trials as a requirement for the granting of a product licence. Thus Bradford Hill established the gold standard by which the merits of modern drug therapy must be measured.[29]

Epidemiological Proof: The Case of Smoking and Lung Cancer

Bradford Hill's second indestructible achievement in his *annus mirabilis* of 1950 was to show that smoking causes lung cancer. Nowadays this seems so obvious as to be unremarkable, but back in 1950 it was not, for the simple reason that as a direct consequence of two world wars in thirty years virtually everyone smoked. Tobacco had proved as much of a solace in the trenches at Passchendaele as during the London Blitz and, when not calming the nerves, 'a smoke' was at least something to accompany the endless cups of tea that filled the long, empty hours so characteristic of total war, when citizens were unable to pursue their legitimate occupations. It is easy to appreciate how difficult it could be to show that smoking caused lung cancer if everyone smoked, because both those with and those without the disease would be smokers. Indeed, only statistical methods could

resolve this question, because statistics can see 'below the surface' of things to identify relationships that would otherwise remain obscure.

It has been noted that lung cancer replaced tuberculosis in a metaphorical sense as part of the paradigm shift from one pattern of disease to another, but lung cancer also replaced tuberculosis in a literal sense in 1950, as for the first time the number of deaths from the disease – 13,000 – exceeded those from tuberculosis.[30] And while the toll of tuberculosis rapidly receded over the next few years under the onslaught of anti-tuberculosis drugs, that of lung cancer soared. There are further interesting comparisons. The tragedy of both diseases was that their victims died young or, in the case of lung cancer, relatively young, in their fifties and sixties. And, just as tuberculosis prior to 1950 was essentially an incurable disease, so was lung cancer. Indeed lung cancer was the more grievous of the two illnesses as, with the very infrequent exception of those in whom the disease was detected early enough to be surgically removed, most patients died within eighteen months.[31] From this perspective it is almost impossible to overstate the importance of Bradford Hill's implication of smoking, as this dreadful, untreatable, escalating disease suddenly became 'preventable' through the simple expedient of people not smoking. And it is almost impossible to overstate just how significant this was for the subsequent development of medicine, as over the next fifty years this example of the 'preventability' of lung cancer was enormously influential in promoting the notion that most cancers and other common causes of death might also be preventable by similar 'lifestyle' changes (as will be explored in detail in the final section of this book).

Bradford Hill's logical inference from statistical data – his demonstration of smoking's causative role in lung cancer – was a masterpiece. The simplest of all medical statistics are, as already noted, the 'vital statistics' recording the unarguable event of death. When analysed over a defined period, they may display a characteristic pattern such as the rise and fall typical of an infectious epidemic. The collection and interpretation of such vital statistics constitute a form of scientific observation little different in its way from 'observing' the effects of disease in an individual. But statistics in this form can only report what has happened; they cannot produce any insights into why it has happened. For this it is necessary to move from simple observation to performing an 'experiment', which, like the Randomised Controlled Trial, is fairly straightforward and again essentially involves making a comparison. When the various aspects of the lives of a group of people with a particular disease are compared to those of another group without the disease, differences might emerge which, it might be inferred, could theoretically be the cause of the disease being studied.

In 1947 Bradford Hill, along with Edward Kennaway of St Bartholomew's Hospital and Percy Stock, the government's chief medical statistician, were asked by the Medical Research Council to investigate whether smoking might explain the 'startling phenomenon' of the fifteen-fold increase in the death rate from lung cancer in Britain over the previous twenty-five years. They were subsequently joined by Dr Richard Doll, who later recalled the division of opinion that reflected the prevailing views of the time:

> Kennaway was particularly interested in the possibility of smoking being a factor, but I don't think anybody else was. Bradford Hill certainly wasn't particularly keen on smoking as a cause, nor was I, while Stock was particularly keen on the effect of general urban atmospheric pollution. I must admit I thought the latter was likely to be the principal cause, though not pollution from coal smoke which was terrible in those days but which had been prevalent for many decades and hadn't really increased. Motor cars, however, were a new factor. If I had to put money on anything at the time I should put it on motor exhausts or possibly on the tarring of roads. But cigarette smoking was such a normal thing and had been for such a long time that it was difficult to think it could be associated with any disease.[32]

