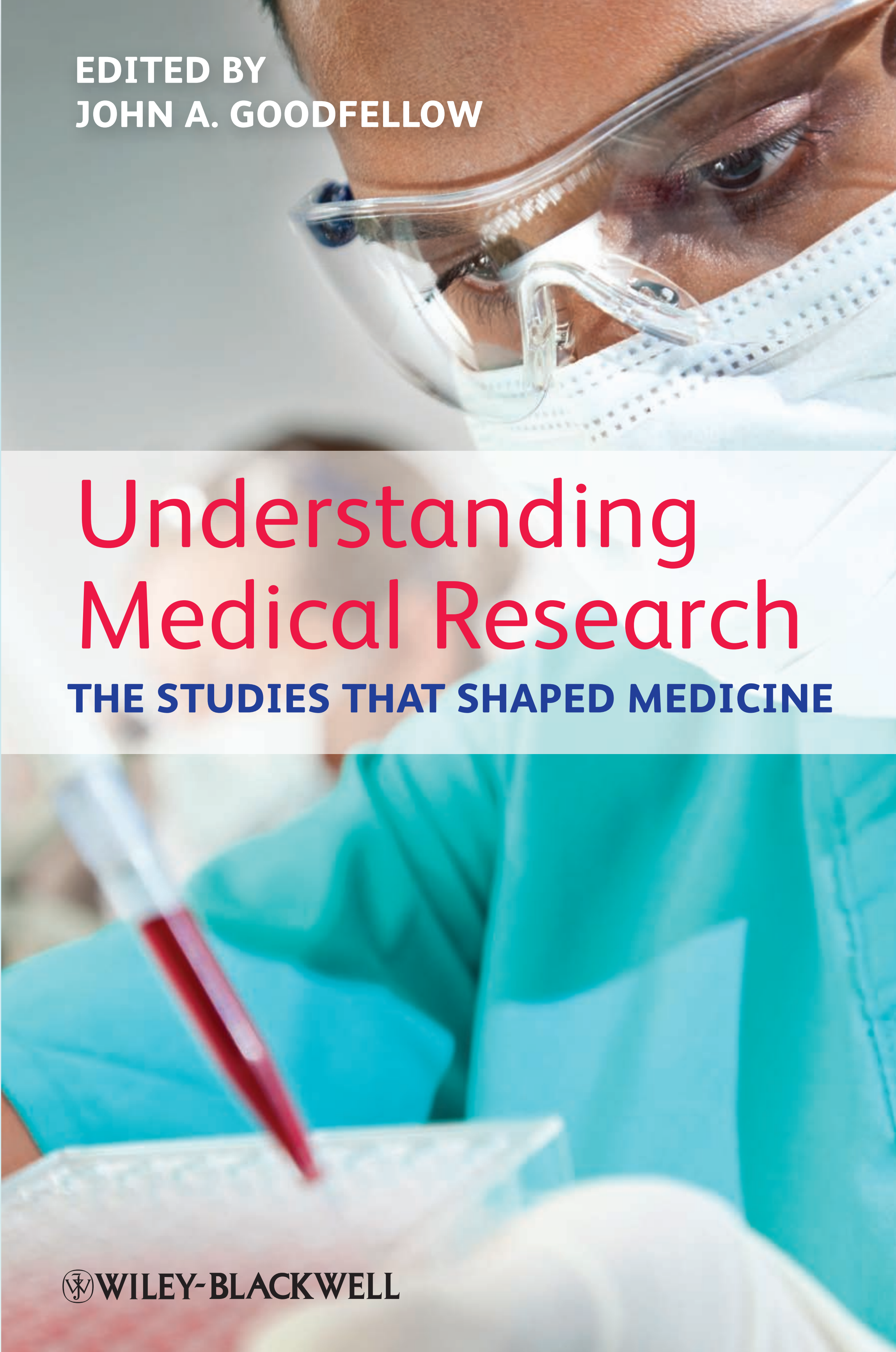

EDITED BY
JOHN A. GOODFELLOW

Understanding Medical Research

THE STUDIES THAT SHAPED MEDICINE

WILEY-BLACKWELL

Understanding Medical Research

To my wife Rosalyn

Understanding Medical Research

The Studies That Shaped Medicine

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WITH FOREWORD BY

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Preface

> *Ars longa, vita brevis, occasio praeceps, experimentum periculosum, iudicium difficile.*
> [The art (of medicine) is long, life is short, opportunity fleeting, experiment treacherous, judgment difficult.]
>
> Hippocrates

Understanding Medical Research is aimed at giving medical students and junior doctors a concise and authoritative overview of the landmark papers in medical research. Rather than summarising only recent developments, as review articles do, in each chapter the authors discuss ten or so papers that have contributed most to our understanding of the topic. It is distinct from *evidence-based medicine* in that it doesn't aim to summarise the 'best available' trial data; rather, it summarises the unique blend of science and pragmatism that has come together to form medical practice.

Such an enterprise is obviously a huge challenge to the authors, and I have allowed them some flexibility in how they approach this. For most a chronological approach is taken, but for some, such as the chapters on stroke, population health and patient safety, a slightly different approach is used. Regardless, the effect is the same: an authoritative summary of the key papers from people at the cutting edge of research.

The range of studies included is broad: from famous randomised clinical trials down to obscure case studies and biochemical reports. Likewise the range of journals from which the articles are selected is equally broad, although one or two recur again and again. These are the papers and journals that have changed our understanding of medicine, and every doctor should be familiar with them.

The reader should use this book as a starting point from which to enter the world of research. The chapters will give you a 'big-picture' overview of the topic. This will put you in an ideal place to then put into context current studies and clinical practice, and to formulate your own research questions.

JOHN A. GOODFELLOW

Foreword

Modern medicine is a discipline that over the last 150 years has developed in response to changing patterns of human disease, scientific understanding and technology. As such its origins, paradigm shifts and breakthroughs have at times come from human ingenuity, scientific scrutiny and serendipity. Much contemporary focus is rightly on determining best clinical practice through rigorous and tightly controlled clinical trials. However, this is only one part of the story of medicine in any given field. *Understanding Medical Research* is a book that seeks to give the reader a succinct and lively account of the colourful research that has made clinical practice what it is today.

For example, the 'shoe-leather epidemiology' of the great physician John Snow looks rather primitive in its methodology to the modern doctor: walking the streets of London to gather data by knocking on doors! This would not earn him a high-impact publication in today's journals, yet his painstaking observations allowed him to go beyond the 'miasma' theory of cholera and propose a waterborne pathogen, before even the germ theory of disease itself was widely accepted! Not to mention the countless lives he directly saved.

Not many of us have seen a case of familial hypercholesterolaemia; fewer still have read Goldstein and Brown's technical article on lipid metabolism in fibroblasts from patients with this disorder in a 1974 issue of the *Journal of Biological Chemistry*. However, we prescribe millions of statins on a daily basis and their Nobel Prize winning work began with this diligent piece of work. Other Nobel Prize winners have begun with more of a flair: the Australian gastroenterology registrar who, determined to convince rightly sceptical colleagues of his new theory on gastric ulcers, uses himself in an '*n* of one' trial by simply walking into his laboratory and swallowing a vial of *H. pylori*.

Of course, many of the most significant publications have been large, well-conducted trials. The Framingham study for example established a standard, perhaps never to be replicated, in conducting long-term observational studies on a large scale. So much of what we now believe about hypertension, ischaemic heart disease and much more comes directly from this mammoth enterprise. Or the trials in heart failure – CONSENSUS, RALES and many others – that now allow us to know with great confidence which drugs really work and save lives.

Understanding Medical Research is an attempt to put in one place these very different types of studies which have come together to shape modern medicine. I hope that in reading it you develop the same sense of enthusiasm and excitement about medicine with which the authors have written.

Sir Liam Donaldson

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First and foremost I must thank each of the authors who have given their time, expertise and energy in making this textbook what it is. It isn't hard to get academics to talk about what they love, but nonetheless it is easy to underestimate the time needed to carefully and succinctly summarise a whole field of research, and to do so in the midst of busy academic and clinical commitments. Your efforts have been legion and will provide a generation of medical students and junior doctors with an introduction to the vast volumes of medical research.

My thanks to the whole team at Wiley-Blackwell in Oxford, particularly Elizabeth Johnston for giving the project a chance when it was just an idea in a medical student's head, and Karen Moore for her endless patience in putting the manuscript together.

Thanks to Sir Liam Donaldson for providing the Foreword.

A final thanks to a few fellow medics who encouraged me along the way: Jakub Scaber, Charles Williams and Wei Yao Lim.

1 Population Health

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Introduction

There are many reasons why a paper could be selected as ‘important’ in public health. Some studies of the epidemiology of a disease have led to a clear understanding of their causation and opened up the scope for prevention. Iconic population studies of cancer, cardiovascular disease and industrial disease fall into this category. Other papers based on observational epidemiological studies of the pattern of disease by time, place or person have also made the case for public health action. Sometimes these have galvanised passion and commitment over long periods of time. Some studies of health inequalities will be seen in this way. Yet again, some contributions have laid the foundation of a new framework or approach to understanding public health problems or acting on them. Often they are associated with particular figures in history who have been the inspiration and guiding light for generations of public health practitioners. In selecting ‘important’ papers for this chapter, we have drawn from all these areas, recognising that in choosing these many other candidates for inclusion have been laid aside.