The main problem facing Bradford Hill was that 90 per cent of the adult male population were smokers, so clearly it would not be possible to implicate tobacco simply on the grounds of whether someone smoked or not. Rather, it was necessary to identify some biological phenomenon from which it would be reasonable to implicate tobacco. The most obvious is the 'dose-response relationship' – the higher the 'dose' of tobacco the greater the 'response', or incidence, of lung cancer. The statistical method was known as the 'case-control' study, where 'every case' of lung cancer was compared with a 'control' who was similar in every way other than suffering from some other disease. Theoretically, then, if the heavy smokers were disproportionately represented among the lung cancer group compared to the controls, one might infer that smoking was the cause of the disease. Though this seems straightforward in principle, in practice it is quite difficult, mainly because it is so difficult to ensure that the 'cases' and 'controls' are truly comparable. The investigation, therefore, had to do much more than record how much a person smoked; rather,

a range of potentially relevant factors had to be taken into account: the age, sex, urban or rural residence, and social class of the subject; occupational history; exposure to air pollutants; forms of domestic heating; and the history of smoking including for those who had smoked, the age of starting and stopping, the amount smoked before the onset of illness, the main changes in smoking history, the maximum amount smoked, the practice in regard to inhaling and the use of cigarettes or pipe.

Starting in April 1948, doctors in twenty hospitals in London notified Doll of any patients suspected of having lung cancer. Doll would then arrange for a 'lady almoner', as social workers were quaintly called in those days, to interview both the patient and two 'controls', one with cancer of the stomach or colon and one from another of the general medical and surgical wards with a disease other than cancer. He found that 99.7 per cent of the lung cancer patients confessed to smoking, compared to 95.8 per cent of those with 'diseases other than cancer'. Such an observation by itself obviously proves nothing at all, but when the patients were subdivided into four groups depending on how much they smoked, ranging from 'one cigarette' to 'fifty cigarettes' a day, then it is possible to discern a trend of a higher risk of lung cancer among the heavy smokers (see page 64). Examining the final set of figures in the table, 4.9 per cent of lung cancer patients smoked fifty cigarettes a day, twice as high a percentage as the 2 per cent of controls – a subtle difference perhaps, but whichever way the smoking habit was investigated, either looking at the amount smoked every day, or the maximum amount smoked, or the total amount smoked over the years, and so on, the same pattern emerged: the greater the amount of tobacco consumed, the higher the risk. For Doll and Bradford Hill the conclusion seemed inescapable: 'It is not reasonable, in our view, to attribute the results to any special selection of cases or to bias in recording. In other words, it must be concluded that there is a real association between carcinoma of the lung and smoking.'[33]

Smoking habits between patients with lung cancer and controls

	Number of patients smoking daily:		
	1 cigarette	**15 cigarettes**	**50 cigarettes**
649 lung cancer patients (99.9%)	33 (5.1%)	196 (30.2%)	32 (4.9%)
649 controls (100%)	55 (8.5%)	190 (29.3%)	13 (2.0%)

(From R. Doll and A. Bradford Hill, 'Smoking and Carcinoma of the Lung', *BMJ,* 30 September 1950, pp. 739–48.)

We now know this only too well, but at the time things appeared very differently. Social habits had been incriminated in lethal diseases before, most notably drinking alcohol as a cause of liver cirrhosis, but this is a fate restricted to a minority of alcoholics. Smoking was different, as virtually everybody 'indulged'. It was an intrinsic part of each and every social occasion and the offering of a cigarette an integral part of social (and often sexual) intercourse. Its incrimination in a lethal disease was thus a matter of the utmost gravity. The director of the Medical Research Council, Sir Harold Himsworth, strongly advised Bradford Hill and Doll that they should delay making their results public, as Doll subsequently recalled: 'Himsworth said the finding was so important he did not think we should publish it until we had found it again' (i.e., repeated the study and found the same results). They duly set to work, this time investigating lung cancer outside London (lest their findings might have been a fluke attributable to some unidentifiable 'London factor'), but this proved unnecessary when a few months later an American study came to exactly the same conclusions.[34]

Doll and Bradford Hill promptly published their first study in the *British Medical Journal* on 30 September 1950, and its distinguishing features merit some comment. Firstly, the 'dose-response' relationship between smoking and lung cancer was very subtle and this could readily have been obscured were it not for the rigorous way in which possible sources of bias had been anticipated and eliminated. Secondly, it is impossible to convey, without publishing the paper in full, the lucidity of its exposition, so its weighty conclusion seems unarguable. Put another way, it is very difficult to appreciate the novelty of their paper. The source of reliable knowledge in medicine had always been in the biological and physical sciences. Now, in the face of considerable scepticism, statistical methods had 'triumphantly' (one can justifiably say) been demonstrated to be capable of providing a new and genuine insight into the nature of disease.