Shoe-Leather Epidemiology

Snow, London, 1855

> *Each epidemic of cholera in London has borne a strict relation to the nature of the water supply of its different districts, being modified only by poverty, and the crowding and want of cleanliness which always attend it.*

There are few doctors who can claim two places in medicine’s hall of fame, but the Victorian physician John Snow (1813–1858) was one. Celebrated in the history of anaesthetics, he helped to develop the early scientific basis for deploying gases to sedate and relieve pain, then popularised their use by administering chloroform to Queen Victoria during childbirth.

Snow’s contribution to public health was arguably even greater. Born in York, and apprenticed to a surgeon in Newcastle upon Tyne, Snow gravitated to London where he found himself in the midst of the great cholera outbreak of 1854. Cholera was one of

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the major pandemic disease scourges of the 19th century. It took the lives of thousands in all walks of life, but particularly the poor who lived in filthy and overcrowded dwellings in the towns and cities of the industrial revolution. It struck fear and despair into the population. The prevailing and firmly held theory on its cause was that it arose in the form of an invisible and noxious gas seeping from rotting vegetation and decaying corpses.

Snow debunked this ‘miasma’ theory with a painstaking piece of public health detective work. He was perhaps the greatest exponent of so-called shoe-leather epidemiology. He quite literally walked the streets of London for weeks, gathering information, talking to people, recording deaths and mapping them. He concluded that the source of the outbreak was a water pump in Broad Street, Soho that had been contaminated by raw sewage. That explained the clustering of cholera deaths of residents in the street near the pump, but it did not explain cases occurring further afield (Figure 1.1). Snow had the answer. His enquiries showed him that a woman had her water sent from the pump because, over the years, she preferred the taste. He explained other exceptions. Snow petitioned the local parish, and the pump handle was removed and the epidemic waned. Some experts dispute whether it was declining anyway.

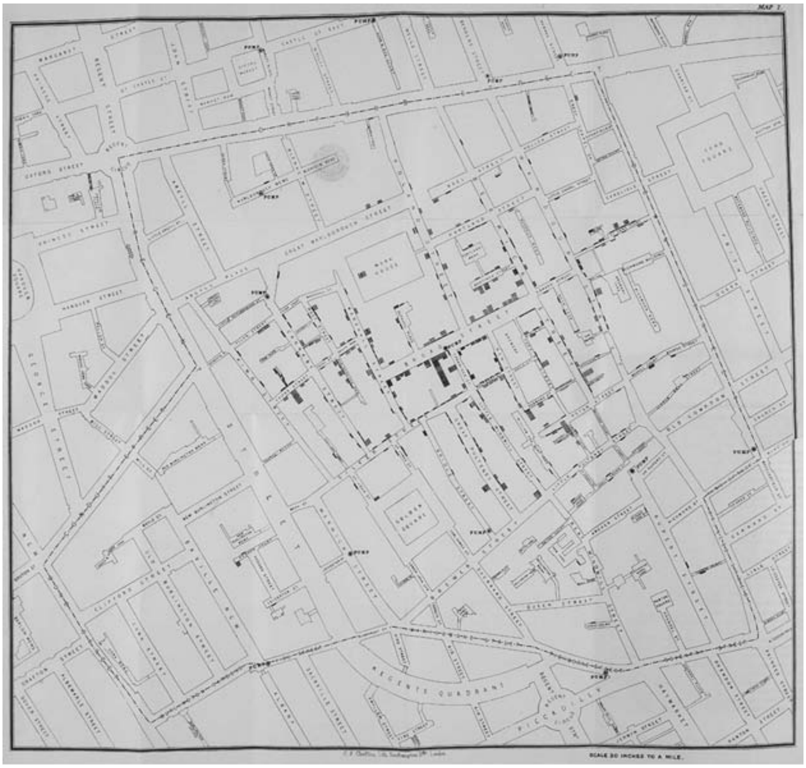

Figure 1.1 Mapping of cases around Broad Street pump. Reproduced with permission from Snow, London, 1855. © British Library Board.

In a less dramatic but equally important piece of work, Snow analysed the rates of attack from cholera in houses supplied by different London water companies. He found that two of these companies drew their supplies from the lower and most polluted parts of the Thames. Snow wrote up his findings in his celebrated monograph and postulated that a transmissible water-borne agent was the cause of cholera. His views were not accepted by establishment opinion at the time, and it would be many years before his conclusions were universally accepted, as the 'germ theory' of disease became established.

Smoking and Cancer: Association and Causality

Doll and Hill, British Medical Journal (1950)

> *It must be concluded that there is a real association between carcinoma of the lung and smoking.*

The early part of the 20th century saw an explosion in the accuracy of collection of epidemiological information. Despite this increased reporting and enquiry, lung cancer incidence appeared to be dramatically increasing. Between 1922 and 1947 the yearly rate of cases causing death had risen from 612 to 9287 in England and Wales. This trend was being observed internationally. Doll and Hill hypothesised that the smoking of tobacco could be causal in the development of lung cancer.

Their first preliminary description in the *British Medical Journal* in 1950 reported on a case-control study in London hospitals. They compared patients with lung cancer versus inpatients with other diseases. Careful epidemiological study involved identifying suitable controls at the level of the hospital ward, within the same age group and of the same sex.

The most striking data revealed that both male and female smokers were more likely to have lung cancer compared with other diseases (males: 647/649 versus 622/649, $p < 0.05$; females: 41/60 versus 28/60, $p < 0.02$).

Further analysis of amount of smoking revealed that for males, increasing numbers of cigarettes per day equated with a higher likelihood of lung cancer (Figure 1.2).

There were many possible biases. The samples only represented London hospital patients and controls. The case-control method, whilst ideal for this type of study, has inherent weaknesses of recall bias, especially in cases where there is an increased likelihood of remembering possible causal factors when faced with severe terminal disease.

Despite these criticisms a compelling case for smoking being statistically associated with lung cancer had been made. Causality could not be proven from this study; Austin Bradford Hill himself was to develop a framework for implying causality, which would rest on far more than just statistical association. Yet the authors continued their quest to prove causality, publishing regularly on smoking and lung cancer from 1950 to 2004, including the famous study examining smoking habits and mortality in British doctors.

Doll and Hill not only went on to show conclusively the link between lung cancer and smoking, but also established smoking as a cause of premature death, as well as demonstrating causality with heart disease and other illnesses. Studies in the United States around the same time revealed the same findings.

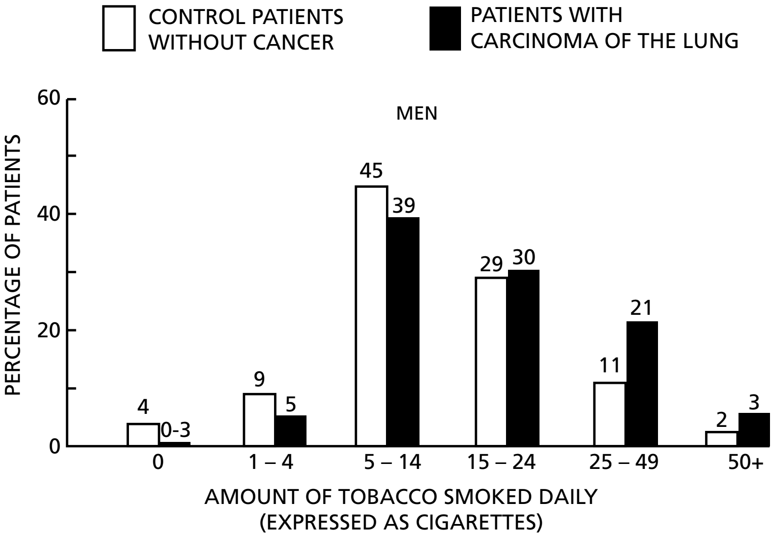

Figure 1.2 Increasing numbers of cigarettes per day equated with a higher likelihood of lung cancer. Reproduced with permission from Doll and Hill, *British Medical Journal* (1950), with permission from BMJ Publishing Group Ltd.

In the short term, Doll and Hill's paper had little influence on behaviour. Health education advice to the public was slow to emerge from the Ministry of Health as the powerful influence of the tobacco industry held sway. Their later longitudinal study of smoking amongst doctors, showing the now familiar smoking-related disease patterns, and the reduction of risk for quitters, ignited the war against tobacco. It is a war that is still being fought today around the world as the impact of tobacco on health is as great as any of the historical infectious disease pandemics. Doll and Hill's first study, however, remains the foundation stone of evidence from which the impetus for all subsequent public health progress was built.

The Inverse Care Law

Hart, Lancet (1971)

> *In areas with most sickness and death, general practitioners have more work, larger lists, less hospital support, and inherit more clinically ineffective traditions of consultation, than in the healthiest areas.*

Some papers in the history of public health have been influential less for the underpinning analysis than for the central idea that they communicate. It is no coincidence that the terminology used to describe the idea is often memorable in its own right. Julian Tudor-Hart practised for a whole professional lifetime as a general practitioner in one of the most deprived communities in Wales. Passionate about the links between poverty and poor health, angry about the opportunities for healthier lives denied to the populations he served and convinced of the benefits of a National

Health Service unfettered by the need to pay, he practised, researched and campaigned with equal passion.