Nonetheless, it would take more than this for people to stop smoking. Bradford Hill looked around for some other way by which the link could be demonstrated and – in a masterly stroke of imagination – invented an entirely new method of investigation. The 'case-control' study he had just conducted was 'retrospective', in that it

tried to make sense of something that had happened in the past, how the habits of a lifetime may have contributed to one disease in particular. But if the association between lung cancer and smoking was valid, he should get the same result looking forward, starting with a large number of men and women, asking them pertinent questions about their lives, including their smoking habits, and then sitting back and watching what happened to them over the years. They would die from diverse diseases, but the smokers should die in disproportionate numbers from lung cancer. The elegance of this 'prospective' or 'cohort' study is the simplicity of the open-ended question – 'What do smokers die of?' – to which time will inevitably provide an answer.

Bradford Hill chose as his cohort the 60,000 doctors on the Medical Register, who were likely to be reliable in answering the questions posed to them. There could be no more forceful way of bringing home to the profession the hazards of tobacco – which hopefully would then be passed on to patients – than by incorporating them in this scientific endeavour to provide further proof that smoking caused lung cancer. In November 1951 Bradford Hill wrote a letter to the *British Medical Journal* which was published under the headline 'Do You Smoke?':

> Last week I sent a letter personally to every man and woman on the Medical Register of the UK asking them to help me. I asked them to fill in a very simple form about their smoking habits.
>
> This, I think, is a new method of approach. May I therefore repeat my appeal through your column? If every doctor, whatever his field of work, will spare only a moment or two this research can be founded on a firm basis and in time give, I believe, firm and important answers. I am, etc.[35]

In a short period, a mere two and a half years, Bradford Hill had his answer. Of the 40,000 doctors who replied to the questionnaire, 789 had subsequently died, a mere 36 from lung cancer. But when the smoking habits of the deceased were tabulated (see below), lung cancer was the only disease in which there was a clear dose-response relationship – the more tobacco smoked, the greater the death rate, rising from 0.48 per 1,000 doctors smoking 1g of tobacco daily, to 0.67 for those smoking 15g, to 1.14 for those smoking 25g or more, compared to those who had died from 'all causes', in whom there was no gradient with increase in smoking habit.[36]

Mortality rate per 1,000 male doctors in relation to the most recent amount of tobacco smoked

Cause of death	Number of deaths recorded	Death rates of men smoking a daily average of tobacco of:		
		1g	15g	25g+
Lung cancer	36	0.48	0.67	1.14
All causes	789	13.42	13.48	16.3

(From R. Doll and A. Bradford Hill, 'The Mortality of Doctors in Relation to Their Smoking Habit', *BMJ,* 26 June 1954, pp. 1451–5.)

The final verdict on the statistical proof of the causative role of tobacco in lung cancer can be found in a reply from Bradford Hill to the following small item in *The Lancet* of 14 December 1957:

> Yesterday the morning post brought an embarrassing revelation from my husband's past. It was an innocent-looking letter from the Medical Research Council and ran: 'Dear Doctor: In 1951 you stated that you smoked an average of three cigarettes a day …'
>
> *Three* cigarettes a day! When I met him, around that time, *thirty-three* would have been a conservative estimate. The mean had hovered around there ever since, plus or minus a few standard deviations. We sat dumbfounded, our bacon cooling uneaten. I broke the silence first. 'Why you hypocritical old …'
>
> Then I was aware that this was superfluous. My husband stared before him, automatically buttering toast.
>
> 'How could I,' he began brokenly, 'how could I say such a thing?'
>
> But already it was obvious. My husband is a heavy smoker except when Giving Up Smoking. This happens three or four times a year and lasts anywhere from half an hour to two horrible weeks. During these interludes he is very virtuous, and impossible to live with. Clearly the questionnaire had caught him whilst he was Giving Up Smoking or, more accurately, tapering off.