He formulated the following principle: 'The availability of good medical care tends to vary inversely with the need for the population served'. Stated more simply, those who most need healthcare get less of it, whilst those who need less get more.

Hart based his assertion on a series of different sources of evidence. This included the observation that general practitioners saw more poor than wealthier patients, but with inadequate time to treat properly or keep themselves adequately skilled. The incentive was full waiting rooms, with each patient paying a low fee that resulted in a tidy profit. There were also quantitative studies that indicated the unfairness. In 1961 a study of 1370 patients and 552 doctors revealed that for the middle classes younger than 45 years old, general practitioner attendances were more than 50% less compared to working classes. However, over 75, the pattern was reversed. Hart infers that this leads to the conclusion that for all ages the middle classes received higher quality care.

The fabric of healthcare facilities also reflected the trend. In working-class areas 80% of practices were built before 1900, compared to 50% in middle-class areas.

The skill and time of doctors followed suit. In middle-class areas lists under 2000 were more common; four times as many general practitioners had a degree from Oxford or Cambridge; double the number had post-graduate qualifications; and five times as many had ready availability of physiotherapy. Hart argues this is because of the preponderance of higher social classes in medical school.

Hart showed himself a canny and brilliant advocate of his ideas. Years later he admitted that he had thought long and hard about what to call his principle. He thought of the 'inverse square law' which all adults would remember from their school mathematics classes. With one change of word he had the 'inverse care law', a term that has endured and continued to inspire idealists and pragmatists alike.

Framingham and the Heart

Dawber et al., American Journal of Public Health (1951)

> *The study is focused on arteriosclerotic and hypertensive cardiovascular disease, because these are the most important of the cardiovascular diseases and the least is known about their epidemiology.*

Epidemiologists often dream of 'population laboratories' – places which make sense in social and geographical terms, where the community is relatively stable, where data on health status are comprehensively collected and where partnership with the local community can be made with willing participants in generating evidence that will provide deep insights into disease causation and the scope for prevention. Framingham, Massachusetts, United States was such a place.

The Framingham heart study, established in 1948, studied cardiovascular disease over time. Naming one paper is problematic given that over 1000 studies have been published linked to this program. The study population initially included over 5000 participants of both sexes, ages 30–62, who had not experienced any symptoms of cardiovascular disease. Each of the participants initially underwent lifestyle interviews and detailed physical examinations. Participants returned every two years for continued follow-up, including medical histories, examination and laboratory investigations. In the 1970s the research extended the study to include over 5000 of the initial cohort's offspring and their partners. Over the last 20 years, it has continued to evolve and successive new groups of participants have been added, including the grandchildren of the first group.

The Framingham cohorts have allowed causality to be established between a range of risk factors and cardiovascular disease. These have included diabetes mellitus, hypercholesteroleamia, hypertension, lack of exercise, obesity and smoking. These core findings have transformed the understanding of cardiovascular disease the world over; few patients with symptoms suggestive of cardiovascular disease would fail to be screened for these core risk factors. They are comprehensive in establishing risk of disease and formative in determining individual patient management plans and population-level public health interventions. Findings have also included the link between cardiovascular disease and demographic factors, such as age and sex.

Ecological studies of this sort are complex to manage. They are susceptible to a well-described error, the ecological fallacy. This infers that the overall aggregated population statistics will apply to any one individual member of the population, which may not be true given the varying characteristics of every individual member of that population. Furthermore, the generalisability of the study to populations distinct from Caucasian Americans has been questioned. Yet, despite these epidemiological limitations, the principal findings have been reproduced in independent studies in many other population groups.

Much of the knowledge the world formed about the risks of cardiovascular disease initially came from the Framingham study. It set a new standard for the organisation and quality of methodologies needed to run effective large-scale longitudinal studies of natural populations.

The Evidence-Based Revolution

Cochrane, London, 1989

> *It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials*

At a march before the Second World War to advocate the introduction of a national health service, participants were given placards which read 'All healthcare should be free'. One young marcher, Archie Cochrane, a medical student, amended his sign to read: 'All effective healthcare should be free'. Nearly 80 years later, that student's insight is astonishing. Health services and patients around the world continue to waste large sums of money on treatments that either do no good or actively harm people.

Cochrane was one of the generation of British doctors who fought fascism in the Spanish Civil War. He then came back to make his career in public health, for much of it carrying out seminal studies of lung disease with the population of the Welsh Valleys, many of them dominated by mining. He came to wider attention, though, through the publication of an extended essay which laid the foundation for the modern concept of evidence-based healthcare.

Cochrane's compelling thesis demanded that clinical practice be based on evidence of effectiveness and not reliant solely on tradition or subjective opinion. This was of profound public health significance effectively calling for a paradigm shift from gross and wasteful clinical variation to evidence-based treatments.

He argued for more than just evidence-based practice and policies. He recognised the age-old public health paradigm that demand always outstrips supply. In face of this truth of scarce resources, he upheld that intervention should always be based on evidence, not clinical preference or hearsay.

Critics warned that individual patients would be disadvantaged with treatments that may have been proven for a population of patients, but were not necessarily effective for individuals. Yet despite these objections, over the next 40 years evidence has become the cornerstone of modern clinical practice. Medical students are versed internationally with the critical appraisal demanded by Cochrane for medical intervention: 'What is the evidence for effectiveness?'

Cochrane advocated the use of randomised control trials as the highest form of medical evidence. Today the Cochrane name is immortalised in the Cochrane Library and Cochrane Collaboration. These resources are sustained by the tireless work of experts in all corners of the world who provide an accessible, readable database of world-class evidence for medical practice in multiple specialities.

The Black Report

Black Report, London (1980)

> *It will come as a disappointment to many that over long periods since the inception of the NHS there is generally little sign of health inequalities in Britain actually diminishing and in some cases, they may be increasing.*

Ever since the gathering of statistics on population health began, epidemiologists have used them to study the pattern of disease in the triad of time, place and person. For almost all diseases, causes of death, or known risk factors to health there is a gradient. The worst health is found amongst those in the lowest strata of society. This has been examined by social class (defined by occupation) or socioeconomic status as well as by comparing communities according to various population indices of deprivation.

The gap between the health of the worst and the least deprived has at different points of the United Kingdom's history been very wide. At times it has narrowed, but it has never closed. Globally the gap in health status between rich and poor communities is quite shocking.

The Black report did not coin the term 'health inequalities' to describe this phenomenon, but it did bring it to wider prominence and public attention.

Sir Douglas Andrew Kilgour Black was commissioned in 1977 by David Ennals, the Labour Government's Secretary of State for Health, to write a review on the state of health inequalities in the United Kingdom. A general election intervened, and the final report was received by an incoming Conservative government led by Margaret Thatcher.

Black's thesis stated that haphazard policy making leading to highly variable public services was important in causality, not just that the differences were accounted for by differences in social mobility, lifestyle, economic or educational factors.

Controversially he advocated radical societal changes, including limiting the advertising of tobacco, as well as changes to benefits.

The legacy of the Black Report has endured for three main reasons. Firstly, it was the first report since Victorian times to provide a comprehensive and compelling analysis of the key statistics linked to a proposed strategic programme of action. Secondly, it was led by a mainstream medical figure who could not be dismissed as a public health idealist or radical. Thirdly, the method of publication of the report (plain cover, limited print run, release over a bank holiday weekend) made it a *cause célèbre*.

Many reports and books have followed. Sadly, the problem of health inequalities in the United Kingdom and worldwide persists. However, the centrality of health inequality to government policy making and NHS strategy is impressive. It is a transformation that would not have been possible without the touchstone of the original Black Report.

The Prevention Paradox

Rose, British Medical Journal (1981)

> *But, however much it [the public health intervention] may offer to the community as a whole, it offers little to each participating individual.*

Geoffrey Rose described the concept, the prevention paradox: ‘a measure that brings large benefits to the community offers little to each participating individual’.

Firstly, Rose deals with prevention at an individual level. Captured by the story of the man who arrives to see his doctor and is discovered to have high blood pressure, the man leaves a patient, confirmed by the endowing of pills. Rose confirms the perception that doctors do not traditionally interfere with men, only patients. Yet, in the above scenario this is not therapeutics; it is preventive medicine.

Secondly, intervention may have a high relative risk reduction, but if the population at risk is small in comparison to the whole population, absolute risk reduction will be less significant. Decision making, Rose argues, needs to be taken based on absolute figures. For example, if any one population were to simply target familial hypercholesterolemia (a condition with a high relative risk of cardiovascular disease), those individuals would benefit as they have a 50% higher mortality rate, but only 1% of all those at risk of death of cardiovascular disease would be targeted.

Rose refers to the Whitehall study (of the health of civil servants) and notes that those with marginally raised blood pressure were higher in number than those with very high blood pressure. More cases of stroke were observed in the marginally raised population. A strategy to target the high risk will not suffice as they are relatively few in numbers; to target the majority at risk of complications, a whole-population approach is required. Yet it is wasteful and of little benefit to any given individual with only a marginally raised blood pressure. Rose also gives the example of the first diphtheria programme in the United Kingdom. One child saved equated with 599 ‘wasted’ vaccines. Likewise if male doctors adhered to seat belt laws their entire working life, 399/400 doctors for 40 years would have ‘wasted’ their time fastening their seat belt – it wouldn’t have mattered whether they did or not.

Rose establishes this background as the basis for the prevention paradox – high benefits to the community overall has little impact on the individual person.

Rose's paradox has greatly influenced the practice of public health and in particular the design of interventions aimed at changing a population's behaviour. Many risk factors to health (e.g. blood pressure, cholesterol, obesity and physical inactivity) vary within the population. Sometimes if plotted graphically, they approximate a bell-shaped curve: the two tails representing the outliers (the best and the worst) with the majority falling on either side of the median. The challenge in prevention is to move the whole curve in the direction of the best, rather than target the small extreme ends. That is most effectively done by influencing the behaviour or risk factors of the many (the mass of people around the median of the distribution) and not the few (the outliers at the tails of the distribution).

The Principles of Screening

Wilson and Junger, Geneva, 1968

> *The central idea of early disease detection and treatment is essentially simple. However, the path to its successful achievement (on the one hand, bringing to treatment those with previously undetected disease, and, on the other, avoiding harm to those persons not in need of treatment) is far from simple though sometimes it may appear deceptively easy.*

Ask the person in the street, the politician, the journalist or even a doctor whether a society should concentrate effort on diagnosing disease early, and most would answer unequivocally 'Yes'. As a general principle it certainly holds true for individuals and in the assessment of patients. If symptoms and abnormal signs are recognised early, by and large the outcome of treatment is better. The problem comes when the same argument is applied to pro-actively offering a diagnostic test to a population whose members believe themselves to be healthy. Conceptually and ethically, this is different. It is no longer simply early diagnosis; it is presymptomatic or population screening.

This carries the implicit promise that people who are called forward with an offer of a test will benefit from earlier treatment. Unfortunately this is not always the case – a positive test result may simply reveal the knowledge of the presence of disease for the screened person earlier than for a patient who presents symptomatically. Both may live as long after treatment, but the screened person will appear to have lived longer than the symptomatic patient (so-called lead time bias) and the benefit of screening will be fallacious rather than real.

In the early 1960s, when cheap, quick tests to detect disease early were becoming more available, the pressure was to offer them to populations without a necessary sound basis. A discipline was brought to the screening bandwagon by a seminal set of scientific criteria to be applied before embarking on any population screening for a particular condition. This led to proper evaluation, sometimes including randomised controlled trials, before a decision to introduce a screening programme was made.

Wilson and Junger's criteria, published by the World Health Organisation in 1968, had ten conditions to be met before a screening programme should be initiated (Table 1.1).

Today in many countries extensive screening programmes have developed steered by Wilson and Junger's original criteria, and they have been developed further over time. Programmes of population screening in routine use include those for common cancers

Table 1.1 Wilson and Junger's Original Screening Criteria

The condition sought should be an important health problem.
There should be an accepted treatment for patients with recognized disease.
Facilities for diagnosis and treatment should be available.
There should be a recognizable latent or early symptomatic stage.
There should be a suitable test or examination.
The test should be acceptable to the population.
The natural history of the condition, including development from latent to declared disease, should be adequately understood.
There should be an agreed policy on whom to treat as patients.
The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
Case finding should be a continuing process and not a 'once and for all' project.

Source: Wilson and Junger (1968).

such as breast, bowel and cervix, as well as rarer but devastating conditions such as fetal anomalies. This small but vital evaluation framework has stood the test of time and has prevented untold harm and wastage of resources on ineffective population screening programmes, whilst ensuring that money and effort have been targeted ethically on those that could save lives and prevent disease progression.

Determining Causation

Hill, Proceedings of the Royal Society of Medicine (1965)

> *Upon what basis . . . can we pass from observed association to a verdict of causation?*

Statistical association is at the heart of epidemiological study. Yet, simple association, be it statistically robust or not, does not prove causation.

The jump from statistical association to causation was becoming increasing prominent post-war, especially with the advent of computers that handled ever larger data sets. This gap in public health thinking was addressed by Hill some years after he and Richard Doll had embarked upon the famous smoking studies reviewed earlier in this chapter. There was an identified gap in practice in how to establish causation. Hill's paper outlined nine criteria for strengthening the case for causation. It is not dogmatic or prescriptive, but brought together many common elements required to uphold the case for assuming agent A caused effect B.

The nine criteria are as follows:

Strength of association: Mainly statistical, but of course in certain cases where numbers studied are so large and effect of an agent so likely even statistical tests do not add much evidence. Hill gives the 18th-century example of the vast increase of scrotal cancer in chimney sweeps. He also argues the importance of using relative risk when establishing aetiology, the commonest technique used in public health today.

Consistency of findings: Research findings replicated by separate study techniques, at different times, by new researchers in dissimilar places. This is particularly important for drawing causality about rare risks.

Specificity: The clarity of link between one agent and one effect. Whilst two or more agents may be responsible for causing disease, where one agent is identified the likelihood of causation is strengthened.

Temporality: This addresses the question: which is the chicken and which is the egg? This is an important factor especially in illnesses with very long incubation periods. Are those selected to work in a certain environment more susceptible to contracting a certain disease, or is that workplace the source of the vector of disease?

Biological gradient: Enabling a dose–response to be plotted. For example, increasing numbers of cigarettes smoked per day causes a concomitant increase in lung cancer.

Plausibility: Covering the biological sense of the mechanism. However, this criterion depends on current levels of knowledge.

Coherence: The apparent association should not be significantly contrary to the natural history of the disease in question.

Experiment: Does the removal of a supposed pathogen reduce the association of agent and disease? Hill suggests that this is where the strongest evidence of causality may lie.

Analogy: Making an inference to causality for similar agents. For example, it is a reasonable starting point to think that a drug closely related to thalidomide could cause foetal deformity.

These nine criteria have been variously used, tested, added to and modified. Over time they create a viable and lasting way of weighing statistical evidence of association with postulated causality. Clearly some, such as reversibility, have more credence, but all nine offer evidence of establishing the verdict of cause and this checklist has become a cornerstone of public health practice.

On the State of Public Health

Simon, London, 1858

> *The essential points which I deem it necessary to bring under your lordships' consideration ... the inequality with which deaths are distributed in different districts of the country.*

The post of Chief Medical Officer for England was established by the government of the day as part of its response to the great cholera epidemics that swept Victorian England. The post continues to present times and remains the main source of advice on medical and public health matters to the government. Although working for and within government, the Chief Medical Officer post is politically independent and public facing. One of the highest profile elements of the role is the production of an annual report on the nation's health. Over the years, post holders have used this opportunity differently. The best have highlighted a serious problem, championed the need for action and done so without fear or favour.

In 1858, the first Chief Medical Officer of the United Kingdom, Sir John Simon, wrote a report to the Privy Council on the state of the nation's health. His report was crucial in helping to set the direction for future public health laws and reforms. It also set clarity of focus in health communication that was a beacon to light the path of his successors.

Simon was a surgeon at St Thomas' Hospital, and he fought hard for the right to provide independent advice to the government. Appointed as the medical officer of health for London in 1848, he wrote a series of reports on issues including vaccination and sanitation. By working closely with the government, and contributing to the development of the Public Health Acts that went through parliament, he was able to secure the crucial function of an annual independent report on public health to the highest level of government.

Many of the issues he mentioned in his first report as Chief Medical Officer sound familiar today, even if the diseases involved do not. He described the epidemics sweeping England at the time, including an outbreak of cowpox in Wraybury and typhoid in Windsor. He also highlighted the problems of health inequalities between different parts of the country. This was a well-observed fact, given that the life expectancy of a young man in Liverpool was 26 years, compared to his peer in the leafy market town of Oakhampton, who could expect to live to 57.

This description of the health of a population, and in particular the independent nature of the report, is fundamental to the public health function. Working with government, but also maintaining distance and objectivity, Simon was well respected by his superiors and by influential newspapers of the day and consequently was able to push for real change.

Conclusion

Population health is a broad topic but one that has included some of the most influential and insightful studies and reports in the history of medicine. From the shoe-leather epidemiology of John Snow explaining cholera outbreaks; through the work of Doll and Hill establishing the link between smoking and lung cancer; the mammoth Framingham ‘study’; to population screening, it is at once a discipline of immense practical benefit to millions and also one of academic rigour. Political and practical, academic and pragmatic, it represents the interface between society and healthcare and will continue to spearhead health policy for many generations.

Key Outstanding Questions

1. Can we improve health without increasing health inequalities?
2. What role will genetics play in the future of public health?
3. What future infectious disease threats remain unknown?

Key Research Centres

1. Johns Hopkins Bloomberg School of Public Health, Baltimore, United States
2. London School of Hygiene and Tropical Medicine, London, United Kingdom
3. The Cochrane Collaboration, Oxford, United Kingdom

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